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Hypertension and Periodontitis-A Review

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Abstract: Periodontal Disease is an inflammatory process affecting the Periodontium, the tissue that surrounds and supports the teeth. The process usually starts with an inflammatory process of the gum (gingivitis) but it may progress with an extensive involvement of the gum, as well as the periodontal ligament and the bone surrounding the teeth resulting in substantial bone loss. Current evidence suggested that there is a potential correlation between increased blood pressure and periodontitis. However there are only limited cross sectional studies are emerging now to associate the relation between the hypertension, periodontitis, gingivitis and healthy gingiva. This study is basically done to evaluate the relation between hypertension, periodontitis gingivitis and healthy gingiva.

Key words: Chronic Periodontitis · Hypertension · C Reactive Protein · Reactive Oxygen Species

INTRODUCTION

Periodontal disease, the most prevalent diseases throughout the world [1] and are predominantly caused by gram –negative anaerobic bacteria present on the tooth root surfaces as a biofilm.

Periodontal disease has recently drawing increased attention because of its potential relationship with cardiovascular disease, as a chronic inflammatory condition linked with systemic markers of inflammation and endothelial dysfunction [2]. Hypertension is also prevalent affecting 30 % of adults and is a major cause of cardiovascular morbidity and mortality. This two condition seems to be unrelated to each other. There are upcoming studies showing a strong relation between cardiovascular disease and periodontitis. The relationship may be either a direct through adverse systemic ramification including inflammatory generalization [3, 4]. There are also some studies have been focused on antihypertensive treatment and periodontitis [5] stating that patients under antihypertensive treatment show positive effects on periodontitis i.e. they have increased number of pockets and there is a linear trend between periodontal disease severity and antihypertensive treatment.

Evidence Associated Between Periodontitis and Hypertension: The study population consists of 31,543 participants of the Health Professionals' Follow-Up Study (HPFS) prospective cohort who were 40–75 years old at baseline, had no prior hypertension history and had complete baseline information on oral health. The information regarding periodontal disease, hypertension was recorded biennially. The criteria's included were age, calendar time, race, comprehensive smoking, diabetes, alcohol consumption, family history of hypertension, BMI, Physical activity, diet pattern multivitamin, calcium & Vitamin D intake.

The Results found that 10,828 individuals out of 31543 showed hypertension over 20 yrs of age. Follow up after, adjusting for potential confounders, we did not observe significant associations between incident hypertension and periodontal disease at baseline (relative risk (RR) = 1.04; 95% confidence interval (CI): 0.98–1.10), periodontitis during follow-up (RR = 1.01; 95% CI: 0.96–1.05), tooth loss during follow-up (RR = 1.03; 95% CI:

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0.98–1.09), or when comparing men with 0–10 teeth to men with ≥25 teeth at baseline (RR = 1.05; 95% CI: 0.91–1.21). Participants reporting severe periodontal bone loss had a RR for incident hypertension of 1.02 compared to those without bone loss (95% CI: 0.77–1.35).

They did not observe an association between periodontal disease measures and incident hypertension in this cohort of middle-aged men [7]. In one of the study BP is checked 2 times point one year apart was performed in a study of 364 apparently healthy but predominantly male young individuals, that's applied a case definition of periodontitis [8].The affected subjects compared to controls has shown higher diastolic blood pressure and a least trend for higher systolic blood pressure at the two visits though hypertension prevalence did not differ.

In a large Swedish population study a through periodontal examination including an x-ray was performed in a total over 4200 adult participants of a wide range. There was an association between periodontitis and hypertension prevalence was noted. Age stratification revealed that the findings remain significant in subjects over 60 years of age [5].

The conclusion was derived from 653 patients of oral infections an vascular disease epidemiological study (INVEST) on multiethnic cohort concluded that there is a direct assessment of subgingival periodontal bacterial burden and its relation to blood pressure. There was an increased percentage of sites per mouth with 3 mm or more the probing depth was associated with the higher diastolic blood pressure. After adjustment of the confounding factors such as cardiovascular risk factors, inflammatory markers and non causative bacteria, the highest compared with lowest of etiological bacterial burden was associated with the four fold risk of hypertension. Men are affected twice more than the women. Some putative and beneficial bacteria were found to be absent and inverse associated with hypertension. This findings suggested that there was diverse mixture of periodontal bacteria may have a different impact on Blood pressure [9].

