British Journal of Medicine & Medical Research
8(5): 367-383, 2015, Article no.BJMMR.2015.461
ISSN: 2231-0614

SCIENCEDOMAIN *international*
www.sciencedomain.org

Periodontal Disease and Stroke: An Updated Review of Their Association

Ourania Schoinohoriti[1,2*], Aristeidis H. Katsanos[2,3], Ioannis Iatrou[1], Nikos Triantafyllou[4], Sokratis G. Papageorgiou[2], Spyridon Vasdekis[5], Efstathios Boviatsis[6], Konstantinos Voumvourakis[2] and Georgios Tsivgoulis[2,7,8]

[1]Department of Oral and Maxillofacial Surgery, Dental School, University of Athens, Greece.
[2]Second Department of Neurology, "Attikon" Hospital, School of Medicine, University of Athens, Greece.
[3]Department of Neurology, School of Medicine, University of Ioannina, Greece.
[4]Department of Neurology, "Eginition" Hospital, School of Medicine, University of Athens, Greece.
[5]Vascular Unit, Third Department of Surgery, "Attikon" Hospital, School of Medicine, University of Athens, Greece.
[6]Second Department of Neurosurgery, "Attikon" Hospital, School of Medicine, University of Athens, Greece.
[7]Department of Neurology, University of Tennessee Health Science Center, Memphis, Tennessee, USA.
[8]International Clinical Research Center, St. Anne's University Hospital in Brno, Brno, Czech Republic.

Authors' contributions

This work was carried out in collaboration between all authors. Authors OS and GT conceived and designed the study. Authors II and KV were responsible for selecting the literature included in the review. The first draft was written by author OS and was approved by author GT. Then all authors read and corrected the manuscript and approved its final version.

Article Information

DOI: 10.9734/BJMMR/2015/17516
Editor(s):
(1) Joao Paulo Steffens, Department of Dentistry, University of Uberaba, Brazil.
Reviewers:
(1) Soumya Mishra, Department of Physiology, JIPMER, Puducherry, India.
(2) Aşkın Ender Topal, Cardiovascular Surgery, Dicle University, Medicine Faculty, Turkey.
(3) Anonymous, India.
Complete Peer review History: http://www.sciencedomain.org/review-history.php?iid=1117&id=12&aid=9080

Review Article

Received 18th March 2015
Accepted 14th April 2015
Published 2nd May 2015

**Corresponding author: Email: our_schoinohoriti@yahoo.com;*

ABSTRACT

Objective: To review the literature regarding the association of periodontal disease with stroke that has been gaining interest during the last two decades.
Methods: A search was conducted through MEDLINE and SCOPUS databases for all literature related to the combination of terms “periodontitis” or “periodontal disease” and “stroke” or “cerebrovascular diseases”. The selected articles included cross-sectional, case-control and longitudinal studies, as well as interventional trials published up to August 2014 that were classified according to their design and critically reviewed.
Findings: Periodontal disease appears to be moderately associated with stroke but the nature of their association is not fully elucidated. The great heterogeneity of the reviewed studies does not allow but a rough estimate of its significance either as a causal or risk factor for stroke. Large-scale randomized clinical trials are warranted to determine whether periodontal intervention may contribute to the primary or secondary prevention of atherosclerotic disease and stroke as its end-point.
Conclusion: The bulk of evidence from the reviewed studies suggests that periodontal disease may represent a contributing factor for stroke but further appropriately designed clinical trials, focusing on the impact of periodontal treatment on stroke are necessary.

Keywords: Stroke; periodontal disease; association, causality; risk factor.

1. INTRODUCTION

Despite recent advances in acute stroke treatment effective primary stroke prevention by means of improved control of vascular risk factors has the greatest potential to reduce stroke burden [1]. However, up to 25% of all strokes are not attributable to recognized risk factors [1,2]. In this context systemic inflammation, reflected by increased biomarkers such as C-reactive protein (CRP), is thought to promote atherogenesis [3]. Oral infections such as periodontal disease represent potential sources of systemic infectious and inflammatory stress that contribute to stroke morbidity and mortality, thus acquiring significance as a potential novel risk factor for stroke [4-6].

Periodontal disease (PD) is one of the most common oral infections, affecting the tooth supporting tissues; it is divided into periodontitis (leading to progressive destruction of the periodontal ligament and alveolar bone with pocket formation, recession or both) and gingivitis (affecting the gingivae), which are clinically distinguished by detectable tooth attachment loss [7]. Various predominantly Gram-negative microorganisms described as “periodontal pathogens” have been implicated in the initiation and progression of PD by activating both local and systemic immune and inflammatory reactions [8,9].

This narrative review aims to summarize the available cross-sectional, case-control and longitudinal evidence on the association between periodontal and cerebrovascular diseases with special emphasis on the end-point of ischemic stroke.

2. METHODS

Our literature search through MEDLINE and SCOPUS databases was based on the combination of terms “periodontitis” or “periodontal disease” and “stroke” or “cerebrovascular diseases”. Last literature search was conducted on August 31, 2014. We also searched abstract lists and conference proceedings of the International Stroke Conferences and European Stroke Conferences. Reference lists of all articles that met the criteria and of relevant review articles were examined to identify studies that may have been missed by the database search. Titles, abstracts and, whenever appropriate, full texts of all identified studies were screened independently by two reviewers (OS and GT); disagreements were resolved by consensus of all contributing authors. Duplicate publications, case reports and publications in other than the English language were excluded from further evaluation. Research articles that were considered eligible to be included in this review, were classified according to their study design to one of the following: cross-sectional, case-control, longitudinal and interventional studies. For each study design articles were placed in chronological order of publication and the respective data were summarized in four different tables (Tables 1-4).

3. RESULTS

3.1 Cross-sectional Studies

Cross-sectional studies investigating the association of PD-related parameters with stroke and/or its surrogate markers (subclinical carotid atherosclerosis or cardiovascular risk measures) are summarized in chronological order on Table 1 [10-24].

Clinical, radiographic or laboratory markers of PD have been used as exposure variables in cross-sectional studies. Similarly, different outcomes such as incident stroke, sonographic signs of subclinical carotid atherosclerosis or cardiovascular risk measures have been investigated (Table 1). Among the histopathologically validated, easily measurable signs of carotid atherosclerosis is the intima-media thickening of the carotid wall that has received considerable attention as a surrogate marker of early atherosclerosis with prognostic significance for stroke development [20,24,25].

