8

Periodontal Disease and Carotid Atherosclerosis: Mechanisms of the Association

Maria Serena De Franceschi[1,2] et al.[*]
[1]*Metabolic Diseases Unit,*
[2]*Institute of Dentistry, Department of Clinical and Experimental Medicine "G. Salvatore", "Magna Græcia" University, Viale Europa, Catanzaro*
Italy

1. Introduction

Despite advances in its diagnosis and management, cardiovascular disease remains the leading cause of death in western countries. Many risk factors are involved in the development of cardiovascular disease; recently, periodontal disease was recognized as a new risk factor in many epidemiological studies. The association between dental and cardiovascular disease is intriguing for the potential clinical implications, and it is independent of other risk factors. This association has been demonstrated for several localization of atherosclerotic plaques, involving coronary, cerebral and/or peripheral arteries. The finding that patients with periodontitis show also more evident carotid atherosclerotic plaques is clinically important because this disease localization is the most important cause of cerebral ischemia, in turn the main cause of disabilities in western world (A.H.A, 2002).

On this basis, the following chapters highlight the links between periodontal disease and carotid atherosclerosis, focusing on the mechanisms of this association: inflammation, dental pathogens and toxins, endothelial dysfunction, with the addition of hemorheology as a new evidence.

In details, the first chapters exploit the main features of these processes (chronic periodontitis, atherosclerosis, wall shear stress in hemorheology); then, we report and analyze a series of cross sectional, prospective and intervention studies in this field. In the last section will elucidate the interplays between periodontal disease, hemodynamic forces and atherosclerosis.

[*]Leonzio Fortunato[2], Claudio Carallo[1], Cesare Tripolino[1], Concetta Irace[1], Michele Figliuzzi[2], Antonio Crispino[2] and Agostino Gnasso[1]
[1]*Metabolic Diseases Unit,*
[2]*Institute of Dentistry, Department of Clinical and Experimental Medicine "G. Salvatore", "Magna Græcia" University, Viale Europa, Catanzaro,*
Italy

2. Chronic periodontitis

Chronic periodontitis affects a large proportion of the adult population; it can be regarded as a progression of infection and inflammation of gingivae into the deep tissues of the periodontium (Mitchell DA et al, 2003).

All periodontitis develops out of gingivitis but not all gingivitis progresses to periodontitis. In fact, even if it is true that gingivitis is a successful response to the bacterial onslaught, in certain occasion it may progress to periodontal disease in which the soft tissues and bone are destroyed (Cawson RA et al, 2009).

Dental plaque is the principal etiological factor in nearly all forms of periodontal disease although the role of bacteria is unclear; current hypotheses suggest that periodontal disease may be due to bacterial accumulation irrespective of its composition, or the result of an infection with a single specific pathogen, or the result of infection with a relatively small number of interacting bacterial species (Palmer R. M. et al, 2008). There are a number of currently identified risk factors for the progression of the disease such as poor plaque control, smoking, age, systemic diseases, stress, genetics and various other medical conditions. Therefore, periodontitis is initiated and sustained by microbial plaque but host factors determine the pathogenesis and rate of progression of disease. In most cases progression is slow to moderate but periods of rapid tissue destruction may occur.

Periodontal disease is characterized by breakdown of periodontal fibre bundles at the cervical margin, resorption of alveolar bone, and apical proliferation of junctional epithelium beyond the amelocemental junction.

Periodontal abscess, a complication of periodontitis, is a localized collection of pus within a periodontal pocket. Clinically there may be swelling, pus from pocket or sinus, pain tenderness to percussion and signs of periodontitis.

The diagnosis of periodontal disease is based on a thorough clinical examination of periodontal tissues, instrumental examinations and laboratory tests. All this is addressed to appreciate the degree of oral hygiene (presence of plaque and tartar), predisposing local factors (incongruous restorations, abnormal shape and position of teeth), clinical signs of gingival inflammation (redness, swelling, bleeding), destruction of periodontal tissues (gingival recession, clinical attachment loss, alveolar bone loss).

