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MINIREVIEWS

Relationship between vascular endothelium and periodontal disease in atherosclerotic lesions: Review article

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Abstract

Inflammation and endothelial dysfunction are linked to the pathogenesis of atherosclerotic disease. Recent studies suggest that periodontal infection and the ensuing increase in the levels of inflammatory markers may be associated with myocardial infarction, peripheral vascular disease and cerebrovascular disease. The present article aimed at reviewing contemporary data on the pathophysiology of vascular endothelium and its association with periodontitis in the scenario of cardiovascular disease.

Key words: Endothelium; Vascular; Atherosclerosis; Periodontal diseases; Nitric oxide; Cardiovascular diseases

Core tip: Recent studies underscore the importance of endothelial dysfunction and inflammatory markers for the development of atherosclerotic disease. In addition, the literature suggests a direct association between periodontal and cardiovascular diseases. Nevertheless, more robust intervention studies are required to clarify specific gaps, especially in relation to the biological and clinical effects of periodontal disease on the genesis and progression of atherosclerotic disease.

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INTRODUCTION

Cardiovascular disease is still the leading cause of morbidity and mortality worldwide. Nevertheless, as a

result of new and effective strategies to prevent and treat atherosclerosis, the number of deaths associated with cardiovascular events has not increased, and seems to have stabilized in some countries[1].

Because it has regulatory, secretory, metabolic, immunological, and synthesizing properties, the vascular endothelium may be regarded as a heterogeneous and dynamic organ. An imbalance of these properties is linked to the onset of endothelial dysfunction and atherogenesis, and to increased risk of cardiovascular events[2]. Added to that, in the past years, the role of inflammation in the development of atherosclerosis has also been explored. Data from epidemiologic studies confirm the association between high levels of inflammatory markers and the progression of cardiovascular disease[3,4].

Emerging evidence suggests that periodontal infection may be an independent risk factor for myocardial infarction, peripheral vascular disease, and cerebrovascular disease[5,6]. A metanalysis has shown increased incidence of coronary heart disease [relative risk (RR) = 1.14; 95%CI: 1.07-1.21; $P < 0.001$] in patients with periodontal disease even after adjustment for confounding factors such as smoking, diabetes, alcohol intake, obesity, and arterial hypertension, also suggesting a positive correlation between dental loss and coronary artery disease[6]. It should be noted that much of this evidence was generated by observational studies. In this sense, additional studies with more robust designs should be carried out to provide answers regarding the association between periodontal and cardiovascular diseases.

With the aim of furthering the understanding of the relationship between vascular endothelium, periodontal disease, and the process of atherosclerosis, this article will review contemporary data about endothelial pathophysiology and its association with periodontitis in cardiovascular disease. For that, the MEDLINE-PubMed database was searched to retrieve articles published between 1980 and 2014, using the following DeCS terms: "endothelium, vascular"; "atherosclerosis"; "periodontal diseases"; "nitric oxide"; "cardiovascular diseases".

VASCULAR ENDOTHELIUM AND ATHEROSCLEROSIS

Endothelial cells (ECs) form an organ weighing approximately 1 kg; they are distributed along the body (total estimated area: 7000 m^2), and are characterized by heterogeneous structure and function, with phenotypic variation according to their location in different organs, tissues, or blood vessel type[7]. Located at the interface between blood and tissues, the vascular endothelium plays an important role in the cardiovascular system, including regulation of vascular tone (smooth muscle), synthesis and secretion of molecules, and control of homeostasis, coagulation, and inflammatory and atherogenic responses[8].

