Journal of
PERIODONTAL RESEARCH

*J Periodont Res 2016*


JOURNAL OF PERIODONTAL RESEARCH
doi:10.1111/jre.12376

# Relation between periodontal disease and arterial stiffness

**L. N. Nicolosi[1,2,†], P. G. Lewin[2], J. J. Rudzinski[2], M. Pompeo[2], F. Guanca[2], P. Rodríguez[2], R. J. Gelpi[3], M. C. Rubio[1,2,†]**

[1]Department of Cardiology, Spanish Hospital of Buenos Aires, Buenos Aires, Argentina, [2]Department of Buccodental and Clinical Pathology, Cardiovascular Physiopathology Institute, School of Dentistry, University of Buenos Aires, Buenos Aires, Argentina and [3]Department of Pathology, Cardiovascular Physiopathology Institute, School of Medicine, University of Buenos Aires, Buenos Aires, Argentina

*Nicolosi L.N, Lewin PG, Rudzinski JJ, Pompeo M, Guanca F, Rodríguez P, Gelpi RJ, Rubio MC. Relation between periodontal disease and arterial stiffness. J Periodont Res 2016; doi:10.1111/jre.12376. © 2016 John Wiley & Sons A/S. Published by John Wiley & Sons Ltd*

*Background and Objective:* Periodontal disease has been described as playing a role in the atherosclerosis process, and its relation with intimal thickness and vascular endothelial function (EF) has been investigated. The present study sought to determine whether there are differences in parameters of arterial stiffness and EF between patients with and without severe periodontal disease (SPD).

*Material and Methods:* Patients referred to the School of Dentistry University of Buenos Aires, were assessed. Demographic characteristics, atherogenic risk factors and concomitant pathologies were recorded. Patients with known cardiovascular pathology were excluded. Using carotid Doppler ultrasound an operator assessed arterial stiffness parameters: compliance, elastic modulus (EM), β stiffness index (βSI) and vascular EF by brachial artery flow-mediated dilatation. The patients were divided into two groups: with and without SPD.

*Results:* Forty patients were included; 60% were women; 15 were in the SPD group and 25 in the group without SPD. Respective results of the studied variables were: age 56.53 ± 17.58 vs. 51.12 ± 12.97 years (NS); probing depth 2.53 ± 1.30 (95% CI 1.81–3.25) vs. 1.25 ± 0.51 (95% CI 1.31–1.73) $p = 0.02$; clinical attachment level 4.80 ± 2.00 (95% CI 3.69–5.91) vs. 1.72 ± 0.93 (95% CI 1.33–2.11) $p = 0.001$; intimal thickness 0.10 ± 0.17 (95% CI 0.095–0.11) vs. 0.82 ± 0.18 (95% CI 0.074–0.98) (NS); EM 48.33 ± 12.53 vs. 38.86 ± 7.69 ($p = 0.005$); βSI 4.21 ± 1.03 vs. 3.64 ± 1.02 ($p = 0.004$); EF 16.13 ± 5.02 vs. 22.76 ± 4.50 ($p = 0.0003$). Correlation between: EM and clinical attachment level $r = 0.58$ ($p < 0.001$), βSI and clinical attachment level $r = 0.66$ ($p < 0.001$), EF and clinical attachment level 0.59 ($p < 0.001$).

*Conclusions:* Parameters of arterial stiffness and EF were worse in patients with SPD and correlated moderately with clinical attachment level. Correlation with compliance and EF was negative.

Prof. Liliana N. Nicolosi, MD, Department of Buccodental and Clinical Pathology, School of Dentistry, University of Buenos Aires. Marcelo T de Alvear 2142, Buenos Aires 1113AR, Argentina
Tel: +54 11 4964 1278
Fax: +54 11 4959 6298
e-mail: lnicolosi@hotmail.com
[†]Equal contribution to the manuscript.