Yohsuke Hanaoka *et al*. 2013 investigated that periodontal disease and serum antibody level associated with hypertension. 127 patients were studied (93 men and 34 women, mean age 68±9 years) who were admitted with ischemic heart disease in their institution. The Periodontal risk scores were calculated. The level of serum antibodies against porphyromonas gingivalis (Pg) was measured. Pulse pressure, mean blood pressure (BP) and pulse wave velocity were as indices of atherosclerosis. They divided patients into 2 groups according to the level of serum antibody against Pg: higher or equal to the median (high Pg serum antibody group) and lower than median(lower Pg serum antibody group).There was no difference in use of anti hypertensive agents between the two groups. The composite risk periodontal score (P=0.0003), systolic BP (P=0.030), diastolic BP(P=0.038),Pulse Pressure(P=0.050) and mean BP(P=0.055) were higher in Pg antibody group than in the lower Pg antibody group. An elevated antibody level against Pg indicates advanced periodontal disease and suggests advancement of atherosclerosis and hypertension [10].

Role of Inflammation in Periodontitis: Inflammation is your body's *natural reaction* to invasion by an infectious agent, toxin or physical, chemical or traumatic damage. One purpose of inflammation is to protect the site of an injury. During inflammation it fights with the disease and protects the body with the normal immune response and certain metabolic progress. When the duration is short it does not cause any problem but when it is long term process it causes constant damage. Inflammation is therefore acting as a "double edge sword" as this adaptive response becomes maladaptive after a chronic time. In blood vessels inflammation increases vascular permeability and alters the cytoskeletal elements in the endothelial cells, disrupting endothelial function in controlling vascular health.

Over a past 3 decade's vascular inflammation as a mechanism participates as a progression of hypertension. Recent evidence supported that hypertension in the Okamoto spontaneous hypertensive rat (SHR) may be the result of autoimmune disorder. To test this hypothesis SHRs were given chronic immunosuppressive therapy (cylophosphamide). The development of hypertension was studied in SHRs receiving cyclophosphamide beginning at the age of 3 wks. The arterial pressure of the cyclophosphamide-treated SHRs was significantly lower than that of untreated control SHRs once the rats were 8 wk old and this reduction in blood pressure was maintained for the duration of treatment. Also the effect of chronic immunosuppressive therapy on the maintenance of spontaneous hypertension was determined by beginning treatment in 16-wk-old SHRs. Arterial blood pressure was significantly less than that of untreated control SHRs after 2 wks of treatment.

According to the Tail cuff measurements, the level of hypertension in SHRs rats was reduced by approximately to 50% following 6weeks of immunosuppressant therapy. The mean arterial blood pressure was significantly reduced after 3 weeks to 158 ± 5.0 mm Hg in immunosuppressed SHRs n=10 compared with 175± 2.6 mmHg in control SHRs (n=7). Cylophosphamide treatment did not have any significant effect on blood pressure of Wistar or Wistar–Kyoto rats or on the development or maintenance of deoxycorticosterone acetate hypertension. The results indicated that chronic immune suppression attenuates hypertension in Okamoto SHR. These results support the hypothesis that spontaneous hypertension may be due in part of auto immune disorder [10]. Then Norman *et al* demonstrated that the development of hypertension was delayed by correcting the immune balance state in SHR. They found that immunological dysfunction is one of the key etiologies of hypertension [11].

Dzielak noted inflammatory involvement in hypertension by observing alternations in serum immunoglobulin levels both in patients and laboratory animals and there was an interaction in the inflammatory cells both in patients and laboratory animals. Furthermore the interaction between inflammatory cells and endothelial cells was increased in hypertensive patients [12].

The overall concept of inflammation and the immune response to vascular damage in hypertensive patients has thrown light on the scientist to undergo various research based on the Periomedicine

Periomedicine: A broad term that defines a rapidly emerging branch of Periodontology focusing on the wealth of new data establishing a strong relationship between the periodontal health or disease and systemic health or disease [13].