Atherosclerosis is a progressive disease, characterized by accumulation of lipid particles and fibrous elements on the arterial wall. A more recent concept has introduced the notion that, in addition to the thrombotic process, inflammation and endothelial dysfunction are also directly related to all stages of atherosclerosis. In the undamaged endothelium, ECs resist leukocyte adhesion and aggregation, in addition to promoting fibrinolysis. However, when associated with inflammatory factors, such as periodontal disease, cardiovascular risk factors (smoking, obesity, sedentary lifestyle, dyslipidemia, diabetes) promote changes in endothelial permeability and hence endothelial function[9]. At this initial stage, ECs express adhesion molecules that selectively recruit various leukocyte classes into the tunica intima[10]. Monocytes mature into macrophages, forming foam cells that release cytokines and factors that affect ECs. This process induces migration of smooth muscle cells from the media to the intima and affects metabolism of the arterial extracellular matrix (metalloproteinase), synthesis and release of procoagulant factors, and the bioavailability of nitric oxide (NO)[9]. NO, initially defined by Furchgott *et al*[11] as an "endothelium-derived relaxing factor", is synthesized by the action of an enzyme, endothelial nitric oxide synthase (eNOS), from the amino acid L-arginine. NO plays a fundamental part in endothelial function, promoting smooth muscle relaxation and consequently vasodilatation. In addition, NO supports inhibition of platelet aggregation, smooth muscle cell proliferation, and maintenance of anti-sclerotic effect[12].

The inflammatory process may also contribute to atherosclerotic plaque rupture and thrombosis. Inflammation regulates the fragility of the fibrous cap and the thrombogenicity of the atherosclerotic plaque, influencing collagen metabolism, which provides strength and stability to the cap[13]. Pro-inflammatory cytokines such as C-reactive protein (CRP), fibrinogen, tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and IL-6 reduce the endothelial expression of NOS[14], increasing endothelial synthesis of NADPH oxidases and promoting endothelial expression of vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), E-selectin and P-selectin[14,15]. As a result, the absence of anti-atherogenic properties in the endothelium increases leukocyte migration and platelet activation to form the atherosclerotic plaque[4].

In this sense, endothelial function and inflammatory markers are important predictors of future cardiovascular events in individuals at risk for atherosclerotic disease.

CELL ADHESION MOLECULES

Cell adhesion molecules (CAMs) are glycoproteins expressed on the cellular surface. CAMs are involved in cell-cell and cell-extracellular matrix binding and encompass immunoglobulins such as ICAM-1 and VCAM-1, as well as the selectin family, including leukocyte-endothelial adhesion molecules (E-selectin), P-selectin and leukocyte-lymphocyte adhesion molecules (L-selectin), integrins, and cadherins[16].

Selectins are expressed on the surface of endothelial

Table 1 Summary of the involvement of pro-inflammatory cytokines and adhesion molecules in atherosclerosis

Pro-inflammatory cytokines and adhesion molecules	Cells involved	Atherogenic effect
C-reactive protein	Adhesion molecules and endothelial cells	Stimulates production of adhesion molecules and chemokines by endothelial cells[14]
Fibrinogen	Platelet, adhesion molecules and smooth muscle	Activates platelet aggregation and promotes the migration and proliferation of smooth muscle[14]
Tumor necrosis factor-alpha	Monocytes, neutrophils and endothelial cells	Activates monocytes, neutrophils and endothelial cells to express adhesion molecules[14]
Interleukin-6	Epithelial cells, fibroblasts and macrophages/monocytes	Is involved in promoting coagulation, which result in the development of atherosclerosis[14]
Interleukin-1β	Macrophages/monocytes	Impedes fibrinolysis, facilitates coagulation and thrombosis[14]
Vascular cell adhesion molecule-1	Endothelial cells	Suggested as potential candidate markers of endothelial dysfunction[19]
Intercellular adhesion molecule-1	Endothelial cells	Implicated in leukocyte recruitment and migration into the vessel wall[19]
Leukocyte-endothelial adhesion molecules	Endothelial cells	Migration of monocytes down into the subendothelial space[16]

cells, leukocytes, and platelets, and their expression in the endothelium is induced by various inflammatory cytokines. In the first phase of leukocyte migration, selectins mediate the capture and transport of circulating leukocytes into the vascular endothelium. In the second phase, leukocytes adhere to the endothelium through the action of ICAM-1 and VCAM-1, migrating into the interstitial tissue space[17].

Soluble forms of CAMs are found in plasma and correlate to endothelial dysfunction[18]. Thus, these markers are associated with biological mechanisms that promote thrombus formation, plaque rupture, and subsequently acute coronary events[19]. The summary of the involvement of pro-inflammatory cytokines and adhesion molecules in atherosclerosis is described in Table 1.