The gingival recession and loss of clinical attachment is measured using the periodontal probe, looking at the gingival margin and periodontal pockets, producing standard quantitative periodontal parameters of disease. Gingival plaque is generally evaluated with Plaque Index by Silness and Löe, which comprises visual clinical evaluation of each tooth on the mesial, distal, buccal and lingual aspect (Silness J et al, 1964). Inflammation of gingiva is evaluated by Gingival Index: 24 gingival margins are scored 0 to 3 upon inspective signs of inflamed mucosa, and bleeding (Loe H, 1967). Probing depth is a clinical measure of inflammation involving the other periodontal structures of periodontal ligament, dental cementum and alveolar bone; detected in millimeters at 6 sites in each tooth (mesial, center and distal of the buccal and lingual aspects), it gives Pocket Deep index (Ramfjord SP, 1959). Gingival margin is a reference point for reading of values during probing. A global index is DMFT, the number of Decayed, Missing and Filled Teeth. The loss of alveolar bone is measured by X-ray.

Although periodontal disease is a localized chronic inflammation, it may have important effects on distant organs (Lindhe J et al, 2003). In particular, periodontitis can interfere with

the systemic circulation. Therefore, in the last decade numerous studies have been conducted on the atherosclerotic process in particular. This effect of periodontitis was explained by the possible translocation of periodontal pathogens from the oral cavity to the circulatory system. Furthermore, a large local periodontal production of mediators could invade the circulatory apparatus and inflammation could then cause damage to sites distant from the point of origin. Recently, some other interesting mechanisms of this association have been proposed; these new findings are delineated below, together with an overview of the pathophysiology of the arterial system.

3. Atherosclerosis

Atherosclerosis is commonly considered a chronic inflammatory disease that affects large and medium-sized arteries (Ross R, 1999). Atherosclerotic lesions are at the basis of common cardiovascular disease as myocardial infarction, stroke, claudicatio intermittens. Common risk factors for atherosclerosis development include arterial hypertension, diabetes mellitus, dyslipidemia, obesity (A.H.A, 2002). Although all arteries are exposed to the risk of atherosclerotic lesions, plaques grow in areas of disturbed blood flow and altered hemodynamic forces, in particular at arterial bifurcations (Chatzizisis YS et al., 2007).

Atherosclerotic lesions develop during many years and in a stepwise manner. Anatomically, earliest lesion is represented by the so-called "fatty streak": this is a yellow lesion of few millimeters, that develops from the first years of life as demonstrated at autopsy. Histologically, this lesion consists in *foam cells* (macrophages that absorb oxidized – Low Density Lipoproteins and other fats, then migrate under tunica intima of the vessels) with some T-lymphocytes, platelets and smooth muscle cells.

Later, the progression of atherosclerosis leads to the atheroma formation. In fact, it continues the deposition of lipids, platelets and macrophages; these cells release growth factors that leads to SMC proliferation. SMC create a cap that contains a *core* of intra- and extracellular lipids (Cotran R et al, 1999).

The final stage is represented by the complication of atherosclerotic plaque: the rupture of the atheroma. In fact, for inflammation and/or production of metalloprotease, the rupture of the fibrous cap may occur; consequently, the exposition of thrombogenic lipid material to the circulating platelets induces thrombus formation in the lumen. Intraluminal thrombus can occlude arteries (e.g. coronary occlusion), but more often it detaches, moving downstream and eventually occluding smaller branches (thromboembolism, e.g. stroke as a complication of carotid atherosclerosis) (Davies MJ, 1998).

Recently, a subclinical early level of atherosclerosis has been recognized in a microscopic alteration called intima-media thickening. It is the increase of the thickness of intimal and medial layers of arterial wall, usually measured by external ultrasound. Intima-media thickening appears as a hypo- or iso-echogenic space delimitated by two hyper-echogenic lines. These lines are generated by the lumen-intima interface and the media-adventitia interface. The measurement of intima-media thickening using ultrasound has been evaluated and validated by in vitro measurements of specimens of common carotid arteries and in vivo measurement in normal subjects (Coll B et al, 2008). A large number of studies have demonstrated that intima-media thickening is a risk factor and a marker for coronary heart disease that accurately represents subclinical vascular disease but not plaque formation or atherosclerosis per se (Johnsen SH et al, 2009).

However, probably there is a earlier step of atherosclerotic process, the *response to endothelial injury* or *endothelial dysfunction* (Ross R, 1998).