Since Friedlander and Lande [26] first reported carotid calcifications on orthopantomograms, several studies have investigated the usefulness of this finding for identifying clinically significant carotid artery stenosis and its relationship to history and/or risk of stroke [27-29]. Carotid calcifications have been correlated with alveolar bone loss as a marker of severe periodontitis, determined from the same orthopantomogram [13,30,31]. Thus, orthopantomogram apart from evaluating PD severity is also an adjunctive screening tool for subclinical carotid stenosis [19,30,31]. Therefore, individuals with carotid calcifications detected on routine orthopantomograms, especially if older than 50-55 years or with vascular risk factors, should be referred for ultrasound and further cardiovascular evaluation [26-28,30].

3.2 Case-control Studies

Case-control studies, generating the next level of evidence for the relationship between clinical, radiographic or laboratory markers of periodontal status and stroke or surrogate markers (subclinical carotid atherosclerosis or atherosclerosis risk factors) are summarized chronologically on Table 2 [5,25,32-49].

Studies investigating clinical, laboratory (oral microbiotic burden) and radiographic markers of PD in relation to stroke have registered moderate to strong associations (odds ratios, OR=2.5-48), depending on the examined stroke subtype (ischemic, [33,34,42,47,49] hemorrhagic [4] or combined [39,45]).

Other reports have also investigated the impact of immunological reactions against periodontal pathogens on stroke risk by measuring antibody titers against them and/or their products [35,36,43,46] Antibodies are considered a relatively reliable index of systemic exposure to periodontal pathogens, when compared to clinical measures of periodontal status [37,50]. In patients suffering from PD high IgG titers may reflect a cumulative history of disease activity or a current response to an active phase of PD, often non-protective. However, high titers may also occur in periodontally healthy individuals, reflecting a functionally protective response [20,35].

Numerous investigations have confirmed strong associations between clinical, radiographic and / or laboratory markers of PD and subclinical carotid atherosclerosis, identified sonographically (as carotid intima-media thickening or plaque) or radiographically (as carotid calcifications on orthopantomograms) [25,38,44,48]. Moreover, two studies investigating the relationship between PD clinical markers and established atherosclerosis risk factors or inflammatory markers (CRP, IL-6, TNF-α R1) have also demonstrated independent associations linking the prevalence and severity of PD with the extent of atherosclerosis and inflammation [40].

3.3 Longitudinal Studies

Longitudinal studies investigating the relationship of PD-related parameters with stroke and subclinical carotid atherosclerosis as stroke predictor are summarized in chronological order on Table 3. PD and its surrogates were associated with higher risk of incident stroke, ischemic stroke or hemorrhagic stroke as well as stroke mortality in the majority of studies [51-64]

The discrepant results between a small number of studies is partly attributed to the variety of investigated outcomes (incident or recurrent, total or ischemic stroke, all-cause or cerebrovascular disease mortality including fatal stroke and early or progressive carotid atherosclerosis). Similarly, various exposure variables have been examined (number of missing teeth, alveolar bone loss, self-reported PD and serum antibodies against periodontal pathogens).

3.4 Interventional Trials

Presently, the available evidence demonstrating the beneficial effects of periodontal intervention directly on CVD are still limited. Intervention trials investigating the impact of periodontal treatment on incident ischemic stroke, inflammatory biomarkers and / or surrogate markers of atherosclerosis are summarized chronologically on Table 4 [4,65-75]. Periodontal treatment (PT) was associated with a reduction in inflammatory burden (reduced CRP and improved clinical and surrogate markers of endothelial function) in the majority of available non-randomized intervention studies but limited or no effect on more specific markers of atherosclerosis such as lipid profiles and arterial blood pressure, coagulation and biomarkers of endothelial cell activation.[76] Differences in the sample size and type of evaluated PT may have accounted for potential discrepant findings among different interventional studies [4,65-75]. Although the available evidence to date is consistent with a contributory role of periodontitis to the atherosclerotic cardiovascular disease, well-designed intervention trials regarding the impact of PT on the prevention of atherosclerosis and stroke as its endpoint are warranted [76].

4. DISCUSSION

Since periodontal disease (PD) and stroke appear to have common characteristics, clarifying the nature of and quantifying their association is important for public health and has been the objective of studies with different designs [76]. Critically appraising their findings and deducing conclusions is difficult since, although numerous clinical, radiographic and laboratory markers or combinations have been used to define periodontal status, there is no uniform case definition of PD [77,78]. To further complicate the matter, a wide variation of threshold values for these markers has been applied to identify and grade PD [63,79]. Tooth loss as a surrogate PD marker remains controversial; [14,15,17,22,24] though being a valid marker of long-term cumulative PD for some populations, it is difficult to grasp epidemiologically, as it reflects the result of periodontal treatment, severe PD or both [14]. Alveolar bone loss (ABL) in orthopantomograms or full-mouth periapical radiographs accurately reflects the severity of periodontitis, can be measured blindly and compares favorably with clinical findings of periodontitis [13,34,80,81]. Since periodontal treatment does not typically result in bone regeneration, ABL measures better periodontitis history regardless of treatment, whereas clinical measurements such as probing depth reflect current exposure to periodontal inflammation [82].

Varying prevalence of PD in different populations complicates the assessment of its association with stroke [83]. Moreover, differences in the way observational studies are conducted, i.e. in study population (size, age groups, ethnicities and geographical settings) or inclusion criteria can substantially differentiate the results [25,33,77,78]. Most observational studies investigating the relationship of PD with stroke adjusted for a number of established confounders. However, since the mechanisms associating PD with stroke are not fully elucidated, adjustment for confounders potentially influenced by PD itself (i.e. age, socioeconomic status) is also possible (over-controlling) [14,77,84].

Table 1. Summarized cross-sectional studies, associating PD-related parameters with stroke, subclinical carotid atherosclerosis or cardiovascular risk measures [10-24]

Reference	Population	Exposure	Outcome	Adjusted association
Wu et al. 2000 [10]	selected participants of NHANES III study	BOP, calculus index, pocket depth, AL	serum total and HDL cholesterol, CRP, plasma fibrinogen	i) between BOP/calculus index and increased CRP ii) between calculus index and increased plasma fibrinogen
Beck et al. 2001 [11]	6797 dentate subjects of dental ARIC study, aged 52-75	extent of AL≥3mm (severe periodontitis defined as AL ≥30%)	carotid IMT ≥1mm	between severe periodontitis and IMT ≥1mm (OR=1.31,95%CI:1.03-1.66)