SHEAR STRESS

Even if the multifactorial pathophysiologic nature of atherosclerosis is recognized, special attention should be paid to a specific component in this scenario-shear stress. Shear stress is a biomechanical force determined by blood flow, vessel geometry, and fluid viscosity, aspects modulating the structure and function of the vascular endothelium. The presence of "disturbed" flow-that is, nonlaminar flow-favors atherosclerotic plaque formation. Atherosclerotic plaque development is favored by a combination of cardiovascular risk factors and altered arterial hemodynamics around curvatures, arterial branch ostia and bifurcations[20].

Studies have shown that different types of shear stress correlate with "resistant" or "susceptible" regions in the endothelium during atherogenesis[21]. Pulsatile blood flow triggers many types of hemodynamic, hydrostatic, and cyclic forces that have the ability to influence vascular endothelial physiology[22]. The most susceptible atherosclerotic lesions are associated with certain sites in the proximal branches, bifurcations, and in areas of greater curvature. However, regions with uniform laminar flow are typically more resistant to atherogenic plaque formation[23].

PERIODONTAL DISEASE, INFLAMMATORY MARKERS, AND ENDOTHELIAL DYSFUNCTION

Periodontal disease encompasses two large groups of gum diseases. Gingivitis, which is characterized by inflammation of the gingival margin, is easily reversed with adequate oral hygiene. Periodontitis entails a chronic infectious/inflammatory process involving the supporting tissues of the tooth, including periodontal ligament and alveolar bone. The main consequence of periodontitis is the loss of tooth support structures and tooth loss[24]. Data from different countries show a prevalence of periodontitis reaching up to 50%[25-27]; however, progression is usually slow[28].

Epidemiologic studies provide evidence of an association between periodontitis and cardiovascular disease[6,29]. The biological plausibility for this association is based mainly on the fact that patients with periodontitis present increased levels of CRP, TNF-α, interleukins, and other inflammatory markers, which are associated with endothelial dysfunction and cardiovascular events[30,31]. Most studies employ different inflammatory and endothelial biomarkers, with secondary outcomes, whereas primary outcomes such as death or brain stroke have not yet been evaluated[32-34].

A recent systematic review and metanalysis analyzed the effect of periodontal treatment on cardiovascular risk profile in patients with established periodontitis. The main findings show a significant reduction in CRP (-0.50 mg/dL), IL-6 (-0.48 ng/L), TNF-α (-0.75 pg/mL), fibrinogen (-0.47 g/L) and total cholesterol (-0.11 mmol/L) in the intervention group. In addition, there was improvement of endothelial function and an additional benefit regarding inflammatory markers in patients with traditional cardiovascular risk factors[24]. Investigating the same outcome in a different scenario, another study compared patients with coronary heart disease with or without periodontitis. The results indicate that treatment of periodontal disease promoted a reduction in serum concentrations of CRP, from 2.7 ± 1.9 mg/L to 1.8 ± 0.9 mg/L ($P < 0.05$), and of IL-6, from 2.6 ± 3.4 mg/L to 1.6

Table 2 Summary of the effects of periodontal disease on pro-inflammatory cytokines and adhesion molecules

Pro-inflammatory cytokines and adhesion molecules	Effect of periodontal disease
C-reactive protein	Increased[24]
Fibrinogen	Increased[24]
Tumor necrosis factor-alpha	Increased[24]
Interleukin-6	Increased[24]
Interleukin-1β	Increased[24]
Vascular cell adhesion molecule-1	Increased[30]
Intercellular adhesion molecule-1	Increased[30]
Leukocyte-endothelial adhesion molecules	Increased[30]

± 2.6 mg/L ($P < 0.05$) in patients with periodontitis[32].

In addition to inflammatory markers and adhesion molecules, the measurement of brachial artery flow-mediated dilation (FMD), a technique developed initially in 1992, is also useful to assess the endothelium[35]. This non-invasive technique evaluates the diameter of the brachial artery before and after induced forearm ischemia. A blood pressure cuff is inflated at the distal or proximal section of the arm, and FMD is expressed as the percent change in brachial artery diameter at the end of ischemia. This dilatation is mediated by endothelial release of NO in response to shear stress at the arterial wall[36].