4. Endothelial dysfunction

In order to give a definition of endothelial dysfunction, a brief overview about anatomy and physiology of the arteries is needed (Chien RS et al, 1987).
First of all, the arterial tree can be divided into different compartments, from central to peripheral arteries: elastic arteries, muscular arteries, and arterioles. Large elastic arteries have a dominant role in cushioning against pressure oscillations that result from ventricular ejection and they tend to transform pulsatile flow into a steady flow to better supply oxygen and nutrients to the tissues. Muscular arteries and even more arterioles regulate the amount and distribution of the blood in peripheral tissues.
These physiological mechanisms are warranted by healthy structure and function of the arteries. In fact, it is well known that arteries not only provide a conduit for the blood, but synthesize and release several vasoactive substances in order to meet the peripheral metabolic demand. Among these substances, nitric oxide has a pivotal role in protecting against the initiation and progression of atherosclerosis via its vasodilator activity and its inhibitory activity against vascular smooth muscle cells growth, transcription of cell adhesion molecules, platelet aggregation, and leukocyte adhesion to endothelial cells.
Therefore, in pathophysiology, endothelial dysfunction can be defined a pathological state of the endothelium (the inner lining of blood vessels) characterized by an imbalance between vasodilating and vasoconstricting substances produced by the endothelium. Recently, some physical forces generated by blood movements have been recognized as important players in endothelial dysfunction.

5. Hemodynamic forces

Many physical forces are generated during blood circulation (Bevan JA et al, 1991). Wall shear stress is the frictional force of the flowing blood on the endothelial surface of the arterial wall. It is the product of the blood viscosity and shear rate (wall shear stress = blood viscosity x blood velocity /arterial internal diameter). In fact, shear rate is an expression of the velocity of the blood as a function of radial position in the vessel. According to this formula, apart from blood viscosity changes during circulation, arterial regions with increased internal diameter or reduced blood velocities have a low shear stress.
The features of fluid flow through a tube is also dependent on flow velocity and on the presence of geometric irregularities like arterial bending and/or bifurcation, stenosis etc. Fluid flow is laminar or turbulent. Laminar flow or streamline flow, occurs when a fluid flows in parallel layers, with no disruption between the layers. In turbulent flow the velocity at any given point varies continuously over time, even though the overall flow is steady. In fluid dynamics, a measure of flow turbulence is determined by Reynolds number; for low Reynolds values, flow is laminar, whereas for high Reynolds values (typically above 2,000), flow is turbulent. In relatively straight arterial segments, wall shear stress is pulsatile and unidirectional with a magnitude that varies within a range of 5 to 70 dyne/cm^2 for mean shear stress. In contrast, mainly in regions of disturbed laminar flow, oscillating or reverse wall shear stress occurs. Wall shear stress could be low also in straight arteries of old or

diseased individuals, in particular if affected by arterial hypertension, excessive body weight or diabetes mellitus.
Wall shear stress deeply influences endothelial cell pathophysiology. Luminal endothelial cell surface is equipped with numerous mechanoreceptors capable of detecting and responding to shear stress stimuli. After activation of mechanoreceptors, a complex network of several intracellular pathways is triggered, a process known as mechanotransduction. In arterial regions of healthy people without flow problems, where wall shear stress varies among individuals within a physiological range, the endothelial cells express various atheroprotective genes and suppress the production of several pro-atherogenic substances, leading to arterial stability and a proper endothelial function in that region. In contrast, in regions where low and/or disturbed wall shear stress occurs, the atheroprotective genes are suppressed and the pro-atherogenic genes are upregulated, thereby promoting endothelial dysfunction and atherosclerotic process (Chatzizisis YS et al., 2007).

6. Endothelial function measurement

Many efforts have focused on the development and improvement of non-invasive diagnosis of atherosclerosis based on ultrasound technology in order to evaluate arterial structure and function. Celermayer developed an ultrasound technique known as flow mediated dilation to study arterial function. This test allows evaluation of endothelial response to an ischemic stimulus. Briefly, brachial artery is visualized and baseline diameter measured. Then, ischemia is created by inflating a cuff around the forearm. Ischemia causes arteriolar dilation; this, in turn, induces reactive hyperemia for the reduced forearm resistance after cuff release. Reactive hyperemia increases blood flow through the brachial artery creating a wall shear stress elevation which increases arterial diameter. The percentage increase in diameter, calculated by measuring the diameter before and after the test, is an estimate of endothelial function in response to ischemia (Celermajer DS et al, 1992).
Vasodilation generated by the increase in shear stress following ischemia is mediated by nitric oxide, a local vasodilator. Impaired vasodilator reaction is among the earliest changes to occur during the development of atherosclerosis (Agewall S, 2003). A different method to assess vascular function is nitroglycerin mediated vasodilation of brachial artery (an index of endothelium-independent dilatation) or acetylcholine mediated vasodilation (an endothelium-dependent vasodilator) (Kasprzak JD et al, 2006).
The alteration of flow mediated dilation is important for its potential clinical implications; indeed, as demonstrated in the Cardiovascular Health Study, brachial flow mediated dilation is a predictor of future clinical cardiovascular events in older adults, even after adjustment for other conventional cardiovascular disease risk factors (Yeboah J, 2007). Moreover, another study has demonstrated its strong association with coronary artery disease, evaluated by angiography (Neunteufl T et al, 1997).
An epidemiological association has been verified between endothelial dysfunction and periodontal disease, as exploited in the following chapter.