Key words: endothelium; periodontal disease; periodontal medicine; risk factor

Accepted for publication January 29, 2016

Endothelial cells play a fundamental role in vascular homeostasis. Inflammation has a negative impact on endothelial function (EF) as it causes an increase in vascular permeability, generating alterations in the cytoskeleton. Inflammatory injury has been shown to cause an imbalance in the synthesis/secretion of vasodilating substances, such as nitric oxide, prostacyclin and endothelial hyperpolarizing factor, and vasoconstrictors such as endothelin 1, thromboxane and angiotensin II (1,2).

Vascular endothelial dysfunction has been associated with a variety of pathologies and risk factors for atherosclerosis, including age, arterial hypertension, dislipemias, diabetes, smoking, specific cardiovascular pathologies such as coronary, cerebral and peripheral arteriopathy, and infectious and inflammatory processes such as periodontal disease (3–12).

Studies in cohorts of cases and controls have demonstrated that periodontitis is associated with endothelial dysfunction, atherosclerosis and with a higher risk of myocardial infarction and stroke (13–19).

Endothelial dysfunction results in a predominance of the vasoconstrictor effect, which can be quantified by measuring the flow-mediated dilation of the brachial artery. In addition, EF has been found to improve with periodontal disease treatment. There are reports demonstrating a relation between periodontal disease, intima-media thickness of the carotid artery and aorta stiffness, using the cardio-ankle index. However, the usefulness of β index stiffness (βSI), compliance and elastic modulus (EM) of the carotid artery to assess arterial stiffness in patients with severe periodontal disease (SPD) remains to be clarified (20–24).

A number of studies have used pulse wave velocity as a measure of arterial stiffness. It must be pointed out, however, that this parameter is influenced by arterial blood pressure at the time of measurement. In the present study, arterial stiffness was evaluated using the arterial stiffness index, which is a highly reproducible method and is theoretically independent of blood pressure (25,26).

The objective of the present study was to determine whether there are differences in parameters of arterial stiffness and EF between patients with and without SPD.

## Material and methods

### Ethics statement

This study was approved by the Ethics Committee of the School of Dentistry of the University of Buenos Aires-University Dental Hospital, Argentina. Written informed consent was also obtained from all participants before their health examination.

### Study design and population

A prospective study was conducted using data on arterial stiffness and endothelial stiffness parameters obtained from patients with and without periodontal disease.

The study was conducted in patients referred from the Dental Hospital at the School of Dentistry, University of Buenos Aires, Argentina, to the Dental Care Clinic for High Risk Patients: CLAPAR II.

All enrolled patients underwent clinical and radiographic dental examination. The radiographic study included a digital panoramic X-ray using a CS 9000 3D–extraoral imaging system (Carestream Health, Inc., Rochester, NY, USA) digitally analyzed using Kodak Dental Imaging Software, version 6.12.10.0. All permanent teeth, except for the third molars, were evaluated. Patients with fewer than 10 teeth were excluded from the study to ensure that periodontal diagnosis was representative of the clinical dental status of the patient and avoid overestimation of diagnosis of periodontal disease. Decayed, Missing and Filled Teeth (DMFT) scores were recorded.

Clinical periodontal examination was performed by a single calibrated operator. Periodontal measurements were performed at six sites per tooth (mesio-buccal, mid-buccal, disto-buccal, mesio-lingual/palatal, mid-lingual/palatal and disto-lingual/palatal) on all present teeth, using a manual Marquis type periodontal probe (Hu-Friedy Co., Chicago, IL, USA).

The studied periodontal parameters included probing depth and clinical attachment level, which were assessed using standardized protocol (27).

The values of the periodontal parameters were averaged by calculating the arithmetic mean of the six determinations performed on each tooth. This method prevents overdiagnosis of periodontal disease, as a number of patients have very high clinical attachment level values at one periodontal site because of trauma (associated with tooth brushing or with the structure of their removable prosthesis, harmful oral habits, among others).

Intra-examiner reproducibility of probing depth and clinical attachment level measurements was assessed before the study. The weighted $K$ coefficient for probing depth and clinical attachment level was 0.96 and 0.91 respectively.

Probing depth was used as a tool to assess periodontal disease activity and guide patient treatment, but it was not used to establish the severity of periodontal disease, as this parameter varies greatly throughout the course of the disease.