Role of Inflammation: Inflammation plays a central role. The endothelial cells form a inner surface of artery resist adhesion by circulating leukocytes. Exposure to risk factor affects this homeostasis. Smoking hypertension, obesity, insulin resistance hyperglycemia promotes endothelial expression of circulating leukocytes attachment. Vascular adhesion molecule bind monocyte & T lymphocyte found in early atherosclerotic plaque. Certain Inflammatory adhesion molecules are involved in the pathogenesis of hypertension and predictive of further cardiovascular events. Vascular adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule -1(ICAM) are expressed by the endothelial cells. Their expression are up regulated in response to inflammatory insult [14]. Increased expression of these adhesion molecules on endothelial cells is a common process in response to the inflammation [15]. VCAM-1 & ICAM-1 are the important risk markers for cardiovascular events. VCAM-1 and ICAM-1 mediate leukocytic binding to the endothelial lining. Increased leukocytic infiltration and production of cytokines exaggerate oxidative stress and inflammation, eventually causing a disturbance to the normal endothelial function in regulating BP.

Evidence Associated Between Hypertension and Periodontitis: Hypertension is a major global health problem affecting individuals. The population seems to be increasing to 1.56 billion by the year 2025 [16]. Hypertension is defined when a patient has a elevated systolic BP greater than 140mm Hg and or diastolic BP greater than 90 mmHg [17]. Patients with systolic BP ranging between 120mmHg and 139 mmHg and /or diastolic BP of 80mm Hg to 89mmHg is called as Pre Hypertensive.

Oral Biofilm consist of more than 700 species found to be in the oral cavity [18, 19]. They are in a wide range. A Biofilm community comprises of bacterial micro colonies, an extracellular slime layer, fluid channels and a primitive communication system. The Extra cellular slime layer is a protective barrier that surrounds the mushroom-shaped micro colonies from antibiotics, antimicrobials and host defense mechanisms. A series of fluid channels penetrate extracellular slime layer. The biofilm are protected by antimicrobials. Dental Biofilm release variety of biological products including bacterial lipopolysaccharides, chaemotatic peptides, protein toxins and organic acids [20]. The production of Proinflammatory prostaglandin and cytokines such as Interleukin-1 beta (IL-1β), Interleukin (IL-6), Interleukin -8(IL-8) and tumour necrotic factor –alpha (TNF-α) are triggered the response to the stimuli of dental biofilm. These active products are responsible for periodontal tissue destruction.

Recent evidences supported that there is a strong relation between hypertension and periodontitis. The patients with hypertension showing more significant detrimental periodontal Status[21,22]. The table below showing the significant association between hypertension and periodontitis.