7. Periodontitis and endothelial dysfunction: Epidemiological association

Periodontal disease is linked with endothelial dysfunction assessed with both flow mediated dilation and acetylcholine mediated dilation.

A case-control study published in 2003 demonstrated for the first time an endothelial vasomotor dysfunction in a conduit artery in patients with severe periodontal disease. Authors assessed both flow mediated dilation and nitroglycerin-mediated dilation of the brachial artery in 26 subjects with advanced periodontal disease compared with 29 control subjects. Subjects were free of traditional risk factors and underwent a vascular examination. Patients with advanced periodontal disease had lower flow-mediated dilation compared with control patients matched for age and sex. Nitroglycerin-mediated dilation was equivalent in the two groups (Amar S et al, 2003).

Focusing on the additive role that periodontitis may play with traditional risk factors in the impairment of endothelial function, Higashi et al assessed forearm blood flow responses to acetylcholine and sodium nitroprusside in various subtypes of patients with periodontal disease. Aim of this study was to define the effects of periodontitis on endothelial function in humans avoiding the possible confounding factor of endothelial function alterations caused by other factors as hypertension, heart failure, atherosclerosis, hypercholesterolemia, diabetes mellitus, smoking, aging, and menstrual cycle. A normal control group (20 men; 26±3 years of age) was compared with a group of 32 patients with periodontitis without other cardiovascular risk factors (32 men; 25±3 years of age), and hypertensive patients without periodontitis (28 men and 10 women; 56±12 years of age) were compared with hypertensives with periodontitis (18 men and 6 women; 54±13 years of age). Both in healthy and in hypertensive subjects, forearm blood flow responses to acetylcholine were significantly smaller in the periodontitis groups than in the control groups. Sodium nitroprusside–stimulated vasodilation was similar in the 2 groups. Periodontitis impaired endothelium-dependent vasodilation in healthy young men. In patients with hypertension who have impaired endothelial function, clinical complications of periodontitis greatly increased the magnitude of endothelial dysfunction (Higashi Y et al, 2008).

Looking at more advanced atherosclerotic conditions, also carotid intima-media thickening and/or carotid plaques, the commonest cause of cerebral ischemia, resulted associated to periodontal disease.

8. Periodontitis and carotid atherosclerosis: Epidemiological association

Many studies report the association between periodontal disease and clinical or subclinical carotid atherosclerosis. It has been demonstrated, in cross-sectional and longitudinal studies, that periodontal disease is closely related with subclinical carotid atherosclerosis. The ARIC study, a large cross sectional study performed between 1996 and 1998, demonstrated for the first time the relationship between periodontitis and intima-media thickening. The participants received a clinical periodontal examination, and a carotid scan using high-resolution B-mode ultrasound. The results of the study showed that individuals with severe periodontal disease had 1.3 times the odd of thicker carotid arterial walls (>=1 mm) compared with individuals with less severe disease, after adjustment for traditional risk factors for atherosclerosis. The edge of 1 mm for intima-media thickening was chosen because a larger value is associated with an increased risk of cardiovascular events. (Beck JD et al, 2001).

