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Research Progress on the Relationship Between Periodontitis and Hypertension

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Abstract

Being common and chronic diseases, periodontitis and hypertension share risk factors such as smoking, drinking, diabetes, etc. Many evidences have shown that there is a certain correlation between periodontitis and hypertension, but the interaction mechanism between them has not been clarified. This article reviews the research progress of the relationship between periodontitis and hypertension from the aspects of the correlation between periodontitis and hypertension, and the related mechanism between periodontitis and hypertension.

Keywords: periodontitis, hypertension, research progress

1. Introduction

Periodontal disease is a chronic inflammatory and infectious diseases caused by the fixed value of bacteria, which can lead to the destruction of periodontal support tissues (gingiva, periodontal ligament, alveolar bone, cementum), and with the progress of the disease, it can eventually lead to tooth loss (Tonetti MS, Greenwell H & Kornman KS, 2018). The fourth national oral health epidemiological survey report released in 2017 showed that among residents aged 35-44, the periodontal health rate was only 9.1% (Feng Xiping, 2018). At present, the global prevalence of Periodontal diseases is more than 50%, of which more than 10% suffer from severe Periodontal disease (Janakiram C & Dye BA, 2020).

Hypertension is a common chronic disease. According to the latest survey of hypertension epidemics in China, the prevalence rate of hypertension among residents aged 18 and above was 27.9% from 2012 to 2015. Compared with the past, the overall incidence rate is on the rise (Revision Committee of the Chinese Guidelines for the Prevention and Treatment of Hypertension, Hypertension Alliance (China), Chinese Society of Cardiovascular Diseases, et al, 2019). In addition, stroke and ischemic heart disease caused by hypertension remain the main causes of increased global mortality and significantly increase the economic burden on society (Mills KT, Bundy JD, Kelly TN, Reed JE, Kearney PM, Reynolds K, Chen J & He J, 2016).

In recent years, many domestic and foreign research evidences (Pietropaoli D, Del Pinto R, Ferri C, Wright JT Jr, Giannoni M, Ortu E & Monaco A, 2018; Muñoz Aguilera E, Suvan J, Buti J, Czesnikiewicz-Guzik M, Barbosa Ribeiro A, Orlandi M, Guzik TJ, Hingorani AD, Nart J & D'Aiuto F, 2020; Czesnikiewicz-Guzik M, Osmenda G, Siedlinski M, Nosalski R, Pelka P, Nowakowski D, Wilk G, Mikolajczyk TP, Schramm-Luc A, Furtak A, Matusik P, Koziol J, Drozdz M, Munoz-Aguilera E, Tomaszewski M, Evangelou E, Caulfield M, Grodzicki T, D'Aiuto F & Guzik TJ, 2019; Tsakos G, Sabbah W, Hingorani AD, Netuveli G, Donos N, Watt RG & D'Aiuto F, 2010; Pietropaoli D, Del Pinto R, Ferri C, Marzo G, Giannoni M, Ortu E & Monaco A, 2020; Machado V, Aguilera EM, Botelho J, Hussain SB, Leira Y, Proença L, D'Aiuto F & Mendes JJ, 2020; Guan Jing, Zhai Jianlong, Zhang Dong & Chen Shuzhen, 2022) show that Periodontal disease has a certain correlation with the occurrence of hypertension, and hypertensive patients have a higher susceptibility to Periodontal disease (Muñoz

Aguilera E, Suvan J, Buti J, Czesnikiewicz-Guzik M, Barbosa Ribeiro A, Orlandi M, Guzik TJ, Hingorani AD, Nart J, D'Aiuto F, 2020; Martin-Cabezas R, Seelam N, Petit C, Agossa K, Gaertner S, Tenenbaum H, Davideau JL & Huck O, 2016; Khocht A, Rogers T, Janal MN & Brown M, 2017). Although many studies have proved that Periodontal disease and hypertension can interact, further research is still needed to clarify the specific mechanism of interaction between them. Therefore, this article reviews the research progress of Periodontal disease and hypertension in order to provide new ideas for related research.

2. Correlation Between Periodontal Disease and Hypertension

2.1 Study on the Effect of Periodontal Disease on Blood Pressure

The pathogenesis of hypertension is complex, and now many evidences prove that there is a close relationship between Periodontal disease and hypertension.