Reference	Population	Exposure	Outcome	Adjusted association
Katz et al. 2002 [12]	10,590 Israeli military service men and women	CPITN	serum total and LDL cholesterol	between CPITN score 4 and hypercholesterolemia in men
Persson et al. 2002 [13]	1084 subjects, aged ≥ 65	ABL, CC	CC, self-reported stroke history, confirmed by medication lists	i) between PD and CC (OR=2.1,95%CI:1.3-3.2) ii) between CC and stroke (OR=4.2,95%CI:1.9-9.1)
Desvarieux et al. 2003 [14]	711 participants of INVEST study, aged 57-75	tooth loss (number of missing teeth)	carotid plaque prevalence	between tooth loss and carotid artery plaque prevalence (46% for subjects missing <9, 60% for those missing ≥10 teeth)
Elter et al. 2003 [15]	6436 dentate examined, 2979 dentate not examined & 1491 edentulous participants of dental ARIC study	extent of AL≥3mm for dentate subjects, edentulousness	incident stroke/TIAs	i) between the highest quartile of AL and stroke/TIAs (OR=1.3,95%CI:1.02-1.7) ii) between edentulousness and stroke/TIAs (OR=1.4,95%CI:1.5-2)
Furuichi et al. 2003 [16]	1,314 Japanese subjects, aged ≥ 40	CPITN	CRP, WBC counts, serum IgG against P.g., serum IgA against A.a.	of CPITN score 4 with: i) CRP (OR=2.39) ii) WBC counts (OR=1.24) iii) IgG P.g. (OR=1.54) iv) IgA A.a. (OR=1.19)
Desvarieux et al. 2004 [17]	1710 subjects aged 45-75	AL, tooth loss	carotid plaque prevalence, IMT	of plaque prevalence with: i) AL among males (10% > in highest tertile of AL) ii) tooth loss among males (66% for missing <8 and 75% for missing ≥16 teeth)
Joshipura et al. 2004 [18]	468 male participants of Health Professionals' Follow-up Study, aged 47-80	self-reported PD	CRP, t-PA, LDL-C	between self-reported PD and: i) CRP (30%> among cases) ii) t-PA (11%> among cases) iii) LDL-C (11%> among cases)
Engebretson et al. 2005 [19]	203 participants of INVEST study, aged 54-94	ABL	carotid plaque thickness	between ABL and carotid plaque thickness (OR=3.64,95%CI:1.37-9.65)
Beck et al. 2005 [20]	4585 participants of ARIC study	IgG antibodies to periodontal pathogens	carotid IMT≥1mm	between antibodies to C.r. and carotid IMT ≥1mm (OR=2.3,95%CI:1.83-2.84)

Reference	Population	Exposure	Outcome	Adjusted association
Vilkuna-Rautiainen et al. 2006 [21]	1107 subjects (734 from Finland 373 from Russia), aged 25-55	combined serum IgA and IgG to A.a. and P.g.	HDL cholesterol	inversely between combined antibody response to A.a. and P.g. and HDL cholesterol
Syrjälä et al. 2009 [22]	392 elderly (>75) non-smokers with history of MI or ischemic stroke	edentulousness, number of teeth	incident MI or ischemic stroke	non-significant
You et al. 2009 [23]	22,862 participants of REGARDS study, aged ≥45	self-reported tooth loss	prevalent stroke, CRP	of prevalent stroke with: i) ≥17 missing teeth (OR=1.28,95%CI:1.09-1.49) ii) CRP
Holmlund & Lind 2012 [24]	947 subjects, aged ≥70	self-reported tooth loss	carotid plaque prevalence, IMT	between number of teeth and carotid plaque prevalence (OR=0.89,95%CI:0.82-0.98)

(PD = periodontal disease, BOP = bleeding on probing, AL = attachment loss, CPITN = Community Periodontal Index of Treatment Needs, ABL= alveolar bone loss, CC = carotid calcifications, IMT = intima-media thickness, TIAs = transient ischemic attacks, MI = myocardial infarction, t-PA = tissue plasminogen activator, OR = odds ratio, CI = confidence interval, C.i = Campylobacter rectus)

Table 2. Summarized case-control studies, associating PD-related parameters with stroke, subclinical carotid atherosclerosis or cardiovascular risk measures [5,25,32-49]

Reference	Population	Exposure	Outcome	Adjusted association
Buhlin et al. 2003 [32]	50 cases of severe periodontitis 46 periodontally healthy controls	probing depth, BOP, HI	HDL and total cholesterol, CRP, IL-6, TNF-α R1, antibodies against human HSP60	non-significant serological differences between cases and controls, indicating association of periodontitis with established atherosclerosis risk factors
Grau et al. 2004 [33]	303 cerebral ischemia cases 300 age- & sex-matched population controls 168 hospital controls with non-vascular, non-inflammatory neurological diseases	DMFT, GI, PI, mean CAL, ABL	ischemic stroke / TIAs	of cerebral ischemia with: i) severe gingivitis (GI>1.2) (OR=7.27,95%CI:2.94-18) in men < 60 ii) moderate periodontitis (4.5<CAL<6mm) (OR=2.7,95%CI:1.4-5.3) in men <60 iii) severe periodontitis (CAL>6mm) (OR=4.3,95%CI:1.85-10.2) in men <60
Dörfer et al. 2004 [34]	303 cerebral ischemia cases 300 age- & sex-matched population controls	GI, PI, mean CAL, ABL	ischemic stroke / TIAs	of cerebral ischemia with: i) GI >1.2 (OR=18.3,95%CI:5.8-57.26) ii) CAL>6mm (OR= 7.38,95%CI:1.55-15.3) iii) ABL>5.5mm (OR=3.6,95%CI:1.58-8.28)