Studies Showing Significant Association Between Hypertension an Periodontitis

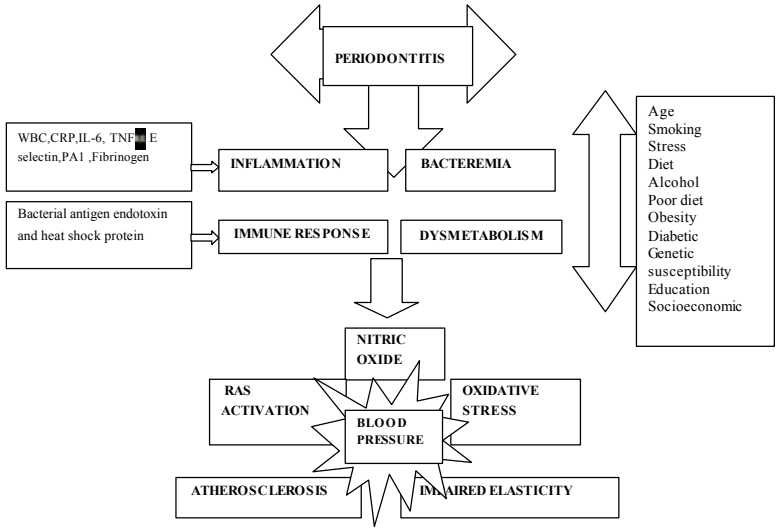
Study	Year	Country studied	Sample size	Type of study	Findings	Adjusted for
Ogawa *et al*. [23]	1998	Japan	2000	Cross-sectional	Hypertensive subjects had higher CPITN	None
Angeli *et al*. [24]	2003	Italy	104	Cross-sectional	↑ SBP with ↑ periodontitis severity	None
Taguchi *et al*. [25]	2004	Japan	98	Cross-sectional	↑ SBP (), ↑ DBP (), hypertension in subjects with missing teeth (OR: 3.59; CI: 1.1–11.7)	Obesity, hypercholesterolemia, hypertriglyceridemia
Inoue *et al*. [26]	2005	Japan	364	Cross-sectional (2 time points)	Periodontitis associated with ↑ BP and WBC count	Age, gender, BMI, smoking, drinking, hypertension, DM, WBC count
Holmlund *et al*. [5]	2006	Sweden	4254	Cross-sectional (Retrospective)	Periodontal pocket related to hypertension (), ↑ periodontitis severity with hypertension (OR: 1.32; CI: 1.13–1.54;)	Age, gender, number of teeth, smoking
D'Aiuto *et al*. [27]	2006	England	40	Prospective intervention randomized controlled trial	7±3↑mmHg of SBP after 2 months of intensive treatment	None
Völzke *et al*. [28]	2006	Germany	4185	Cross-sectional (SHIP)	↑ SBP () and OR: 1.91 (CI: 1.21–3.02;) for hypertension in male with 0–6 teeth compared to fully dentate	Age, BMI, education, smoking, diet, DM, antihypertensive medication
Engström *et al*. [29]	2007	Sweden	390	Cross-sectional	DBP associated with deep periodontal pockets	Age, gender, tobacco use, number of teeth
Völzke *et al*. [30]	2007	Germany	1913	Cross-sectional (SHIP)	↑ SBP (female: 11.7↑mm Hg; male: 5.7↑mmHg) in edentulous compared to fully dentate	None
Franek *et al*. [31]	2009	Poland	99	Cross-sectional	Periodontitis severity associated with central BP and pulse pressure ()	Age, gender, BMI, hypertension duration, smoking, number of drugs taken
Fujita *et al*. [32]	2009	Japan	54551	Cross-sectional data	Female (OR: 1.52; CI: 1.14–2.03;); male (OR: 1.24; CI: 1.06–1.45;) for hypertension in no brushing compared to brushing after every meal	Age, BMI, smoking, alcohol, walking time
Nesse *et al*. [33]	2010	The Netherlands	1208	Cross-sectional	↑ hypertension prevalence in periodontitis subjects compared to controls ()	None
de Oliveira *et al*. [34]	2010	Scotland	11869	Cross-sectional (Scottish Health Survey)	↑ hypertension prevalence in subject with rare teeth brushing ()	None
Morita *et al*. [35]	2010	Japan	1023	Prospective cohort	Periodontal pocket associated with hypertension (OR: 1.5; CI: 1.0–2.3)	Age, gender, smoking, regular exercise, eating between meals, healthy body weight
Franek *et al*. [36]	2010	Poland	155	Cross-sectional	Periodontitis severity associated with central SBP () & DBP ()	Age, gender, BMI, hypertension and insulin treatment
Tsakos *et al*. [37]	2010	United States of America	11948	Cross-sectional data (NHANES III)	↑ SBP () OR: 1.1 (CI: 1-1.1;) for hypertension in ↑ 10% gingival bleeding	Age, gender, BMI, ethnicity, CRP, creatinine, Na^+/K^+ ratio, chronic conditions, smoking, alcohol, education, income
Desvarieux *et al*. [38]	2010	United States of America	653	Cross-sectional data (INVEST)	↑ SBP & DBP OR: 3.13 (CI: 1.62–6.03;) for hypertension when etiological bacterial burden is high	Age, gender, BMI, race, education, smoking, DM, LDL-C, HDL-C, nonetiological periodontal bacteria
Zhang *et al*. [39]	2011	Xinjang Uygur	1415	Cohort	Periodontitis associated with hypertension (OR: 1.75; CI: 1.30–2.36;)	Age, gender, BMI, waist circumference, glycometabolism disorder, hyperlipidemia, chronic kidney disease