2.1.1 Higher Mean Systolic Blood Pressure in Individuals with Periodontal Disease

Among various types of hypertension, the increase of systolic blood pressure is the most common and more difficult to control, and with the increase of systolic blood pressure, the risk of cardiovascular and cerebrovascular diseases is also increasing (Huang Jianfeng, Rachel P. Wildman, Gu Dongfeng, Paul Muntner & Su Shaoyong, 2005). Some research results show that the average systolic pressure of patients with Periodontal disease is 4.5 Millimetre of mercury higher than that of patients without Periodontal disease (Muñoz Aguilera E, Suvan J, Buti J, Czesnikiewicz-Guzik M, Barbosa Ribeiro A, Orlandi M, Guzik TJ, Hingorani AD, Nart J & D'Aiuto F, 2020). Other research results show that (Muñoz Aguilera E, Leira Y, Miró Catalina Q, Orlandi M, Czesnikiewicz-Guzik M, Guzik TJ, Hingorani AD, Nart J & D'Aiuto F, 2021), the average systolic pressure of patients with Periodontal disease is greater than or equal to 140 Millimetre of mercury, which is 0.1 to 2.5 times higher than that of patients without Periodontal disease, suggesting that the average systolic pressure of individuals with Periodontal disease is higher.

2.1.2 Individuals with Periodontal Disease Are Prone to Hypertension

Porphyromonas gingivalis is a common pathogen of Periodontal disease. Animal experiments have found that the immune response to Porphyromonas gingivalis can lead to endothelial dysfunction, elevated blood pressure, and vascular inflammation (Czesnikiewicz-Guzik M, Nosalski R, Mikolajczyk TP, Vidler F, Dohnal T, Dembowska E, Graham D, Harrison DG & Guzik TJ, 2019). Another study (Shen Daonan, Wu Yafei & Zhao Lei, 2021) found that high levels of anticardiolipin induced by gingivain and phosphoglycerate kinase can appear in the serum of some patients with Periodontal disease/ β 2 Glycoprotein 1 antibody. β Glycoprotein 1 can regulate platelet aggregation, affect endothelial function and promote the development of Atherosclerosis plaque. Meta analysis of 15 cross sectional studies and Case-control study abroad shows that moderate and severe Periodontal disease is associated with a higher incidence rate of hypertension, showing a positive linear correlation. The more severe Periodontal disease is, the longer the course of disease, the higher the risk of hypertension (Muñoz Aguilera E, Suvan J, Buti J, Czesnikiewicz-Guzik M, Barbosa Ribeiro A, Orlandi M, Guzik TJ, Hingorani AD, Nart J & D'Aiuto F, 2020). Weng Hong published Meta analysis results in China, showing that exposure to Periodontal disease can increase the risk of hypertension by 1.86 times (Weng Hong, Yan Jinzhu, Tian Guoxiang, Leng Weidong, Xia Lingyun & Zeng Xiantao, 2015).

Furthermore, age seems to be an influential factor. A large-scale epidemiological study on 102330 adult participants in the Paris Medical Center assessed whether oral health status was associated with hypertension risk (Darnaud C, Thomas F, Pannier B, Danchin N & Bouchard P, 2015), This phenomenon seems to indicate that young people suffering from Periodontal disease have a stronger relationship with hypertension than older people.

2.1.3 The Effect of Periodontal Therapy on Blood Pressure

Tonetti et al. found that basic periodontal treatment can lead to short-term acute systemic inflammatory reaction and endothelial dysfunction, but six months after treatment, the levels of C-reaction protein (CRP), Interleukin 6 and other inflammatory factors significantly decreased, and vascular endothelial function improved (Tonetti MS, D'Aiuto F, Nibali L, Donald A, Storry C, Parkar M, Suvan J, Hingorani AD, Vallance P & Deanfield J, 2007). Marta et al. also found that after enhanced periodontal treatment, the 24-hour average systolic and diastolic blood pressure in hypertensive patients significantly decreased by 7.5mmHg and 5.8mmHg, respectively, and periodontal treatment can improve vascular endothelial function (Czesnikiewicz-Guzik M, Osmenda G, Siedlinski M, Nosalski R, Pelka P, Nowakowski D, Wilk G, Mikolajczyk TP, Schramm-Luc A, Furtak A, Matusik P, Koziol J, Drozdz M, Munoz-Aguilera E, Tomaszewski M, Evangelou E, Caulfield M, Grodzicki T, D'Aiuto F & Guzik TJ, 2019). In addition, the research results of Qian Bing Zhou et al. show that intensive periodontal treatment is more conducive to reducing the blood pressure level and endothelial microparticle level of hypertension patients with Periodontal disease than general periodontal treatment, and propose that, while strengthening periodontal intervention, not adding antihypertensive drugs may be an effective means to reduce

the blood pressure of Periodontal disease patients (Zhou QB, Xia WH, Ren J, Yu BB, Tong XZ, Chen YB, Chen S, Feng L, Dai J, Tao J & Yang JY, 2017; Zhou Qianbing, Zhang Limin, Li Kunman, et al, 2019).