Reference	Population	Exposure	Outcome	Adjusted association
Johansson et al. 2005 [35]	273 stroke cases 546 age- and sex-matched controls	antibodies to A.a.-leukotoxin	total stroke (ischemic, hemorrhagic or unclassified)	negative association between antibodies to A.a.-leukotoxin and stroke in women (OR=0.28,95%CI:0.13-0.59)
Pussinen et al. 2007 [36]	407 stroke cases 486 age- and sex-matched controls	IgA & IgG to P.g. / IgA & IgG to A.a.	total stroke	of stroke with: i) IgA to P.g. (OR=3.31,95%CI:1.31-8.4) in male non-smokers ii) IgG to P.g. (OR=2.30,95%CI:1.39-3.78) in women
Söder & Yakob 2007 [37]	46 women with periodontitis 21 periodontally healthy women	PI, GI, BOP, CAL, probing depth, number of teeth, ABL	carotid IMT, cIMA	of periodontitis with: i) increased IMT (OR=6.05,95%CI:1.34-27.35) ii) increased cIMA (OR=5.41,95%CI:1.2-24.43)
Cairo et al. 2008 [38]	45 cases of severe periodontitis (≤ 40) 45 periodontally healthy age- and sex-matched controls	number of teeth, probing depth, CAL	IMT ≥0.82mm	between severe periodontitis and IMT (OR=8.55,95%CI:2.38-39.81)
Sim et al. 2008 [39]	265 non-fatal stroke cases 214 age-matched population controls (Koreans)	CAL, probing depth	total stroke	between periodontitis (CAL≥6mm) and total stroke (OR=4,95%CI:2.3-7)
Buhlin et al. 2009 [40]	68 cases of periodontitis 48 periodontally healthy controls	probing depth, BOP, HI, tooth mobility	CRP, plasma fibrinogen, IL-18, HSP60, HSP65, HSP70	association of periodontitis with: i) CRP (OR=4.0,95%CI:1.4-11.4) ii) fibrinogen (OR=8.7,95%CI:2.6-28.4) iii) IL-18 (OR=6.5,95%CI:2.2-19.5)
Friedlander et al. 2010 [41]	36 cases with CC 36 age- and sex-matched controls (without CC)	CC on ortho / grams	ABL >4mm as part of MPI index (= chronic dental infection marker), tooth loss	of CC with MPI and specifically ABL>4mm
Kim et al. 2010 [5]	165 hemorrhagic stroke cases 214 non-stroke controls in Korea	CAL	hemorrhagic stroke	between periodontitis (CAL≥6mm) and hemorrhagic stroke (OR=2.5,95%CI:11-5.6)
Pradeep et al. 2010 [42]	100 ischemic stroke cases 100 age- and sex- matched healthy controls in India	CAL, probing depth, GI, PI	ischemic stroke	between probing depth >4.5mm and stroke (OR=8.5,95%CI:1.1-68.2)
Tabeta et al. 2011 [43]	66 cerebral infarction cases 330 age- and sex-matched controls in	IgG to P.g.	cerebral infarction	of cerebral infarction with: i) 2nd tertile category of IgG to P.g. (OR=7.12,95%CI:1.51-33.5)

Reference	Population	Exposure	Outcome	Adjusted association
	Japan			ii) 3rd tertile category of IgG to P.g. (OR=9.03,95%CI:1.97-41.5)
Yakob et al. 2011 [44]	88 cases of periodontitis 40 controls without periodontitis	number of teeth, BOP, probing depth, CAL, PI, GI, ABL, oral microbiotic burden	cIMA	of increased cIMA with: i) periodontitis (OR=4.2,95%CI:1.2-14.7) ii) P.g. presence (OR=7.63,95%CI:1.7-34.1) iii) P.n. presence (OR=4.08,95%CI:1.1-15)
Ghizoni et al. 2012 [45]	20 stroke cases 60 healthy controls	probing depth, CAL, BOP, PI, number of teeth, oral microbiotic burden	total stroke	between PD and total stroke (OR=48.06,95%CI:5.96-387.72)
Hosomi et al. 2012 [46]	132 ischemic stroke cases 77 healthy controls	IgG to A.a., P.g., P.i., CRP	ischemic stroke subtypes	i) between IgG to P.g. and atrial fibrillation (OR=4.36,95%CI:1.71-12.1) ii) between IgG to P.i. and bulb/ICA atherosclerosis (OR=23.6,95%CI:2.65-298.2)
López-Jornet et al. 2012 [25]	30 cases of chronic periodontitis 30 controls without periodontitis	BOP, probing depth, CAL	IMT, carotid plaque	i) non-significant between periodontitis and IMT ii) significant between periodontitis severity and carotid plaque presence
Palm et al. 2013 [47]	98 ischemic stroke cases 100 healthy controls	salivary levels of periodontal pathogens, IL-1β, serum LPS	ischemic stroke	of ischemic stroke with: severe periodontitis, edentulousness and salivary burden of A.a.
Pinho et al. 2013 [48]	35 cases with carotid plaque or IMT≥1mm 15 controls without carotid plaque or IMT<1mm	carotid plaque or IMT≥1mm	CAL	between severe periodontitis and carotid plaque presence
Lafon et al. 2014 [49]	48 minor ischemic stroke cases 47 healthy controls	PI, GI, probing depth, BOP, ABL, CRP	ischemic stroke	of ischemic stroke with : i) BOP (OR=1.04,95%CI=1-1.88) ii) ABL>20% (OR=1.05,95%CI=1.01-1.09)

(HSP = heat shock protein, BOP = bleeding on probing, HI = hygiene index, TIAs = transient ischemic attacks, OR = odds ratio, CI = confidence interval, DMFT = decayed, missing or filled teeth, GI = gingival index, PI = plaque index, CAL = clinical attachment loss, ABL = alveolar bone loss, IMT = carotid artery intima-media thickness, cIMA = carotid artery intima-media area = IMT+lumen diameter, CC = carotid calcifications, MPI index = Mattila pantomography index, i.e. sum of periapical and furcal lesions+pericoronitis sites+carious roots+teeth with pulpal caries+vertical bony defects >4mm, P.n. = Prevotella nigrescens)

Despite their usefulness for hypothesis generation cross-sectional studies cannot determine the temporal relationship of exposure and outcome.80 Stroke is the end-point of a long-term process and PD is chronic in nature; since both outcome and exposure are measured simultaneously, neither temporal sequence can be established nor causal relationship can be

inferred [19,22,24,80]. It is also a matter of concern, whether certain PD-related clinical findings are sequels rather than precursors of stroke [85].

A substantial aspect of case-control studies is the selection of controls. The difficulty of recruiting appropriate controls in sufficient numbers often compromises the study results. Furthermore, controls are occasionally matched to cases on characteristics that influence either the outcome or the exposure (gender, age, smoking status) [86]. An inherent limitation of case-control studies using PD-related clinical measurements as exposure variables is their evaluation retrospectively, after the outcome has occurred [4]. For obvious reasons the dentist performing the clinical examination cannot be fully blinded for the patients' status and this may lead to an ascertainment bias in the evaluation [40].