Alveolar bone loss, determined on the radiographic images, was assessed as an adjuvant parameter to confirm diagnosis of SPD, as explained below. Hence, the radiographic studies were only examined in such cases.

Diagnosis of periodontal disease was performed based on clinical attachment level values, in keeping with the 1999 International Workshop for a Classification of Periodontal Disease accepted by the American Academy of Periodontology (28).

SPD was established when:

1 Average clinical attachment level values were $\geq 5$ mm, according to the calculation described above.
2 Average clinical attachment level values were $< 5$ mm but with values $\geq 5$ mm in $> 30\%$ of studied sites, in addition to horizontal alveolar bone loss $> 1/3$ of the root length in at least 30% of teeth, as measured on the radiographic images.

The patients were divided into two groups, with and without SPD.

Patients with known cardiovascular disease, under treatment with vasodilator agents, calcium blockers or angiotensin-converting enzyme inhibitors were excluded from the study. All enrolled patients were studied using a Philips CX 30 ultrasound system (Philips Healthcare, Andover, MA, USA) with a 7.5 MHz linear transducer. Arterial blood pressure was determined three times, and mean systolic arterial pressure (SAP) and mean diastolic arterial pressure (DAP) were calculated. Assuming equivalence of mean and diastolic pressures at carotid and brachial sites, the following equations were used to calculate the five parameters of arterial elasticity (29):

1 Arterial compliance (AC) ($mm^2/kPa$) = $\pi$ $(Ds(2) - Dd^2)/4(SAP - DAP)$.
2 EM (Ep) (kPa) = $(SAP - DAP) Dd/(Ds - Dd)$.
3 $\beta SI = \ln (SAP - DAP)/[(Ds - Dd)/Dd]$.

Carotid intima-media thickness was measured at the posterior wall of the common carotid artery, according to the Mannheim carotid intimal-media thickness consensus. The images were stored on a digital system, and determinations were performed again manually (30). The average of the three determinations was calculated and the maximum value was determined.

EF was estimated using flow-mediated dilation of the brachial artery, in keeping with the Guidelines of the International Brachial Artery Reactivity Task Force (31).

The following covariables of atherogenic risk were evaluated: age, arterial hypertension, diabetes, hypercholesterolemia, obesity and smoking.

### Statistical analysis

Continuous variables are reported as mean ±1 SD. The data were statistically analyzed using IBM SPSS Statistics for Windows, Version 20 software (IBM Corp., Armonk, NY, USA). The mean and SD of continuous variables were calculated, and variables were compared using ANOVA, *t*-test and Pearson's coefficient correlation. The level of significance was set at a $p < 0.05$ and 95% CIs were calculated.

## Results

Forty patients, 24 (60%) of whom were women, were enrolled between March and August 2014; 15 patients were in the group with SPD, and 25 patients were in the group without SPD (no-SPD).

The following population and periodontal parameters were observed in the SPD and no-SPD groups respectively: age 56.53 ± 17.58 vs. 51.12 ± 12.97 years (NS); probing depth 2.53 ± 1.30 (95% CI 1.81–3.25) vs. 1.25 ± 0.51 (95% CI 1.31–1.73) $p = 0.02$; clinical attachment level 4.80 ± 2.00 (95% CI 3.69–5.91) vs. 1.72 ± 0.93 (95% CI 1.33–2.11) $p = 0.001$. Arterial parameters of SPD and no-SPD groups were as follows: intima-media thickness: 0.10 ± 0.17 (95% CI 0.095–0.11) vs. 0.082 ± 0.18 (95% CI 0.074–0.98) (NS); and stiffness parameters were: AC ($mm^2$/kPa) 2.41 ± 1.32 vs. 3.08 ± 1.02 ($p = 0.004$); EM (kPa) 48.33 ± 12.53 vs. 38.86 ± 7.69 ($p = 0.005$); βSI 4.21 ± 1.03 vs. 3.64 ± 1.02 ($p = 0.004$) (Fig. 1). EF parameters of SPD and no-SPD groups were as follows: EF 16.13 ± 5.02% vs. 22.76 ± 4.50% ($p = 0.0003$). Correlation was observed between AC and clinical attachment level $r = -0.60$ ($p < 0.001$), EM and clinical attachment level $r = 0.64$ ($p < 0.001$), βSI and clinical attachment level $r = 0.66$ ($p < 0.001$), and between EF and clinical attachment level $r = -0.59$ ($p < 0.001$) (Fig. 2). No significant differences in arterial hypertension, diabetes, hypercholesterolemia, obesity or smoking were observed between groups.