The above clinical studies suggest that periodontal treatment may help to reduce Hypotension by improving vascular endothelial function to some extent, and potentially reduce the need for additional drugs. However, some randomized clinical trials showed that periodontal treatment did not effectively improve the vascular status of patients with cardiovascular diseases (Saffi MAL, Rabelo-Silva ER, Polanczyk CA, Furtado MV, Montenegro MM, Ribeiro IWJ, Kampits C, Rösing CK & Haas AN, 2018). Therefore, more long-term and large-scale studies are needed to determine whether periodontal treatment is beneficial to the cardiovascular health of patients, and whether it can reduce the incidence rate and mortality of hypertension.

2.1.4 The Effect of Periodontal Disease on Antihypertensive Treatment

Davide et al. (Pietropaoli D, Del Pinto R, Ferri C, Wright JT Jr, Giannoni M, Ortu E & Monaco A, 2018) reviewed and analyzed the cross-sectional data of hypertension patients in the United States from 2009 to 2014. The results showed that the risk of failure of antihypertensive treatment for hypertension patients with Periodontal disease was significantly increased by about 20% compared with patients without Periodontal disease, indicating that the antihypertensive treatment with Periodontal disease might not be as effective as that without Periodontal disease. In addition, the research results also show that the severity of Periodontal disease also seems to affect the probability of treatment failure.

2.2 A Related Study on the Impact of Hypertension on Periodontium

2.2.1 Hypertensive Individuals Are Prone to Periodontal Disease

A study examined the gingival crevicular fluid levels of hypertensive patients (21 patients) and non hypertensive patients (26 patients), and the results showed that the clinical attachment loss (CAL) of periodontal tissue in hypertensive patients was almost twice that of the control group (Albush MM, Razan KK & Raed AD, 2013), suggesting that the periodontal conditions of hypertensive patients were generally poor, which could easily lead to Periodontal disease. In addition, Fumiaki et al. (Tokutomi F, Wada-Takahashi S, Sugiyama S, Toyama T, Sato T, Hamada N, Tsukinoki K, Takahashi SS & Lee MC, 2015) found through animal experiments that experimental Periodontal disease was also induced by Porphyromonas gingivalis. Compared with normal blood pressure rats, stroke prone spontaneous hypertensive rats are more likely to form Periodontal disease.

2.2.2 The Effect of Antihypertensive Drugs on Periodontium

Angiotensin converting enzyme inhibitors are commonly used antihypertensive drugs in clinical practice, mainly by inhibiting the angiotensin converting enzyme in the surrounding and tissue, resulting in a decrease in the production of angiotensin II. A study record analyzed the periodontal conditions of 30 patients taking angiotensin converting enzyme inhibitors (case group) and 35 patients taking non angiotensin converting enzyme inhibitors (control group) (Rodrigues M, Barbirato D, Luiz RR, Scharfstein J, Salles GF & Feres-Filho EJ, 2016). The results showed that the prevalence of chronic Periodontal disease in the case group was higher. The study also showed that taking ACE inhibitor may increase the severity of chronic Periodontal disease in patients. Amlodipine is a calcium antagonist, which can relax smooth muscle and achieve the purpose of lowering blood pressure by inhibiting the action of calcium Ion channel on smooth muscle. Its side effect is that it will cause gingival hyperplasia. Excessive gingival growth will provide a favorable environment for the accumulation of Dental plaque, and may become a risk factor to increase the severity of Periodontal disease (Lauritano D, Martinelli M, Baj A, Beltramini G, Candotto V, Ruggiero F & Palmieri A, 2019). In addition, a cross-sectional study showed that (Kim HJ, Shim KW, Na HS, Kim SY, Yu Y, Song Y, Lee HA, Lee JY, Lee JH & Chung J, 2022), the relative abundance of major periodontal pathogens in supragingival plaque of Periodontal disease patients taking antihypertensive drugs increased, especially some Przewalski bacteria, which may increase the severity of Periodontal disease. A common side effect of antihypertensive drugs is insufficient saliva secretion (Habbab KM, Moles DR & Porter SR, 2010), which may be one of the mechanisms leading to an increase in periodontal pathogens.