Table 3. Summarized longitudinal studies, associating PD-related parameters with stroke and early or progressive carotid atherosclerosis [51-64]

Reference	Population	Follow-up length	Exposure	Outcome	Adjusted association
Wu et al (2000) [51]	9,962 participants of NHANES I and follow-up study	21 yrs	periodontal status categories: 1) no PD 2) gingivitis 3) periodontitis 4) edentulousness	total CVA (incident, fatal, ischemic, hemorrhagic stroke, TIAs)	of periodontitis with: i) incident total CVA (OR = 1.66, 95% CI:1.15-2.39) ii) incident non-hemorrhagic stroke (OR=2.11,95%CI:1.3-3.42)
Howell et al (2001) [52]	22,037 male participants of Physicians' Health Study I	12.3 yrs	self-reported PD	CVD events including stroke (incident or fatal)	non-significant between PD and stroke
Jansson et al (2001) [53]	1,393 subjects in Sweden	26 yrs	oral health score (=sum of various parameters, including tooth loss and ABL>10%)	CVD deaths including fatal stroke	between CVD mortality and ABL>10%: i) OR=2.7 in subjects <45 yrs ii) OR=3.4 in smokers <45 yrs
Joshipura et al (2003) [54]	41,380 male participants of Professionals' Follow-up Study	12 yrs	self-reported PD, number of teeth	ischemic stroke	of ischemic stroke with: i) self-reported PD (OR=1.33,95%CI:1.03-1.7) ii) number of teeth ≤24 (OR=1.57,95%CI:1.24-1.98)
Ajwani et al (2003) [55]	364 participants (>75) of Helsinki Ageing Study	5 yrs	number of teeth, probing depth, CPITN	CVD mortality including fatal stroke	of periodontitis with CVD mortality (OR=2.28,95%CI:1.03-5.05)
Pussinen et al (2004) [56]	173 cases of stroke and 2 age- and sex-matched controls per	13 yrs	IgG & IgA to A.a. and P.g.	incident and recurrent stroke	i) of IgA to A.a. with incident stroke (OR=1.6,95%CI:1-2.6) ii) of IgA to P.g. with

Reference	Population	Follow-up length	Exposure	Outcome	Adjusted association
	case				recurrent stroke (for stroke or CHD history at baseline) (OR=2.6,95%CI:1-7)
Abnet et al. 2005 [57]	29,584 participants of a chemopreventi on trial in China	15 yrs	tooth loss	all-cause mortality including fatal stroke	between tooth loss and: i) all-cause mortality (13%>risk) ii) fatal stroke (12%>risk) compared to median tooth loss for subjects of same age
Söder et al. 2005 [58]	82 PD cases and 31 periodontally healthy controls	16 yrs	number of teeth , GI, PI, probing depth, AL, ABL	IMT, cIMA	of PD with: i) increased cIMA (OR=5.2,95%CI:1.73 -15.67) ii) increased IMT (OR=4.64,95%CI:1.6 4-13.1)
Schillinger et al. 2006 [59]	411 participants of ICARAS study	7.5 months	DMFT, SLI, CPITN	carotid stenosis progression	of carotid stenosis progression with: i) edentulousness (OR=2.1,95%CI:1.06 -4.16) ii) DMFT (OR=1.11,95%CI:1.0 1-1.22) iii) SLI (OR=1.77,95%CI:1.0 9-2.79)
Tu et al. 2007 [60]	12,223 students of Glasgow Alumni Cohort, aged ≤30	up to 57 yrs	tooth loss	all-cause & CVD mortality including fatal stroke	between CVD mortality and ≥9 missing teeth (OR=1.35,95%CI:1.0 3-1.77)
Choe et al. 2009 [61]	867,256 Koreans, participants of the KCPS study	14 yrs	tooth loss	total stroke (ischemic and hemorrhagi c)	of total stroke with ≥7 missing teeth in: i) men (OR=1.3,95%CI:1.2-1.4) ii) women (OR=1.2,95%CI:1-1.3)
Jimenez et al. 2009 [62]	1,137 male participants of Veteran Affairs Normative Aging Study	24 yrs	ABL, probing depth	ischemic stroke/TIAs	i) of ABL with stroke/TIAs (OR=3.52,95%CI:1.5 9-7.81) ii) non-significant of probing depth with stroke/TIAs
Holmlund et al. 2010 [63]	7,674 subjects	12 yrs	number of teeth, number of periodontal pockets, BOP	CVD mortality including fatal stroke	non-significant between number of teeth and stroke mortality

Reference	Population	Follow-up length	Exposure	Outcome	Adjusted association
Hoke et al. 2011 [64]	411 subjects with asymptomatic carotid atherosclerosis	6.2 yrs	DMFT, CPITN, SLI	all-cause mortality including fatal stroke	of all-cause mortality with: i) edentulousness (OR=1.99,95%CI:1.18-3.02) ii) DMFT (OR=1.06,95%CI:1-1.12) iii) SLI (OR=1.43,95%CI:1.01-2.03) iv) non-significant association of all-cause mortality with CPITN

(CVA = cerebrovascular accidents, CVD = cardiovascular disease, GI = gingival index, PI = plaque index, ABL = alveolar bone loss, CHD = coronary heart disease, IMT = intima-media thickness, cIMA = calculated intima-media area = IMT+lumen diameter, DMFT = decayed, missing or filled teeth, SLI = Silness-Löe index, CPITN = Community Periodontal Index of Treatment Needs, BOP = bleeding on probing)

Table 4. Summarized intervention trials investigating the impact of periodontal treatment on incident ischemic stroke, inflammatory biomarkers and surrogate markers of atherosclerosis [4,65-75]

Reference	Population	PT type	Outcome	Follow-up length	Conclusion
Iwamoto et al. 2003 [65]	15 cases of chronic periodontitis	minocyclin into pockets & debridement	CRP, TNF-α	_	locally applied minocyclin & debridement reduces inflammatory burden
D'Aiuto et al. 2004 [66]	94 cases of severe generalized periodontitis	standard	CRP, IL-6	6 months	PT reduces inflammatory burden and CVD risk
Mercanoglu et al. 2004 [67]	28 cases of chronic periodontitis 26 periodontally healthy controls	standard	brachial artery FMD	_	periodontitis causes ED – PT improves endothelial function
Seinost et al. 2005 [68]	30 cases of severe periodontitis 31 periodontally healthy controls	standard & pharm/cal	brachial artery FMD	3 months	periodontitis causes ED – PT improves endothelial function and inflammatory burden
Yamazaki et al. 2005 [69]	24 cases of moderate to advanced periodontitis 21 controls without periodontitis	standard	CRP, IL-6, TNF-α	3 months	PT non-significantly reduced inflammatory burden
Elter et al. 2006 [70]	22 cases of moderate to severe	standard	brachial artery FMD, CRP, IL-6, total and	1 month	PT improves endothelial function and inflammatory