Later, a similar study, carried out in 711 subjects with no history of stroke or myocardial infarction, demonstrated also a significant association between teeth loss, considered as a sign of past periodontitis, and carotid artery plaque prevalence. Among patients with 0 to 9

missing teeth, 46% had carotid artery plaque, whereas among those with 10 or more missing teeth, carotid artery plaque prevalence was 60% (Desvarieux M et al, 2003).
Shortly after, INVEST cross-sectional study demonstrated that carotid IMT correlated with periodontal microbiota. The analysis was adjusted for age, gender and traditional risk factors. Overall, periodontal bacterial burden was related to carotid intima-media thickening (Desvarieux M et al, 2005).
The relationship between periodontal disease and carotid atherosclerosis was further highlighted in longitudinal studies.
In fact, Soder et al. assessed the role of periodontitis in the development of atherosclerosis, evaluating the relationship between periodontal disease and development of subclinical signs of carotid atherosclerosis. Eighty two subjects with periodontitis 16 years before were compared to 31 patients without periodontitis. In the follow up, patients with periodontal disease developed significantly more intima media thickening than patients without documented periodontitis. This result confirm in a longitudinal manner that periodontal disease is associated with the development of early atherosclerotic carotid lesions (Söder PO et al, 2005).
Moreover, chronic oral inflammatory diseases seem responsible of atherosclerotic plaque progression. Another longitudinal study with a follow-up of 7.5 months showed that dental and periodontal disease was significantly associated with progression of carotid atherosclerosis. The authors used known periodontal indexes: DMFT as a measure of global teeth status was predictor of prevalence and progression of the disease, irrespective of traditional cardiovascular risk factors and baseline degree of stenosis. Edentulous patients also had a significantly increased risk for disease progression as compared with dentate patients. Particularly, during the follow-up period, 11.7% of patients showed progression of carotid atherosclerosis: they had significantly higher DMFT indices compared with patients with stable carotid disease. A further analysis of the subcategories of DMFT revealed that the number of missing teeth was strongly associated with disease progression, whereas filled teeth showed only a borderline significance, and the number of decayed teeth was not significantly associated with progressive disease (Schillinger T et al, 2006).
But the presence of periodontitis is linked to carotid atherosclerosis and at its earlier step, endothelial dysfunction, also in intervention studies.

9. Periodontitis, carotid atherosclerosis and endothelial dysfunction: Intervention studies

A strong evidence for the link between endothelial dysfunction and periodontitis comes from intervention studies, evaluating patients with periodontal disease before and after dental treatment.
Apart from previous reports, (Mercanoglu F et al, 2004; Seinost G et al, 2005), in 2007 a large study showed that periodontal treatments lead to an improvement of endothelial function. One hundred twenty patients with severe periodontitis were randomized to receive current periodontal care or intensive treatment. Endothelial function was assessed with flow-mediated dilatation before the treatment and up to 6 months after treatment. Twenty-four hours after treatment, flow-mediated dilatation was significantly lower in the intensive-treatment group than in the control-treatment group. Then, flow-mediated dilatation was

greater in the intensive-treatment group than in the control-treatment group 60 and 180 days after therapy. The degree of improvement was associated with improvement in measures of periodontal disease. Therefore, intensive periodontal treatment resulted in acute, short-term systemic inflammation and endothelial dysfunction. Thereafter, the improvement of oral health was associated with improvement in endothelial function.
Furthermore, recently, an intervention study has been performed in a small sample of patients suffering from periodontal disease. This study confirmed that periodontal therapy decreases total oral bacterial load, inflammation biomarkers, adhesion and activation proteins, and in addition it showed a regression of carotid IMT (Piconi S et al, 2009).

10. Mechanisms of association

Studies reporting the association between periodontitis, atherosclerosis and endothelial dysfunction have been discussed above. The present chapter elucidates the mechanisms linking these factors.
First of all, it has been demonstrated that oral pathogens as Porphyromonas gingivalis can infect endothelial cells (Deshpande RG et al, 1998). Furthermore, exposure of cultured endothelial cells to this pathogen is associated with endothelial activation and expression of cell adhesion molecules (Khlgatian M et al, 2002).
However, probably the key event driving patients affected by periodontal disease to atherosclerosis development is systemic inflammation characterizing periodontal disease. In fact, severe periodontal disease was associated with increased serum C-reactive protein levels, Interleukin-6 and many others inflammation factors (De Nardin E, 2001); furthermore, intervention studies reported a reduction of these indexes after therapy (Elter JR et al, 2006). There are at least three ways by which inflammation in periodontal disease might cause a carotid atherosclerotic development (Figure).
First, chronic inflammation leads to endothelial dysfunction, as demonstrated by the findings that patients with chronic inflammatory disease like systemic lupus erythematosus have impairment of flow mediated vasodilation in brachial artery (Lima DS et al, 2002). The reason of this finding can be found in experiments conducted in cell cultures. In fact, in vitro experiments have demonstrated that elevated levels of C-reactive protein, characteristics of inflammatory state, lead to reduction of nitric oxide through a reduction of nitric oxide synthase mRNA; this might impair brachial flow mediated dilation (Verma S et al, 2002).
Moreover, a systemic inflammatory state leads to an impairment of wall shear stress also in carotid artery territory. Recently it has been demonstrated for the first time, a relationship between periodontal disease and low wall shear stress. Different periodontal indices were evaluated during dental examination: Plaque Index, Gingival Index, Pocket Deep. Common carotid wall shear stress was associated with extension and severity of periodontitis. This association was independent of classical cardiovascular risk factors and age (Carallo C et al, 2010). This is important because it has been demonstrated a strong association between low wall shear stress and intima-media thickening increase (Gnasso A et al, 1997). The way through which periodontitis influences hemodynamic forces might be systemic inflammation, by an enlargement of arterial diameter as in rheumatoid arthritis (Irace C et al, 2004). Furthermore, low shear stress might in turn also locally enhance vascular inflammation (Ridger V et al, 2008). As above reported, in regions where low shear stress