Vidal *et al*. [40]	2011	Brazil	137	Case-control	Hypertension associated with severe chronic periodontitis (OR: 4.04; CI: 1.92–8.49), with generalized chronic periodontitis (OR: 2.18; CI: 1.04–4.56)	Gender, race, DM, alcohol, smoking
Peres *et al*. [41]	2012	Brazil	1720	Cross-sectional	Edentulous subjects had a SBP 8.3↑mmHg (CI: 0.1–16.7) higher than those with 10 or more teeth in both dental arches	Age, gender, BMI, education, income, smoking, alcohol, DM, leisure physical activity, use of dental prosthesis, self-rated health status
Rivas-Tumanyan *et al*. [42]	2013	Puerto Rica	182	Cross-sectional	Periodontitis severity associated with high BP (OR: 2.93; CI: 1.25–6.84) OR: 4.20 (CI: 1.28–13.80) restricted to those with hypertension history and/or taking antihypertensive medications	Age, gender, smoking, drinking

Symbolsindicate:↑:increased; ↓:decreased.

BMI: Body mass index; CI: confidence interval; CPITN: community periodontal index of treatment needs; CRP: C-reactive protein; DBP: diastolic blood pressure; DM: diabetes mellitus; HDL-C: high-density lipoprotein cholesterol; INVEST: Oral Infections and Vascular Disease Epidemiology Study; LDL-C; low-density lipoprotein cholesterol; NHANES: National Health and Nutrition Examination Survey; OR: odds ratio; SADHS: South African Demographic and Health Survey; SBP: systolic blood pressure; SHIP: Study of Health in Pomerania; WBC: white blood cell.

Possible Linking Pathway Showing Association Between Hypertension and Periodontitis:



1. Proposed pathophysiology link of periodontitis to hypertension. In periodontitis, a series of alterations have been documented that are associated with a) the periodontal bacterial load and transient bacteremia, b) the subsequent immune response, c) a systemic inflammatory generalization, d) glucose and lipid metabolism and can all contribute to a pathogenetic substrate for an increase in blood pressure. In the whole process, common risk factors may interfere, thus enhancing the association as well as the clinical extent of the two disorders. WBC, white blood cells; CRP, C-reactive protein; IL-6, interleukin-6; TNF-_, tumor necrosis factor-a; vWf, von Willebrandfactor; PAI-1, plasminogen activator inhibitor -1; RAS, renin–angiotensin system.

Alternation in BP regulatory components such as the central and peripheral nervous system, the circulating and tissue renin angiotensin mechanism, the kidney and complex feedback loops have been investigated as the substrate for the development of hypertension [43].

Role of C Reactive Protein in Hypertension: Inflammation is the important marker for all the cardiovascular events and C - reactive protein is the most important circulating marker which emerged as a independent determinants for cardiovascular events. Various experimental data and

investigation showed that CRP is most important for arterial stiffness showing specific interaction between CRP and blood pressure.

There are numerous cross sectional studies showing association between inflammatory markers and measures of arterial stiffness.

Studies done by Mattace Raso FU in 2010 examined the association of between inflammatory markers and arterial stiffness they prospectively examined the association of high specificity C reactive protein with incident isolated systolic hypertension as a model of arterial stiffness in a large population based study. The study included 1637 apparently healthy participants from the Rotterdam study, Mean age include 64+/-6.4 yrs.252 participants developed systolic hypertension. The results were supporting the role of C reactive protein in development of isolated systolic hypertension in apparently healthy older adults.

Sesso *et al* 2003 did a study to examine whether C-reactive protein levels, a marker of systemic inflammation are associated with the incident of hypertension. The study designed as a cohort study in 1992 of 20 525 female US health professionals aged 45 years or older who provided baseline blood samples with initially a normal levels of BP systolic BP <140 mm Hg and diastolic BP <90 mm Hg and no history of hypertension or antihypertensive medications) and then followed up for a median of 7.8 years for the development of incident hypertension. Plasma C-reactive protein levels were measured and baseline coronary risk factors were collected. They concluded that C-reactive protein levels are associated with future development of hypertension, which suggests that hypertension is in part an inflammatory disorder.