FMD is decreased in individuals with cardiovascular risk factors (diabetes, hypertension, obesity, and smoking, among others) and established atherosclerosis[37]. A study published in 2005 evaluated endothelial function in patients with a diagnosis of severe periodontitis. The main findings following periodontal treatment show significant improvement in FMD, of 9.8% ± 5.7% ($P = 0.003$) as compared to baselines measures, accompanied by a reduction in the levels of CRP from 1.1 ± 0.9 to 0.8 ± 0.8 ($P = 0.026$)[34]. In this sense, evaluation of FMD and cardiovascular disease biomarkers have recently been studied and associated with endothelial dysfunction and occurrence of cardiovascular events[38,39]. The summary of the effects of periodontal disease on pro-inflammatory cytokines and adhesion molecules is depicted in Table 2.

CONCLUSION

The present literature review suggests that periodontal treatment reduces the risk of cardiovascular disease by improving plasma levels of inflammatory markers (CRP, TNF-α, IL), thrombotic markers (fibrinogen) and adhesion molecules (VCAM-1, ICAM-1, P-selectin), in addition to improving endothelial function as assessed by FMD. Future intervention studies are required to further elucidate the association between periodontal and cardiovascular disease, especially in terms of the biological effects of periodontal disease on the atherogenic cascade affecting the vascular endothelium.

REFERENCES

1 **Bautista LE**, Oróstegui M, Vera LM, Prada GE, Orozco LC, Herrán OF. Prevalence and impact of cardiovascular risk factors in Bucaramanga, Colombia: results from the Countrywide Integrated Noncommunicable Disease Intervention Programme (CINDI/CARMEN) baseline survey. *Eur J Cardiovasc Prev Rehabil* 2006; **13**: 769-775 [PMID: 17001217 DOI: 10.1097/01.hjr.0000219113.40662.dd]

2 **Faulx MD**, Wright AT, Hoit BD. Detection of endothelial dysfunction with brachial artery ultrasound scanning. *Am Heart J* 2003; **145**: 943-951 [PMID: 12796748 DOI: 10.1016/S0002-8703(03)00097-8]

3 **Packard RR**, Libby P. Inflammation in atherosclerosis: from vascular biology to biomarker discovery and risk prediction. *Clin Chem* 2008; **54**: 24-38 [PMID: 18160725 DOI: 10.1373/clinchem.2007.097360]

4 **Hansson GK**. Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med* 2005; **352**: 1685-1695 [PMID: 15843671 DOI: 10.1056/NEJMra043430]

5 **Stassen FR**, Vainas T, Bruggeman CA. Infection and atherosclerosis. An alternative view on an outdated hypothesis. *Pharmacol Rep* 2008; **60**: 85-92 [PMID: 18276989]

6 **Bahekar AA**, Singh S, Saha S, Molnar J, Arora R. The prevalence and incidence of coronary heart disease is significantly increased in periodontitis: a meta-analysis. *Am Heart J* 2007; **154**: 830-837 [PMID: 17967586 DOI: 10.1016/j.ahj.2007.06.037]

7 **Münzel T**, Sinning C, Post F, Warnholtz A, Schulz E. Pathophysiology, diagnosis and prognostic implications of endothelial dysfunction. *Ann Med* 2008; **40**: 180-196 [PMID: 18382884 DOI: 10.1080/07853890701854702]

8 **Simionescu M**. Implications of early structural-functional changes in the endothelium for vascular disease. *Arterioscler Thromb Vasc Biol* 2007; **27**: 266-274 [PMID: 17138941 DOI: 10.1161/01.ATV.0000253884.13901.e4]

9 **Libby P**, Okamoto Y, Rocha VZ, Folco E. Inflammation in atherosclerosis: transition from theory to practice. *Circ J* 2010; **74**: 213-220 [PMID: 20065609 DOI: 10.1253/circj.CJ-09-0706]

10 **Cybulsky MI**, Gimbrone MA. Endothelial expression of a mononuclear leukocyte adhesion molecule during atherogenesis. *Science* 1991; **251**: 788-791 [PMID: 1990440 DOI: 10.1126/science.1990440]

11 **Furchgott RF**, Zawadzki JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. *Nature* 1980; **288**: 373-376 [PMID: 6253831]

12 **Tousoulis D**, Kampoli AM, Tentolouris C, Papageorgiou N, Stefanadis C. The role of nitric oxide on endothelial function. *Curr Vasc Pharmacol* 2012; **10**: 4-18 [PMID: 22112350 DOI: 10.2174/157016112798829760]