occurs, the atheroprotective genes are suppressed and the pro-atherogenic genes are upregulated, promoting the atherosclerotic process.
Finally, systemic chronic inflammation could cause atherosclerosis per se. Ridger et al demonstrated that the presence of chronic respiratory, urinary tract, dental, and other infections amplified the risk of atherosclerosis development in the carotid arteries. Moreover, among subjects with chronic infections, atherosclerosis risk was higher in those with a prominent inflammatory response (Ridger V et al, 2008).

11. Conclusions

In conclusion, periodontal diseases, mainly by a consequent systemic inflammation, have a deep influence on several old and new vascular parameters that are strictly interrelated each other, as endothelial function and hemodynamic forces. This mechanisms might contribute to explain the link between major cardiovascular disease and oral affections.

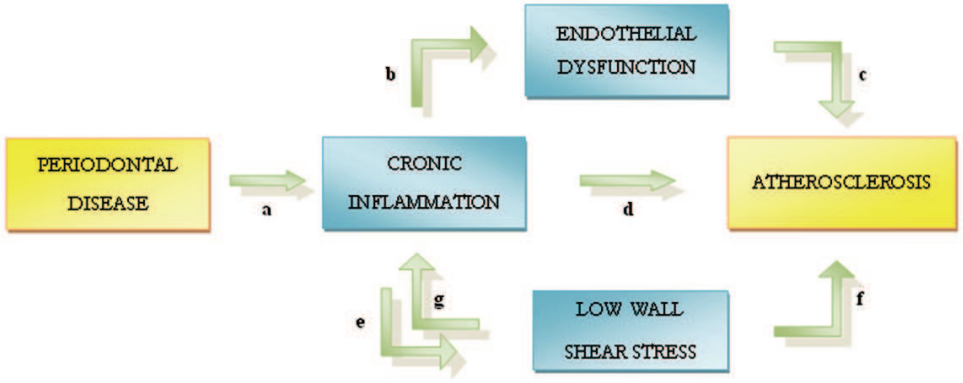


Fig. 1.

Figure describes the relationship between periodontal disease and atherosclerosis, showing that this link might be mediated by various factors. First of all, periodontitis is characterized by systemic inflammation (arrow 'a'); chronic inflammation itself leads to development of atherosclerotic disease (arrow 'd'). Chronic inflammation could act also via endothelial dysfunction (arrow 'b'), that represents the first step of atherosclerotic disease (arrow 'c'). Moreover, periodontal disease is linked with an impairment of hemodynamic force of wall shear stress, probably via the inflammation (arrow 'e'). In turn, low wall shear stress could cause a worsening of atherosclerosis directly (see arrow 'f') or via a worsening of chronic inflammation (arrow 'g').

12. References

A.H.A. Heart Disease and Stroke Statistics—2003 Update. Dallas, Tex: American Heart Association; 2002.

Agewall S. Is impaired flow-mediated dilatation of the brachial artery a cardiovascular risk factor? Curr Vasc Pharmacol. 2003; 1: 107-109.

Amar S, Gokce N, Morgan S, et al. Periodontal disease is associated with brachial artery endothelial dysfunction and systemic inflammation. Arterioscler Thromb Vasc Biol. 2003; 23: 1245-1249.

Beck JD, Elter JR, Heiss G, et al. 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.

Bevan JA, Laher I. Pressure and flow-dependent vascular tone. FASEB J. 1991; 5: 2267-2273.