## Discussion

Epidemiological studies have shown an increase in intima-media wall thickness in patients with SPD, linking the latter with atherosclerosis (14). In addition, subjects with substantial tooth loss, probably because of long-term SPD, showed an increase in intima-media wall thickness (32).

Alterations in EF and arterial distensibility have been associated with atherosclerosis, and have been suggested as an important predictor of cardiovascular disease (33–37).

When EF is healthy, the endothelium is able to respond to physical and chemical signals by production of a wide range of factors that regulate vascular tone, cellular adhesion, thromboresistance, smooth muscle cell proliferation and vessel wall inflammation (38).

Arterial distensibility is evaluated measuring compliance, EM and βSI. Compliance is the ability of a vessel to distend and increase volume with increasing transmural pressure. It is the reciprocal of "elastance," hence EM is a measure of the tendency of a vessel to recoil toward its original dimensions upon removal of a distending or compressing force. AC is the absolute change in area for a given pressure step at a fixed vessel length. The EM is the stress/strain ratio. In most biologic materials, this

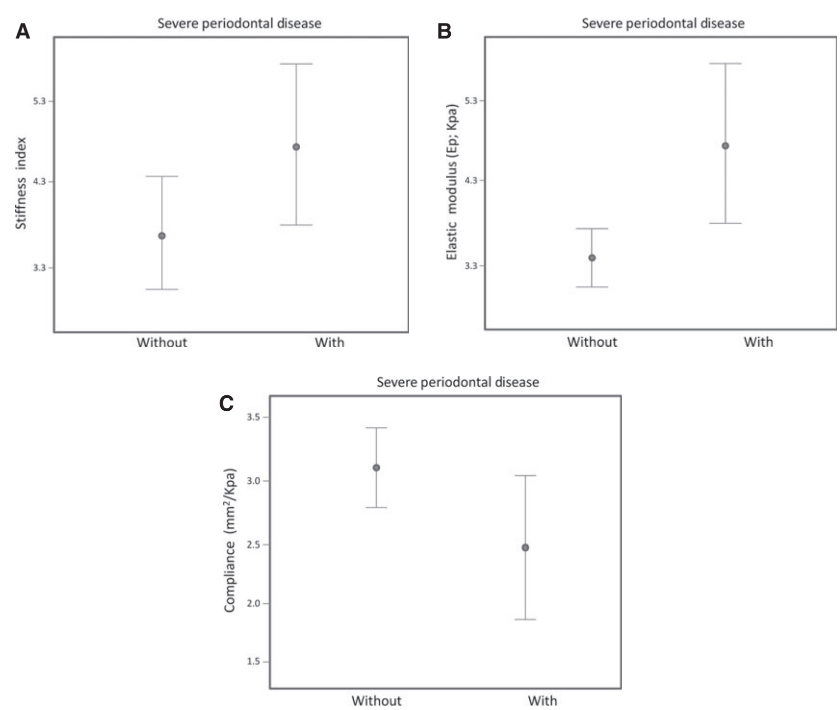


*Fig. 1.* Differences in arterial stiffness parameters between patients with and without severe periodontal disease. (A) 95% CI stiffness index β between patients with and without severe periodontal disease. (B) 95% CI elastic modulus (kPa) between patients with and without severe periodontal disease. (C) 95% CI compliance ($mm^2$/kPa) between patients with and without severe periodontal disease.