13 **Mestas J**, Ley K. Monocyte-endothelial cell interactions in the development of atherosclerosis. *Trends Cardiovasc Med* 2008; **18**: 228-232 [PMID: 19185814 DOI: 10.1016/j.tcm.2008.11.004]

14 **Zhang J**, Patel JM, Li YD, Block ER. Proinflammatory cytokines downregulate gene expression and activity of constitutive nitric oxide synthase in porcine pulmonary artery endothelial cells. *Res Commun Mol Pathol Pharmacol* 1997; **96**: 71-87 [PMID: 9178369]

15 **Papapanagiotou D**, Nicu EA, Bizzarro S, Gerdes VE, Meijers JC, Nieuwland R, van der Velden U, Loos BG. Periodontitis is associated with platelet activation. *Atherosclerosis* 2009; **202**: 605-611 [PMID: 18617175 DOI: 10.1016/j.atherosclerosis.2008.05.

035]
16 **Yong K**, Khwaja A. Leucocyte cellular adhesion molecules. *Blood Rev* 1990; **4**: 211-225 [PMID: 1706206]
17 **Zimmerman GA**, Prescott SM, McIntyre TM. Endothelial cell interactions with granulocytes: tethering and signaling molecules. *Immunol Today* 1992; **13**: 93-100 [PMID: 1377920 DOI: 10.1016/0167-5699(92)90149-2]
18 **Burger D**, Touyz RM. Cellular biomarkers of endothelial health: microparticles, endothelial progenitor cells, and circulating endothelial cells. *J Am Soc Hypertens* 2012; **6**: 85-99 [PMID: 22321962 DOI: 10.1016/j.jash.2011.11.003]
19 **Zamani P**, Schwartz GG, Olsson AG, Rifai N, Bao W, Libby P, Ganz P, Kinlay S. Inflammatory biomarkers, death, and recurrent nonfatal coronary events after an acute coronary syndrome in the MIRACL study. *J Am Heart Assoc* 2013; **2**: e003103 [PMID: 23525424 DOI: 10.1161/JAHA.112.003103]
20 **Cunningham KS**, Gotlieb AI. The role of shear stress in the pathogenesis of atherosclerosis. *Lab Invest* 2005; **85**: 9-23 [PMID: 15568038]
21 **Gimbrone MA**, Topper JN, Nagel T, Anderson KR, Garcia-Cardeña G. Endothelial dysfunction, hemodynamic forces, and atherogenesis. *Ann N Y Acad Sci* 2000; **902**: 230-239; discussion 230-239 [PMID: 10865843 DOI: 10.1111/j.1749-6632.2000.tb06318.x]
22 **Topper JN**, Gimbrone MA. Blood flow and vascular gene expression: fluid shear stress as a modulator of endothelial phenotype. *Mol Med Today* 1999; **5**: 40-46 [PMID: 10088131 DOI: 10.1016/S1357-4310(98)01372-0]
23 **Davies PF**. Hemodynamic shear stress and the endothelium in cardiovascular pathophysiology. *Nat Clin Pract Cardiovasc Med* 2009; **6**: 16-26 [PMID: 19029993 DOI: 10.1038/ncpcardio1397]
24 **Teeuw WJ**, Slot DE, Susanto H, Gerdes VE, Abbas F, D'Aiuto F, Kastelein JJ, Loos BG. Treatment of periodontitis improves the atherosclerotic profile: a systematic review and meta-analysis. *J Clin Periodontol* 2014; **41**: 70-79 [PMID: 24111886 DOI: 10.1111/jcpe.12171]
25 **Susin C**, Dalla Vecchia CF, Oppermann RV, Haugejorden O, Albandar JM. Periodontal attachment loss in an urban population of Brazilian adults: effect of demographic, behavioral, and environmental risk indicators. *J Periodontol* 2004; **75**: 1033-1041 [PMID: 15341364 DOI: 10.1902/jop.2004.75.7.1033]
26 **Eke PI**, Dye BA, Wei L, Thornton-Evans GO, Genco RJ. Prevalence of periodontitis in adults in the United States: 2009 and 2010. *J Dent Res* 2012; **91**: 914-920 [PMID: 22935673]
27 **Bourgeois D**, Bouchard P, Mattout C. Epidemiology of periodontal status in dentate adults in France, 2002-2003. *J Periodontal Res* 2007; **42**: 219-227 [PMID: 17451541]