Sesso *et al*. 2007 examined interleukin(IL-6) and C-reactive protein in a case control study of 400 women developing hypertension and an equal number of age-matched normotensive control subjects during 10 years of follow-up as part of the Women's Health Study. All of the women initially had no hypertensive blood pressure values and no history of diagnosis or treatment. Subjects provided self-reported risk factors and IL-6 and CRP were measured from baseline bloods. Case subjects reported elevated systolic (>or=140 mm Hg) or diastolic (>or=90 mm Hg) blood pressure, newly diagnosed hypertension, or initiating antihypertensive treatment during follow-up. After multivariate adjustment and strong confounding by body mass index, IL-6 was weakly associated and CRP strongly associated with hypertension risk. In models simultaneously examining IL-6 and CRP, only CRP remained strongly associated with an increased risk of hypertension.

Oxidative Stress: ROS (REACTIVE OXIDATIVE STRESS) such as superoxide anions and hydrogen peroxides are chemically reactive molecules. They damage the cellular components including, nucleic acids and proteins. ROS are formed as a natural bi products during physiological processes in cell membrane, mitochondria and endoplasmic reticulum. In addition ROS can be generated from tobacco, pollutants drugs and ionizing radiation. However excessive production of ROS leads to oxidative stress with an increase in formation of free radicals as well as decrease in antioxidants.

Studies have shown that periodontitis induces excessive production of ROS in periodontal tissues and thus suggesting that oxidating stress is suggested to be involved in the pathogenesis of periodontal destruction. Oxidative stress in turn is implicated in the development of hypertension, since reactive oxygen species may be regarded as mediators of vasoconstriction and vascular inflammation and bioavailability of nitric oxide is strongly related to the redox state [44].

CONCLUSION

There are numerous cross sectional studies showed positive results in association between hypertension and periodontitis. However there is no causal relation to show strong relationship. Further studies should be conducted to show us a better understanding between hypertension and periodontitis. However some studies showed elevated blood pressure in periodontitis patients prevention approaches should include the controlling of blood pressure in the management of periodontitis patients. Oral health programme should be emphasized in the preventive measure.

REFERENCES

1. Lacopino, AM., 2001. Periodontitis and Diabetics Interrelationships: Role of Inflammation. Ann Periodontol, 6: 125-37.
2. Joshipura, K.J., H.C. Wand, A.T. Merchant and E.B. Rimm , Periodontal Disease and Biomarker related to cardiovascular disease. J. Dent Res., 83: 151-155[Pubmed].