Carallo C, Fortunato L, de Franceschi MS, et al. Periodontal disease and carotid atherosclerosis: are hemodynamic forces a link? Atherosclerosis 2010; 213: 263-267.

Cawson RA, Odell EW. Cawson's Essentials of Oral Pathology and Oral Medicine. Churchill Livingstone 8th ed. Edinburgh 2008.

Celermajer DS, Sorensen KE, Gooch VM, et al. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. Lancet. 1992; 340: 1111-1115.

Chatzizisis YS, Coskun AU, Jonas M, et al. Role of endothelial shear stress in the natural history of coronary atherosclerosis and vascular remodeling: molecular, cellular, and vascular behavior. JACC 2007; 49: 2379-2393.

Chien RS, Dormandy J, Ernst E and Matrai A (eds), Clinical Hemorheology: Applications in Cardiovascular and Hematological Disease, Diabetes, Surgery and Gynecology. Dordrecht: Martinus Nijhoff Publishers, 1987.

Coll B, Feinstein SB. Carotid intima-media thickness measurements: techniques and clinical relevance. Curr Atheroscler Rep. 2008; 10: 444-450.

Cotran R, Kumar V, Collins T. *Robbins Pathologic Basis of Disease*, 6th Edition. W.B. Saunders 1999.

Davies MJ. Pathology of atherosclerosis, In: *Hurst's The Heart, Arteries and Veins.* Alexander RW et al eds .9th ed. McGraw-Hill, pp.(1161–1173), New York 1998.

De Nardin E. The role of inflammatory and immunological mediators in periodontitis and cardiovascular disease. Ann Periodontol 2001; 6: 30–40.

Deshpande RG, Khan MB, Genco CA. Invasion of aortic and heart endothelial cells by Porphyromonas gingivalis. Infect Immun. 1998; 66: 5337–5343.

Desvarieux M, Demmer RT, Rundek T, et al. Periodontal microbiota and carotid intima–media thickness: the Oral Infections and Vascular Disease Epidemiology Study (INVEST). Circulation 2005; 111: 576–582.

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: 2120–2125.

Elter JR, Hinderliter AL, Offenbacher S, Beck JD, Caughey M, Brodala N, Madianos PN. The effects of periodontal therapy on vascular endothelial function: a pilot trial. Am Heart J. 2006; 151: 47.

Gnasso A, Carallo C, Irace C, et al. Association between intima–media thickness and wall shear stress in the common carotid arteries in healthy male subjects. Circulation 1996; 94: 3257–3262.

Gnasso A, Irace C, Carallo C, et al..In vivo association between low wall shear stress and plaque in subjects with asymmetrical carotid atherosclerosis. Stroke. 1997; 28: 993-998

Higashi Y, Goto C, Jitsuiki D, et al.. Periodontal infection is associated with endothelial dysfunction in healthy subjects and hypertensive patients. Hypertension. 2008; 51: 446-453.

Irace C, Mancuso G, Fiaschi E, et al.. Effect of anti TNFalpha therapy on arterial diameter and wall shear stress and HDL cholesterol. Atherosclerosis. 2004; 177: 113-118.

Johnsen SH, Mathiesen EB. Carotid plaque compared with intima-media thickness as a predictor of coronary and cerebrovascular disease. Curr Cardiol Rep. 2009; 11: 21-7.

Kasprzak JD, Kłosińska M, Drozdz J. Clinical aspects of assessment of endothelial function. Pharmacol Rep. 2006; 58: 33-40.

Khlgatian M, Nassar H, Chou HH, Gibson FC3, Genco CA. Fimbria dependent activation of cell adhesion molecule expression in porphyromonas gingivalis-infected endothelial cells. Infect Immun. 2002; 70: 257–267.

Kiechl S, Egger G, Mayr M, et al. Chronic infections and the risk of carotid atherosclerosis: prospective results from a large population study. Circulation 2001; 103: 1064–1070.

Lima DS, Sato EI, Lima VC, Miranda F Jr, Hatta FH. Brachial endothelial function is impaired in patients with systemic lupus erythematosus. J Rheumatol. 2002; 29: 292-297.

Lindhe J, Karring T, Lang NP. Clinical periodontology and implant dentistry. Blackwell/Munksgaard 4th ed, Copenhagen 2003.

Loe H. The gingival index, the plaque index and retention index system. J Periodontol 1967; 38: 610-616.