28 **Haas AN**, Gaio EJ, Oppermann RV, Rösing CK, Albandar JM, Susin C. Pattern and rate of progression of periodontal attachment loss in an urban population of South Brazil: a 5-years population-based prospective study. *J Clin Periodontol* 2012; **39**: 1-9 [PMID: 22093104 DOI: 10.1111/j.1600-051X.2011.01818.x]
29 **Dietrich T**, Sharma P, Walter C, Weston P, Beck J. The epidemiological evidence behind the association between periodontitis and incident atherosclerotic cardiovascular disease. *J Periodontol* 2013; **84**: S70-S84 [PMID: 23631585 DOI: 10.1902/jop.2013.134008]
30 **Joshipura KJ**, Wand HC, Merchant AT, Rimm EB. Periodontal disease and biomarkers related to cardiovascular disease. *J Dent Res* 2004; **83**: 151-155 [PMID: 14742654]
31 **Bokhari SA**, Khan AA, Butt AK, Azhar M, Hanif M, Izhar M, Tatakis DN. Non-surgical periodontal therapy reduces coronary heart disease risk markers: a randomized controlled trial. *J Clin Periodontol* 2012; **39**: 1065-1074 [PMID: 22966824 DOI: 10.1111/j.1600-051X.2012.01942.x]
32 **Higashi Y**, Goto C, Hidaka T, Soga J, Nakamura S, Fujii Y, Hata T, Idei N, Fujimura N, Chayama K, Kihara Y, Taguchi A. Oral infection-inflammatory pathway, periodontitis, is a risk factor for endothelial dysfunction in patients with coronary artery disease. *Atherosclerosis* 2009; **206**: 604-610 [PMID: 19410250 DOI: 10.1016/j.atherosclerosis.2009.03.037]
33 **Tonetti MS**, D'Aiuto F, Nibali L, Donald A, Storry C, Parkar M, Suvan J, Hingorani AD, Vallance P, Deanfield J. Treatment of periodontitis and endothelial function. *N Engl J Med* 2007; **356**: 911-920 [PMID: 17329698 DOI: 10.1056/NEJMoa063186]
34 **Seinost G**, Wimmer G, Skerget M, Thaller E, Brodmann M, Gasser R, Bratschko RO, Pilger E. Periodontal treatment improves endothelial dysfunction in patients with severe periodontitis. *Am Heart J* 2005; **149**: 1050-1054 [PMID: 15976787 DOI: 10.1016/j.ahj.2004.09.059]
35 **Celermajer DS**, Sorensen KE, Gooch VM, Spiegelhalter DJ, Miller OI, Sullivan ID, Lloyd JK, Deanfield JE. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. *Lancet* 1992; **340**: 1111-1115 [PMID: 1359209]
36 **Ross R**. The pathogenesis of atherosclerosis: a perspective for the 1990s. *Nature* 1993; **362**: 801-809 [PMID: 8479518 DOI: 10.1038/362801a0]
37 **Tsuchiya K**, Nakayama C, Iwashima F, Sakai H, Izumiyama H, Doi M, Hirata Y. Advanced endothelial dysfunction in diabetic patients with multiple risk factors; importance of insulin resistance. *J Atheroscler Thromb* 2007; **14**: 303-309 [PMID: 18174660 DOI: 10.5551/jat.E525]
38 **Rubinshtein R**, Kuvin JT, Soffler M, Lennon RJ, Lavi S, Nelson RE, Pumper GM, Lerman LO, Lerman A. Assessment of endothelial function by non-invasive peripheral arterial tonometry predicts late cardiovascular adverse events. *Eur Heart J* 2010; **31**: 1142-1148 [PMID: 20181680 DOI: 10.1093/eurheartj/ehq010]
39 **Weiner SD**, Ahmed HN, Jin Z, Cushman M, Herrington DM, Nelson JC, Di Tullio MR, Homma S. Systemic inflammation and brachial artery endothelial function in the Multi-Ethnic Study of Atherosclerosis (MESA). *Heart* 2014; **100**: 862-866 [PMID: 24714919 DOI: 10.1136/heartjnl-2013-304893]

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