3. Janket, S.J., A.E. Baird, S.K. Chaung and J.A. Jones, 2003. Meta-analysis of Periodontal disease and risk of coronary heart disease Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 95(5): 559-69.
4. Chen, Y.W., M. Umeda, T. Nagasawa, Y. Takeuchi, Y. Huang, Y. Inoue, T. Lwai, Y. Lzumi and L. Ishikawa 2008. Periodontitis may increase a risk of peripheral arterial disease. Eur J. Vasc Endovas Surg., 35: 153-8.
5. Holmlund, A., G. Holm and L. Lind, 2006. Severity of periodontal disease and number of remaining teethare related to the prevalence of myocardial infarction and hypertension in a study based on 4,254subjects. J. Periodontol., 77: 1173-1178.
6. Morita, T., Y. Yamazaki, A. Mita, K. Takada, M. Seto, N. Nishinoue, Y. Sasai, M. Motohashi and M. Maeno, 2010. A cohort study on the association between periodontal disease and the development of metabolic syndrome. J. Periodontol., 81: 512-519.
7. Sona Rivas-Tumanyan, Donna Spiegelmann, Gary C. Curhan, John P. Forman and Kaumudi J. Joshipura, XXXX. Periodontal disease and incidence of hypertension in the health professionals follow-up study. American Journal of Hypertension, 25(7): 770-776.
8. Inoue, K., Y. Kobayashi, H. Hanamura and S. Toyokawa, 2005. Association of periodontitis with increased white blood cell count and blood pressure. Blood Press., 14: 53-8.
9. Desvarieux, M., R.T. Demmer and D.R. Jacobs Jr, 2010. Periodontal bacteria and hypertension:the oral infections and vascular disease epidemiology study (INVEST).J Hypertens, 28: 1413-21.
10. Khraibi, A., R.A. Norman Jr. and D.J. Dzielak, 1984. "Chronic immunosuppression attenuates hypertension in Okamoto spontaneously hypertensive rats," American Journal of Physiology—Heart and Circulatory Physiology, 16(5): H722-H726.
11. Norman Jr., R.A. and D.J. Dzielak, 1986. "Spontaneous hypertension is primarily the result of sympathetic overactivity and immunologic dysfunction, Proceedings of the Society for Experimental Biology and Medicine, 182(4): 448-453.
12. Dzielak, D.J. 1992. Theimmune system and hypertension. Hypertension, 19(1): 136-44.
13. Louis F. Rose, DDS, MD; D. Walter Cohen DDS; and Brian L. Mealey, DDS, MS, Periodontal Medicine (published in 2000 by BC Decker).
14. Kim, Y.M., M.Y. Kim, H.J. Kim, G.S. Roh, G.H. Ko, H.G. Seo, J.H. Lee and K.C. Chaang, 2011. Compound C independent of AMPK inhibits ICAM-1 and VCAM-1 expression in inflammatory stimulants-activated endothelial cells in vitro and in vivo, Atherosclerosis 219(1): 57-64.
15. Chiba T. and O. Ezaki, XXXX. Dietary restriction suppresses inflammation and delays the onset of stroke in stroke-prone spontaneously hypertensive rats, Biochemical and Biophysical Research Communications, 399(1): 98-103.
16. Kearney, P.M., M. Whelton, K. Reynolds, P. Muntner, P. K. Whelton and J. He, 2005. Global burden of hypertension: analysis of worldwide data, Lancet, 365(9455): 217-223.
17. Chobanian, A.V., G.L. Bakris and H.R. Black, 2003. The seventh report of the joint National Committee on Prevention, detection, evaluation and treatment of high blood pressure: the JNC 7 report, Journal of the American Medical Association, 289(19): 2560-2572.
18. Paster, B.J., S.K. Boches and J.L. Galvin, 2001. Bacterial diversity in human subgingival plaque, Journal of Bacteriology, 183(12): 3770-3783.
19. Paster, B.J., I. Olsen, J.A. Aas and F.E. Dewhirst, 2000. The breadth of bacterial diversity in the human periodontal pocket and other oral sites," Periodontology, 42(1): 80-87.
20. Panagakos F. and F. Scannapieco, 2011. Periodontal inflammation: from gingivitis to systemic disease? in Gingival Diseases: Their Aetiology, Prevention and Treatment, F. Panagakos and R. Davies, Eds., pp. 155-168, InTech.
21. Wakai, K., T. Kawamura, O. Umemura, Y. Hara, J. Machida, T. Anno, Y. Ichihara, Y. Mizuno, A. Tamakoshi, Y. Lin, T. Nakayama and Y. Ohno, 1999. Associations of medical status and physical fitness with periodontal disease, Journal of Clinical Periodontology, 26(10): 664-672.
22. Gołebiewska, M., K. Taraszkiewicz-Sulik, A. Kuklińska and W.J. Musial, 2006. Periodontal condition in patients with cardiovascular diseases, Advances in Medical Sciences, 51: 69-72.
23. Ogawa, Y., M. Imaki, Y. Yoshida, M. Matsumoto and S. Tanada, 1998. Epidemiological study on the relationship between hypertension and dental disease in Japanese factory workers, Sangyo Eiseigaku Zasshi, 40(6): 235-240.