Reference	Population	PT type	Outcome	Follow-up length	Conclusion
	periodontitis		HDL cholesterol		burden
D'Aiuto et al. 2007 [71]	55 cases of severe periodontitis	intensive	IL-1β, TNF-α, coagulation & soluble endothelial markers	1 month	acute PT effects: activation of coagulation system, moderate ED
Tonetti et al. 2007 [72]	120 cases of severe periodontitis	standard (59 cases) or intensive + pharm/cal (61 cases)	brachial artery FMD, CRP, IL-6, coagulation markers	6 months	24 hours after PT: inflammation, coagulation activation and moderate ED 6 months after PT: improved endothelial function
Behle et al. 2009 [73]	30 cases of severe periodontitis	intensive (including surgical)	19 biomarkers, serum IgG to periodontal pathogens	1 month	PT non-significantly reduced inflammatory burden
Offenbacher et al. 2009 [4]	303 cases of severe periodontitis	OHI (152 cases) or intensive (151 cases)	CRP	6 months	PT did not reduce CRP
Piconi et al. 2009 [74]	35 cases of mild to moderate PD	standard	microbiotic burden, CRP, IMT	12 months	PT improved microbiotic burden, inflammatory markers, ED and carotid IMT
Lee et al. 2013 [75]	510,762 PD-cases 208674 controls	no treatment or dental prophylaxis or intensive	incident ischemic stroke	10 yrs	PT reduces ischemic stroke risk

(PT = periodontal treatment, standard = supragingival mechanical scaling and polishing, intensive = scaling and root planing under local anesthesia, FMD = flow-mediated dilatation, pharm / cal = pharmacological, ED = endothelial dysfunction, OHI = oral hygiene instructions, IMT = intima-media thickness)

Longitudinal design establishes the temporal relationship between exposure and outcome and may corroborate causal associations with proper adjustment for confounders [79,80]. These studies represent the second highest form of evidence available after large-scale randomized clinical trials, determining the impact of periodontal treatment on stroke [79] However, when investigating novel risk factors (i.e. PD for stroke), the results of longitudinal studies may not be as uniformly or strongly significant as those of cross-sectional studies.[1]

The great heterogeneity of intervention trials suggests that inter-trial differences in study size, follow-up length, bias risk, presence or absence of co-morbidities and/or other cardiovascular risk factors, treatment type and effectiveness play a significant role [87]. The negativity of their results requires careful interpretation: if a cardiovascular outcome is not attenuated through periodontal treatment, this may not necessarily exclude its causal association with PD [88].

5. CONCLUSION

In conclusion, the bulk of evidence from reviewed studies establishes an association between PD and stroke. Although the strength of the reported associations is generally moderate, the consistency of data emerging from geographically and ethnically diverse populations

across a variety of exposure and outcome variables certifies that these findings cannot be ascribed solely to confounding; therefore, PD is highlighted as a moderate risk factor for atherosclerosis. Given the significant morbidity and mortality attributed to atherosclerosis, appropriately designed clinical trials are warranted to determine whether periodontal intervention may contribute to the primary or secondary prevention of atherosclerotic disease and stroke as its end-point.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Ezzati M, Lopez AD, Rodgers A, et al. Comparative Risk Assessment Collaborating Group. Selected major risk factors and global and regional burden of disease. Lancet. 2002;360:1347-60.
2. Goldstein LB, Bushnell CD, Adams RJ, et al. Guidelines for the primary prevention of stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2011;42:517-84.
3. Ridker PM, Silvertown JD. Inflammation, C-reactive protein and atherothrombosis. J Periodontol. 2008;79:1544-51.
4. Offenbacher S, Beck JD, Moss K, et al. Results from the Periodontitis and Vascular Events (PAVE) Study: A pilot multicentered, randomized, controlled trial to study effects of periodontal therapy in a secondary prevention model of cardiovascular disease. J Periodontol. 2009;80:190-201.
5. Kim HD, Sim SJ, Moon JY, et al. Association between periodontitis and hemorrhagic stroke among Koreans: A case-control study. J Periodontol. 2010;81: 658-65.
6. Cotti E, Dessì C, Piras A, Mercuro G. Can a chronic dental infection be considered a cause of cardiovascular disease? A review of the literature. Int J Cardiol. 2011;148:4-10.
7. Armitage GC. Development of a classification system for periodontal diseases and conditions. Ann Periodontol. 1999;4:1-6.
8. Pihlstrom BL, Michalowicz BS, Johnson NW. Periodontal diseases. Lancet. 2005; 366:1809-20.
9. Noack B, Genco RJ, Trevisan M, et al. Periodontal infections contribute to elevated systemic C-reactive protein level. J Periodontol. 2001;72:1221-7.
10. Wu T, Trevisan M, Genco RJ, et al. Examination of the relation between periodontal health status and cardiovascular risk factors: Serum total and high density lipoprotein cholesterol, C-reactive protein, and plasma fibrinogen. Am J Epidemiol. 2000;151:273-82.
11. Beck J, Elter J, Heiss G, et al. Relationship of periodontal disease to carotid artery intimal-media wall thickness: The Atherosclerosis Risk in Communities (ARIC) study. Arterioscler Thromb Vasc Biol. 2001;21:1816-22.
12. Katz J, Flugelman MY, Goldberg A, Heft M. Association between periodontal pockets and elevated cholesterol and low density lipoprotein cholesterol levels. J Periodontol. 2002;73:494-500.
13. Persson RE, Hollender LG, Powell VL, et al. Assessment of periodontal conditions and systemic disease in older subjects. II. Focus on cardiovascular diseases. J Clin Periodontol. 2002;29:803-10.
14. Desvarieux M, Demmer RT, Rundek T, et al. Relationship between periodontal disease, tooth loss, and carotid artery plaque: The Oral Infections and Vascular Disease Epidemiology Study (INVEST). Stroke. 2003;34:2120-5.
15. Elter JR, Offenbacher S, Toole JF, Beck JD. Relationship of periodontal disease and edentulism to stroke/TIA. J Dent Res. 2003;82:998-1001.
16. Furuichi Y, Shimotsu A, Ito H, Namariyama Y, Yotsumoto Y, Hino Y, et al. Associations of periodontal status with general health conditions and serum antibody titers for Porphyromonas gingivalis and

Actinobacillus actinomycetemcomitans. J Periodontol. 2003;74:1491-7.