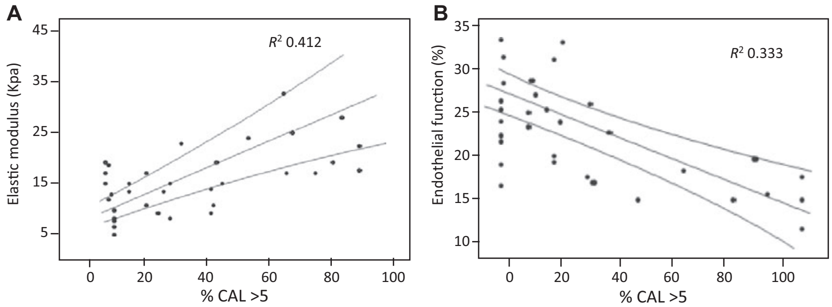


*Fig. 2.* Correlation between the percentage of CAL >5 mm and elastic modulus and endothelial function. (A) Correlation between percentage of CAL >5 mm and elastic modulus. (B) Correlation between percentage of elastic modulus and endothelial function endothelial function. CAL, clinical attachment level.

relation is nonlinear, and the slope defines the intrinsic elastic properties of the wall material. The βSI is the relationship between blood pressure and vascular diameter. There is an exponential relation between intravascular pressure and diameter (39).

Factors of atherogenic risk known to affect EF, arterial stiffness and intimal thickness were evaluated in the present study. The studied parameters were similar in both groups, suggesting that the differences in arterial stiffness observed between groups were associated with periodontal disease.

Studies reported in the literature showed an increase in arterial rigidity in patients with SPD, using different parameters including the augmentation index, pulse wave velocity and/or cardio-ankle vascular index (24,40).

Other parameters used to evaluate arterial stiffness, such as compliance and distensibility, assessed the artery as a hollow structure. EM can be considered a measure of intrinsic stiffness of the arterial wall material, and is inversely associated with elasticity and βSI; it measures the elastic properties of the arterial wall irrespective of the arterial distending pressure (29).

Apart from the present study, there are few reports using these parameters of arterial stiffness in patients with SPD.

The results of the present study showed that patients with SPD exhibited alterations in arterial wall distensibility and EF. Conversely to findings reported by Hayashida et al. (24), there was no correlation between the observed alterations and the increase in intimal wall thickness. The discrepancy between our results and reports in the literature may be associated with early changes in arterial distensibility that precede the changes observed in arterial intimal thickness. Our results establish a relationship between SPD and subclinical markers of atherosclerosis, as are arterial distensibility and EF. These findings are interesting as they precede the observed increase in intima-media thickness. To our knowledge, there are no clinical studies reported in the literature showing vascular changes without morphological alterations in the vessel wall. However, the cross-sectional nature of the study limits inferences regarding causality (24).

In addition, our results showed an endothelium-dependent deterioration of endothelial vasodilatation, likely due to a decrease in the availability of vasodilating substances, because of intrinsic production and/or increase in the degradation of nitric oxide, which results from elevated production of free radicals (OH-) secondary to the inflammatory process generated by the periodontal disease. Lending support to this hypothesis is the finding that EF improves after periodontal treatment, as shown by a number of authors (20–23,41).

Further studies in patient cohorts must be conducted to determine the causal relation between periodontal disease and atherosclerosis, as well as the impact of the aforementioned markers of early arterial dysfunction on the prevention of atherosclerosis and its cardiovascular consequences.

## Conclusions

Parameters of arterial stiffness and EF were worse in patients with SPD, and correlated moderately with clinical attachment level. Compliance and EF correlated negatively with the clinical attachment level.