24. Angeli, F., P. Verdecchia, C. Pellegrino C. Pellegrino R.G. Pellegrino, G. Prosciutti, L. Giannoni, C. Cianetti and S. Bentivoglio M, 2003. Association between periodontal disease and left ventricle mass in essential hypertension, Hypertension, 41(3): 488-492.
25. Taguchi, A., M. Sanada and Y. Suei, 2004. Tooth loss is associated with an increased risk of hypertension in postmenopausal women, Hypertension, 43(6): 1297-1300.
26. Inoue, K., Y. Kobayashi, H. Hanamura and S. Toyokawa, 2005. Association of periodontitis with increased white blood cell count and blood pressure, Blood Pressure, 14(1): 53-58.
27. D'Aiuto, F., M. Parkar, L. Nibali, J. Suvan, J. Lessem and M.S. Tonetti, 2006. Periodontal infections cause changes in traditional and novel cardiovascular risk factors: results from a randomized controlled clinical trial, American Heart Journal, 151(5): 977-984.
28. Völzke, H., C. Schwahn, M. DörrSchwarz, S. Robinson D, M. Dören and R. Rettig, 2006. Gender differences in the relation between number of teeth and systolic blood pressure, Journal of Hypertension, 24(7): 1257-1263.
29. Engström, S., L. Gahnberg, H. Högberg and K. Svärdsudd, 2007. Association between high blood pressure and deep periodontal pockets: a nested case-referent study, Upsula Journal of Medical Science, 112(1): 95-103.
30. Völzke, H., C. Schwahn, M. Dörr, N. Aumann, S.B. Felix John, U., R. Rettig and M. Dören, 2007. Inverse association between number of teeth and left ventricular mass in women, Journal of Hypertension, 25(10): 2035-2043.
31. Franek, E., E. Klamczynska, E. Ganowicz, A. Blach, T. Budlewski and R. Gorska, 2009. Association of chronic periodontitis with left ventricular mass and central blood pressure in treated patients with essential hypertension, American Journal of Hypertension, 22(2): 203-207.
32. Fujita, M., K. Ueno and A. Hata, 2009. Lower frequency of daily teeth brushing is related to high prevalence of cardiovascular risk factors, Experimental Biology and Medicine, 234(4): 387-394.
33. Nesse, W., P.U. Dijkstra and F. Abbas, 2010. "Increased prevalence of cardiovascular and autoimmune diseases in periodontitis patients: a cross-sectional study, Journal of Periodontology, 81(11): 1622-1628.
34. de Oliveira, C., R. Watt and M. Hamer, 2010. "Toothbrushing, inflammation and risk of cardiovascular disease: results from Scottish Health Survey, British Medical Journal, 340: 2451.
35. Morita, T., Y. Yamazaki and A. Mita, 2010. A cohort study on the association between periodontal disease and the development of metabolic syndrome, Journal of Periodontology, 81(4): 512-519.
36. Franek, E., M. Napora, A. Blach *et al*., 2010. Blood pressure and left ventricular mass in subjects with type 2 diabetes and gingivitis or chronic periodontitis, Journal of Clinical Periodontology, 37(10): 875-880.
37. Tsakos, G., W. Sabbah and A.D. Hingorani, 2010. Is periodontal inflammation associated with raised blood pressure? Evidence from a National US survey, Journal of Hypertension, 28(12): 2386-2393.
38. Desvarieux, M., R.T. Demmer and D.R. Jacobs Jr, 2010. Periodontal bacteria and hypertension: the oral infections and vascular disease epidemiology study (INVEST), Journal of Hypertension, 28(7): 1413-1421.
39. Zhang, L., Y.F. Li and Z.Z. Liang, 2011. The association between chronic periodontitis and hypertension in rural adult Uygur residents, Zhonghua Xin Xue Guan Bing Za Zhi, Atherosclerosis, 39(12): 1140-1144.
40. Vidal, F., C.M.S. Figueredo, I. Cordovil and R.G. Fischer, 2011. Higher prevalence of periodontitis in patients with refractory arterial hypertension: a case-control study, Oral Diseases, 17(6): 560-563.
41. Peres, M.A., G. Tsakos, P.R. Barbato, D.A.S. Silva and K.G. Peres, 2012. Tooth loss is associated with increased blood pressure in adults: a multidisciplinary population-based study, Journal of Clinical Periodontology, 39(9): 824-833.
42. Rivas-Tumanyan, S., M. Campos, J.C. Zevallos and K.J. Joshipura, 2013. Periodontal disease, hypertension and blood pressure among older adults in Puerto Rico, Journal of Periodontology, 84(2): 203-211.
43. Singh, M., G.A. Mensah and G. Bakris, 2010. Pathogenesis and clinical physiology of hypertension. Cardiol Clin., 28: 545-59.
44. Androulakis, E.S., D. Tousoulis and N. Papageorgiou, 2009. Essential hypertension: Is there a role for inflammatory mechanisms? Cardiol Rev., 17: 216-21.