17. Desvarieux M, Schwahn C, Völzke H, et al. Gender differences in the relationship between periodontal disease, tooth loss, and atherosclerosis. Stroke. 2004;35:2029-35.
18. Joshipura KJ, Wand HC, Merchant AT, Rimm EB. Periodontal disease and biomarkers related to cardiovascular disease. J Dent Res. 2004;83:151-5.
19. Engebretson SP, Lamster IB, Elkind MS, et al. Radiographic measures of chronic periodontitis and carotid artery plaque. Stroke. 2005;36:561-6.
20. Beck JD, Eke P, Lin D, et al. Associations between IgG antibody to oral organisms and carotid intima-medial thickness in community-dwelling adults. Atherosclerosis. 2005;183:342-8.
21. Vilkuna-Rautiainen T, Pussinen PJ, Roivainen M, et al. Serum antibody response to periodontal pathogens and herpes simplex virus in relation to classic risk factors of cardiovascular disease. Int J Epidemiol. 2006;35:1486-94.
22. Syrjälä AM, Ylöstalo P, Hartikainen S, et al. Number of teeth and myocardial infarction and stroke among elderly never smokers. J Negat Results Biomed. 2009;8:6.
23. You Z, Cushman M, Jenny NS, Howard G. REGARDS. Tooth loss, systemic inflammation, and prevalent stroke among participants in the reasons for geographic and racial difference in stroke (REGARDS) study. Atherosclerosis. 2009;203:615-9.
24. Holmlund A, Lind L. Number of teeth is related to atherosclerotic plaque in the carotid arteries in an elderly population. J Periodontol. 2012;83:287-91.
25. López-Jornet P, Berná-Mestre JD, Berná-Serna JD, et al. Measurement of atherosclerosis markers in patients with periodontitis: a case-control study. J Periodontol. 2012;83:690-8.
26. Friedlander AH, Lande A. Panoramic radiographic identification of carotid arterial plaques. Oral Surg Oral Med Oral Pathol. 1981;52:102-4.
27. Almog DM, Horev T, Illig KA, et al. Correlating carotid artery stenosis detected by panoramic radiography with clinically relevant carotid artery stenosis determined by duplex ultrasound. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2002; 94:768-73.
28. Cohen SN, Friedlander AH, Jolly DA, Date L. Carotid calcification on panoramic radiographs: An important marker for vascular risk. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2002;94:510-4.
29. Friedlander AH, Cohen SN. Panoramic radiographic atheromas portend adverse vascular events. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2007;103:830-5.
30. Beckstrom BW, Horsley SH, Scheetz JP, et al. Correlation between carotid area calcifications and periodontitis: a retrospective study of digital panoramic radiographic findings in pretreatment cancer patients. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2007;103:359-66.
31. Ravon NA, Hollender LG, McDonald V, Persson GR. Signs of carotid calcification from dental panoramic radiographs are in agreement with Doppler sonography results. J Clin Periodontol. 2003;30:1084-90.
32. Buhlin K, Gustafsson A, Pockley AG, et al. Risk factors for cardiovascular disease in patients with periodontitis. Eur Heart J. 2003;24:2099-107.
33. Grau AJ, Becher H, Ziegler CM, et al. Periodontal disease as a risk factor for ischemic stroke. Stroke. 2004;35:496-501.
34. Dörfer CE, Becher H, Ziegler CM, et al. The association of gingivitis and periodontitis with ischemic stroke. J Clin Periodontol. 2004;31:396-401.
35. Johansson A, Johansson I, Eriksson M, et al. Systemic antibodies to the leukotoxin of the oral pathogen *Actinobacillus actinomycetemcomitans* correlate negatively with stroke in women. Cerebrovasc Dis. 2005;20:226-32.
36. Pussinen PJ, Alfthan G, Jousilahti P, et al. Systemic exposure to *Porphyromonas gingivalis* predicts incident stroke. Atherosclerosis. 2007;193:222-8.
37. Söder B, Jakob M. Risk for the development of atherosclerosis in women with a high level of dental plaque and severe gingival inflammation. Int J Dent Hygiene. 2007;5:133-8.
38. Cairo F, Castellani S, Gori AM, et al. Severe periodontitis in young adults is

associated with subclinical atherosclerosis. J Clin Periodontol. 2008;35:465-72.

39. Sim SJ, Kin HD, Moon JY, et al. Periodontitis and the risk of non-fatal stroke in Korean adults. J Periodontol. 2008;79:1652-8.
40. Buhlin K, Hultin M, Norderyd O, et al. Risk factors for atherosclerosis in cases with severe periodontitis. J Clin Periodontol. 2009;36:541-9.
41. Friedlander AH, Sung EC, Chung EM, Garrett NR. Radiographic quantification of chronic dental infection and its relationship to the atherosclerotic process in the carotid arteries. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2010;109:615-21.
42. Pradeep AR, Hadge P, Arjun Raju P, et al. Periodontitis as a risk factor for cerebrovascular accident: A case-control study in the Indian population. J Periodontal Res. 2010;45:223-8.
43. Tabeta K, Tanabe N, Yonezawa D, et al. Elevated antibody titers to Porphyromonas gingivalis as possible predictor of ischemic vascular disease: results from the Tokamachi-Nakasato cohort study. J Atheroscler Thromb. 2011;18:808-17.
44. Yakob M, Söder B, Meurman JH, et al. Prevotella nigrescens and Porphyromonas gingivalis are associated with signs of carotid atherosclerosis in subjects with and without periodontitis. J Periodont Res. 2011;46:749-55.
45. Ghizoni JS, Taveira LA, Garlet GP, et al. Increased levels of Porphyromonas gingivalis are associated with ischemic and hemorrhagic cerebrovascular disease in humans: An *In vivo* study. J Appl Oral Sci. 2012;20:104-12.
46. Hosomi N, Aoki S, Matsuo K, et al. Association of serum anti-periodontal pathogen antibody with ischemic stroke. Cerebrovasc Dis. 2012;34:385-92.
47. Palm F, Lahdentausta L, Sorsa T, et al. Biomarkers of periodontitis and inflammation in ischemic stroke: A case-control study. Innate Immun. 2013;20:511-8.
48. Pinho MM, Faria-Almeida R, Azevedo E, et al. Periodontitis and atherosclerosis: an observational study. J Periodontal Res. 2013;48:452-7.
49. Lafon A, Tala S, Ahossi V, et al. Association between periodontal disease and non-fatal ischemic stroke: A case-control study. Acta Odontol Scand. 2014;72:687-93.
50. Mustapha IZ, Debrey S, Oladubu M, Ugarte R. Markers of systemic bacterial exposure in periodontal disease and cardiovascular disease risk: A systematic review and meta-analysis. J Periodontol. 2007;78:2289-302.
51. Wu T, Trevisan M, Genco RJ, et al. Periodontal disease and risk of cerebrovascular disease: the first national health and nutrition examination survey and its follow-up study. Arch Intern Med. 2000;160:2749-55.
52. Howell TH, Ridker PM, Ajani UA, et al. Periodontal disease and risk of subsequent cardiovascular disease in U.S. male physicians. J Am Coll Cardiol. 2001;37: 445-50.
53. Jansson L, Lavstedt S, Frithiof L, Theobald H. Relationship between oral health and mortality in cardiovascular diseases. J Clin Periodontol. 2001;28:762-8.
54. Joshipura KJ, Hung HC, Rimm EB, et al. Periodontal disease, tooth loss, and incidence of ischemic stroke. Stroke. 2003; 34:47-52.
55. Ajwani S, Mattila KJ, Tilvis RS, Ainamo A. Periodontal disease and mortality in an aged population. Spec Care Dentist. 2003; 23:125-30.
56. Pussinen PJ, Alfthan G, Rissanen H, et al. Antibodies to periodontal pathogens and stroke risk. Stroke. 2004;35:2020-3.
57. Abnet CC, Qiao YL, Dawsey SM, et al. Tooth loss is associated with increased risk of total death and death from upper gastrointestinal cancer, heart disease and stroke in a Chinese population-based cohort. Int J Epidemiol. 2005;34:467-74.
58. Söder PO, Söder B, Nowak J, Jogestrand T. Early carotid atherosclerosis in subjects with periodontal diseases. Stroke. 2005; 36:1195-200.
59. Schillinger T, Kluger W, Exner M, et al. Dental and periodontal status and risk for progression of carotid atherosclerosis: the inflammation and carotid artery risk for atherosclerosis study dental sub study. Stroke. 2006;37:2271-6.
60. Tu YK, Galobardes B, Smith GD, et al. Associations between tooth loss and