## References

1. Lockhart PB, Bolger AF, Papapanou PN *et al.* Periodontal disease and atherosclerotic vascular disease: does the evidence support an independent association? A scientific statement from the American Heart Association. *Circulation* 2012;**125**:2520–2544.
2. Leong XF, Ng CY, Badiah B, Das S. Association between hypertension and periodontitis: possible mechanisms. *ScientificWorldJournal* 2014;**2014**:768237 eCollection 2014. Review.
3. Iwamoto Y, Maruhashi T, Fujii Y *et al.* Intima-media thickness of brachial artery, vascular function, and cardiovascular risk factors. *Arterioscler Thromb Vasc Biol* 2012;**32**:2295–2303.
4. Creager MA, Cooke JP, Mendelsohn ME *et al.* Impaired vasodilatation of forearm resistance vessels in hypercholesterolemic humans. *J Clin Invest* 1990;**86**:228–234.
5. Johnstone MT, Creager SL, Scales KM, Cusco JA, Lee BK, Creager MA. Impaired endothelium-dependent vasodilatation in patients with insulin-dependent diabetes mellitus. *Circulation* 1993;**88**:2510–2516.
6. Celermajer DS, Sorensen KE, Georgakopuolos D *et al.* Cigarette smoking is associated with dose-related and potentially reversible impairment of endothelium-dependent dilation in healthy young adults. *Circulation* 1993;**88**(5 Pt 1):2149–2155.
7. Zeiher A, Schachinger V, Minners J. Long-term cigarette smoking impairs endothelium-dependent arterial coronary vasodilator function. *Circulation* 1995;**92**:1094–1100.
8. Schachinger V, Britten MB. Zeiher AM Prognostic impact of coronary vasodilatation dysfunction on adverse long-term outcome of coronary heart disease. *Circulation* 2000;**25**:1899–1906.
9. Fuster V, Moreno PR, Fayad ZA, Corti R, Badinon JJ. Atherothrombosis and high-risk plaque: part I: evolving concepts. *J Am Coll Cardiol* 2005;**20**:937–954.