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.

Mitchell DA, Mitchell L. Oxford handbook of clinical dentistry. Oxford University Press, 4th ed; Oxford 2009.

Neunteufl T, Katzenschlager R, Hassan A, et al. Systemic endothelial dysfunction is related to the extent and severity of coronary artery disease. Atherosclerosis 1997; 129: 111-118.

Palmer R. M., Floyd P. D. A clinical guide to periodontology. British Dental Association ed, London 2003.

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: 1196–1204

Ramfjord SP. Indices for prevalence of periodontal disease. J Periodontol. 1959; 30: 51-59.

Ridger V, Krams R, Carpi A et al. Hemodynamic parameters regulating vascular inflammation and atherosclerosis: a brief update. Biomed Pharmacother. 2008; 62: 536-540.

Ross R. Atherosclerosis – an inflammatory disease. N Engl J Med. 1999; 340: 115-26.

Ross R. Factors influencing atherogenesis. In: *Hurst's The Heart, Arteries and Veins.* Alexander RW et al, eds. 9th ed. McGraw-Hill, pp.(1139–1159), New York 1998.

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 substudy. Stroke. 2006; 37: 2271–2276.

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.

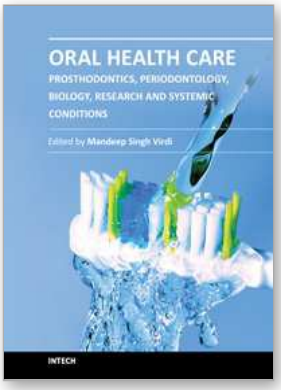
Silness J, Löe H. Periodontal disease in pregnancy. II. Correlation between oral hygiene and periodontal condition. Acta Odontol Scand 1964; 22: 112-135.

Söder PO, Söder B, Nowak J et al. Early carotid atherosclerosis in subjects with periodontal diseases. Stroke 2005; 36: 1195–1200.

Tonetti MS, D'Aiuto F, Nibali L, et al. Treatment of periodontitis and endothelial function. N Engl J Med. 2007; 356: 911-920.

Verma S, Wang CH, Li SH, et al. A self-fulfilling prophecy: C-reactive protein attenuates nitric oxide production and inhibits angiogenesis. Circulation. 2002; 106: 913-919.

Yeboah J, Crouse JR, et al. Brachial flow-mediated dilation predicts incident cardiovascular events in older adults: the Cardiovascular Health Study. Circulation. 2007; 115: 2390-2397.



Oral Health Care - Prosthodontics, Periodontology, Biology, Research and Systemic Conditions

Edited by Prof. Mandeep Virdi

ISBN 978-953-51-0040-9
Hard cover, 372 pages
Publisher InTech
Published online 29, February, 2012
Published in print edition February, 2012

Geriatric dentistry, or gerodontics, is the branch of dental care dealing with older adults involving the diagnosis, prevention, and treatment of problems associated with normal aging and age-related diseases as part of an interdisciplinary team with other healthcare professionals. Prosthodontics is the dental specialty pertaining to the diagnosis, treatment planning, rehabilitation, and maintenance of the oral function, comfort, appearance, and health of patients with clinical conditions associated with missing or deficient teeth and/or oral and maxillofacial tissues using biocompatible materials. Periodontology, or Periodontics, is the specialty of oral healthcare that concerns supporting structures of teeth, diseases, and conditions that affect them. The supporting tissues are known as the periodontium, which includes the gingiva (gums), alveolar bone, cementum, and the periodontal ligament. Oral biology deals with the microbiota and their interaction within the oral region. Research in oral health and systemic conditions concerns the effect of various systemic conditions on the oral cavity and conversely helps to diagnose various systemic conditions.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Maria Serena De Franceschi, Leonzio Fortunato, Claudio Carallo, Cesare Tripolino, Concetta Irace, Michele Figliuzzi, Antonio Crispino and Agostino Gnasso (2012). Periodontal Disease and Carotid Atherosclerosis: Mechanisms of the Association, Oral Health Care - Prosthodontics, Periodontology, Biology, Research and Systemic Conditions, Prof. Mandeep Virdi (Ed.), ISBN: 978-953-51-0040-9, InTech, Available from: http://www.intechopen.com/books/oral-health-care-prosthodontics-periodontology-biology-research-and-systemic-conditions/periodontal-disease-and-carotid-atherosclerosis-mechanisms-of-the-association

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821