mortality patterns in the Glasgow Alumni Cohort. Heart. 2007;93:1098-103.

61. Choe H, Kim YH, Park JW, et al. Tooth loss, hypertension and risk for stroke in a Korean population. Atherosclerosis. 2009;203:550-6.
62. Jimenez M, Krall EA, Garcia RI, et al. Periodontitis and incidence of cerebrovascular disease in men. Ann Neurol. 2009;66:505-12.
63. Holmlund A, Holm G, Lind L. Number of teeth as a predictor of cardiovascular mortality in a cohort of 7,674 subjects followed for 12 years. J Periodontol. 2010; 81:870-6.
64. Hoke M, Schillinger T, Mlekusch W, et al. The impact of dental disease on mortality in patients with asymptomatic carotid atherosclerosis. Swiss Med Wkly. 2011; 141:w13236.
65. Iwamoto Y, Nishimura F, Soga Y, et al. Antimicrobial periodontal treatment decreases serum C-reactive protein, tumor necrosis factor-alpha, but not adiponectin levels in patients with chronic periodontitis. J Periodontol. 2003;74:1231-6.
66. D'Aiuto F. Ready D, Tonetti MS. Periodontal disease and C-reactive protein associated cardiovascular risk. J Periodont Res. 2004;39:236-41.
67. Mercanoglu F, Oflaz H, Oz O, et al. Endothelial dysfunction in patients with chronic periodontitis and its improvement after initial periodontal therapy. J Periodontol. 2004;75:1694-700.
68. Seinost G, Wimmer G, Skerget M, et al. Periodontal treatment improves endothelial dysfunction in patients with severe periodontitis. Am Heart J. 2005;149:1050-4.
69. Yamazaki K, Honda T, Oda T, et al. Effect of periodontal treatment on the C-reactive protein and proinflammatory cytokine level in Japanese periodontitis patients. J Periodontal Res. 2005;40:53-8.
70. Elter JR, Hinderliter AL, Offenbacher S, et al. The effects of periodontal therapy on vascular endothelial function: A pilot study. Am Heart J. 2006;151:47.
71. D'Aiuto F, Parkar M, Tonetti MS. Acute effects of periodontal therapy on biomarkers of vascular health. J Clin Periodontol. 2007;34:124-9.
72. Tonetti MS, D'Aiuto F, Nibali L, et al. Treatment of periodontitis and endothelial function. N Engl J Med. 2007;356:911-20.
73. Behle JH, Sedaghatfar MH, Demmer RT, et al. Heterogeneity of systemic inflammatory responses to periodontal therapy. J Clin Periodontol. 2009;36:287-94.
74. Piconi S, Trabattoni D, Luraghi C, et al. Treatment of periodontal disease results in improvements in endothelial dysfunction and reduction of the carotid intima-media thickness. FASEB J. 2009;23:1196-204.
75. Lee YL, Hu HY, Huang N, et al. Dental prophylaxis and periodontal treatment are protective factors to ischemic stroke. Stroke. 2013;44:1026-30.
76. Tonetti MS, Van Dyke TE; working group 1 of the joint EFP/AAP workshop. Periodontitis and atherosclerotic cardiovascular disease: Consensus report of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. J Periodontol. 2013;84:24-9.
77. Scannapieco FA, Bush RB, Paju S. Association between periodontal disease and risk for atherosclerosis, cardiovascular disease, and stroke. A systematic review. Ann Periodontol. 2003;8:38-53.
78. Belstrøm D, Damgaard C, Nielsen CH, Holmstrup P. Does a causal relation between cardiovascular disease and periodontitis exist? Microbes Infect. 2012; 14:411-8.
79. Joshipura K, Zevallos JC, Ritchie CS. Strength of evidence relating periodontal disease and atherosclerotic disease. Compend Contin Educ Dent. 2009;30:430-9.
80. Meurman JH, Sanz M, Janket SJ. Oral health, atherosclerosis and cardiovascular disease. Crit Rev Oral Biol Med. 2004;15:403-13.
81. Machtei EE, Hausmann E, Grossi SG, et al. The relationship between radiographic and clinical changes in the periodontium. J Periodontal Res. 1997;32:661-6.
82. Page RC, Eke PI. Case definitions for use in population-based surveillance of periodontitis. J Periodontol. 2007;78:1387-99.
83. Persson GR, Persson RE. Cardiovascular disease and periodontitis: An update on

the associations and risk. J Clin Periodontol. 2008;35:362-79.

84. Genco R, Offenbacher S, Beck J. Periodontal disease and cardiovascular disease: Epidemiology and possible mechanisms. JADA. 2002;133:14s-22s.
85. Demmer RT, Desvarieux M. Periodontal infections and cardiovascular disease: The heart of the matter. JADA. 2006; 137Suppl:14S-20S;quiz 38S.
86. Beck JD, Offenbacher S. Systemic effects of periodontitis: Epidemiology of periodontal disease and cardiovascular disease. J Periodontol. 2005;76;2089-100.
87. 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;41:70-9.
88. Armitage GC. Effect of periodontal therapy on general health – is there a missing component in the design of these clinical trials? J Clin Periodontol. 2008;35:1011-2.

© 2015 Schoinohoriti et al.; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history.php?iid=1117&id=12&aid=9080