10. Sanada H, Higashi Y, Goto C, Chayama K, Yoshizumi M, Sueda T. Vascular function in patients with lower extremity peripheral arterial disease and a comparison of function in upper and lower extremities. *Atherosclerosis* 2005;**178**:179–185.
11. Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P. Risk of myocardial infarction and stroke after infection or vaccination. *N Engl J Med* 2004;**16**:2611–2618.
12. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation* 2002;**105**:1135–1143.
13. Loos BG, Craandijk J, Hoek FJ, Wertheim-van Dillen PM, van der Velden U. Elevation of systemic markers related to cardiovascular diseases in the peripheral blood of periodontitis patients. *J Periodontal* 2000;**71**:1528–1534.
14. Beck JD, Elter JR, Heiss G, Couper D, Mauriello SM, Offenbacher S. Relationship of periodontal disease to carotid artery intima-media wall thickness: the atherosclerosis risk in communities (ARIC) study. *Arterioscler Thromb Vasc Biol* 2001;**21**:1816–1822.
15. Amar S, Gokce N, Morgan S, Loukideli M, Van Dyke TE, Vita JA. Periodontal disease is associated with brachial artery endothelial dysfunction and systemic inflammation. *Arterioscler Thromb Vasc Biol* 2003;**23**:1245–1249.
16. Noack B, Genco RJ, Trevisan M, Grossi S, Zambon JJ, Nadin E. Periodontal infections contribute to elevated systemic C-reactive protein level. *J Periodontal* 2001;**72**:1221–1227.
17. Yukihito Higashi, Chikara Goto, Daisuke Jitsuiki, Takashi Umemura, Kenji Nishioka. *et al.* Periodontal infection is associated with endothelial dysfunction in healthy subjects and hypertensive patients. *Hypertension* 2008;**51**:446.
18. Abhijit V Kshirsagar, Ronald G Craig, Kevin L Moss *et al.* Periodontal disease adversely affects the survival of patients with end-stage renal disease. *Kidney* 2009;**75**:746–751.
19. Scannapieco FA, Bush RB, Paju S. Associations between periodontal disease and risk for atherosclerosis, cardiovascular disease, and stroke: A systematic review. *Ann Periodontol* 2003;**8**:38–53.
20. Tonetti MS, D'Aiuto F, Nibali L *et al.* Treatment of periodontitis and endothelial function. *N Engl J Med* 2007;**356**: 911–920.
21. Seinost G, Wimmer G, Skerget M *et al.* Periodontal treatment improves endothelial dysfunction in patients with severe periodontitis *Am Heart J* 2005;**149**: 1050–1054.
22. Elter JR, Hinderliter AL, Offenbacher S *et al.* The effects of periodontal therapy on vascular endothelial function: a pilot trial. *Am Heart J* 2006;**151**:47.
23. 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**:1694–1700.
24. Hayashida H, Saito T, Kawasaki K *et al.* Association of periodontitis with carotid artery intima-media thickness and arterial stiffness in community-dwelling people in Japan: the Nagasaki Islands study. *Atherosclerosis* 2013;**229**:186–191.
25. Asmar R, Benetos A, Topouchian J *et al.* Assessment of arterial distensibility by automatic pulse wave velocity measurement Validation and clinical application studies. *Hypertension* 1995;**26**: 485–490.
26. Park HJ, Rho TH, Park CS *et al.* The relationship between the acute changes of the systolic blood pressure and the brachial-ankle pulse wave velocity. *Korean J Intern Med* 2007;**22**:147–151.
27. Kingman A, Albandar JM. Methodological aspects of epidemiological studies of periodontal diseases. *Periodontol* 2000;**2002**:11–30.
28. Amitage GC. Development of a classification system for periodontal disease and conditions. *Ann Periodontol* 1999;**4**:1–6.
29. Nuñez F, Martinez-Costa C, Sanchez-Zahonero J, Morata J, Chorro FJ, Brines J. Carotid artery stiffness as an early marker of vascular lesions in children and adolescents with cardiovascular risk factor. *Rev Esp Cardiol* 2010;**63**:1253–1260.
30. Tuboul PJ, Hennerici MG, Meairs S, Adams H, Amarenco P, Bornstein N, *et al.* Mannheim carotid intima-media thickness consensus (2004-2006). *Cerebrovasc Dis* 2007;**23**:75–80.
31. Corretti MC, Anderson TJ, Benjamin EJ *et al.* Vogel R; International Brachial Artery Reactivity Task Force. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force. *J Am Coll Cardiol* 2002;**16**:257–265.
32. Desvarieux M, Schwahn C, Volzke H *et al.* Gender differences in the 10 relationship between periodontal disease, tooth loss, and atherosclerosis. *Stroke* 2004;**35**:2029–2035.
33. Nakae I, Matsuo S, Matsumoto T, Mitsunami K, Horie M. Augmentation index and pulse wave velocity as indicators of cardiovascular stiffness. *Angiology* 2008;**59**:421–426.
34. Cecelja M, Chowienczyk P. Role of arterial stiffness in cardiovascular disease. *JRSM Cardiovasc Dis*. 2012;**1**. doi: 10.1258/cvd.2012.012016.
35. Haluska BA, Jeffries L, Carlier S, Marwick TH. Measurement of arterial distensibility and compliance to assess prognosis. *Atherosclerosis* 2010;**209**:474–480.
36. Giannattasio C, Capra A, Facchetti R *et al.* Relationship between arterial distensibility and coronary atherosclerosis in angina patients. *J Hypertens* 2007; **25**:593–598.
37. Saji N, Kimura K, Yagita Y, Kawarai T, Shimizu H, Kita Y. Comparison of arteriosclerotic indicators in patients with ischemic stroke: ankle-brachial index, brachial-ankle pulse wave velocity and cardio-ankle vascular index. *Hypertens Res* 2015;**38**:323–328.
38. Deanfield JE, Halcox JP, Rabelink TJ. Endothelial function and dysfunction: testing and clinical relevance. *Circulation* 2007;**115**:1285–1295.
39. Cavalcante JL, Lima JA, Redheuil A, Al-Mallah MH. Aortic stiffness: current understanding and future directions. *J Am Coll Cardiol* 2011;**57**:1511–1522.
40. Jockel-Schneider Y, Harks I, Haubitz I *et al.* Arterial stiffness and pulse wave reflection are increased in patients suffering from severe periodontitis. *PLoS ONE* 2014;**9** doi: 10.1371/journal.pone.0103449.
41. Blum A, Kryuger K, Mashiach Eizenberg M *et al.* Periodontal care may improve endothelial function. *Eur J Intern Med* 2007;**18**:295–298.