3. The Mechanism of Correlation Between Periodontitis and Hypertension

3.1 Possible Mechanism and Pathway of Hypertension Caused by Periodontal Disease

How Periodontal disease accelerates the occurrence and development of hypertension is still a research hotspot today. The current research mechanism mainly focuses on inflammatory reaction, endothelial dysfunction and other aspects, but the specific mechanism still needs further exploration.

3.1.1 Periodontal Pathogen

Porphyromonas gingivalis is the main periodontal pathogen, which can enter the Systemic circulation from the periodontal pocket when the gingival tissue is damaged, causing transient Bloodstream infections (Chen W, Alshaikh A, Kim S, Kim J, Chun C, Mehrazarin S, Lee J, Lux R, Kim RH, Shin KH, Park NH, Walentin K,

Schmidt-Ott KM & Kang MK, 2019). In addition, Porphyromonas gingivalis can invade the blood vessel wall, cause platelet aggregation, induce Cell adhesion molecule such as ICAM-1 (vascular cell adhesion molecule-1), VCAM-1 (vascular cell adhesion molecule-1), and P-selectin, E-selectin expression, thus activating vascular endothelial cells and damaging their functions, while promoting smooth muscle cell proliferation, ultimately leading to Vasodilation dysfunction, accelerate the occurrence and development of hypertension (Tsioufis C, Kasiakogias A, Thomopoulos C & Stefanadis C, 2011). In addition, the th1 type immune response of Porphyromonas gingivalis antigen can aggravate the hypertension response of angiotensin II and aggravate the inflammation of vascular wall, while the damage of vascular wall can lead to the hardening of Great vessels and the proliferation of small vascular intima media, thereby increasing blood flow resistance, damaging endothelial function, and ultimately leading to increased blood pressure (Czesnikiewicz-Guzik M, Nosalski R, Mikolajczyk TP, Vidler F, Dohnal T, Dembowska E, Graham D, Harrison DG & Guzik TJ, 2019).

3.1.2 Inflammatory Reaction

Experimental and observational evidence supports the important role of systemic inflammation in the occurrence and development of hypertension (Drummond GR, Vinh A, Guzik TJ & Sobey CG, 2019). When a patient suffers from Periodontal disease, Periodontal disease pathogens may invade gingival tissue and cause transient Bloodstream infections even during tooth brushing, and then cause systemic inflammation through Bloodstream infections transfer and diffusion, leading to vascular dysfunction, and promoting the occurrence and development of hypertension (Sandros J, Papapanou PN, Nannmark U & Dahlén G, 1994; Ashworth A, Cutler C, Farnham G, Liddle L, Burleigh M, Rodiles A, Sillitti C, Kiernan M, Moore M, Hickson M, Easton C & Bescos R, 2019). In addition, in the process of Periodontal disease, the host cells will be stimulated to produce CRP and tumor necrosis factor to varying degrees- α (tumor crossing factor)- α, TNF- α), IL-6, Interleukin-1 β Interleukin-1 β, IL-1 β) inflammatory factors enter the bloodstream (Leira Y, Carballo Á, Orlandi M, Aldrey JM, Pías-Peleteiro JM, Moreno F, Vázquez-Vázquez L, Campos F, D'Aiuto F, Castillo J, Sobrino T & Blanco J, 2020; Zare Javid A, Bazyar H, Gholinezhad H, Rahimlou M, Rashidi H, Salehi P & Haghighi-Zadeh MH, 2019; Hoare A, Soto C, Rojas-Celis V & Bravo D, 2019), and the elevated levels of various inflammatory factors in the circulation are closely related to elevated blood pressure (Jayedi A, Rahimi K, Bautista LE, Nazarzadeh M, Zargar MS & Shab-Bidar S, 2019). Xiao Shuai et al. (Xiao Shuai, Yu Jie, He Yang, Li Li & Liu Ling, 2022) studied and analyzed the infection concentration of Porphyromonas gingivalis and IL-1 in serum of 300 patients with Periodontal disease of different degrees β, the IL-6 level showed a positive correlation between the two. These phenomena suggest that inflammatory factors may be one of the mediators between the two diseases.

3.1.3 Endothelial Dysfunction

Endothelial dysfunction is also an important mechanism that can explain the relationship between Periodontal disease and hypertension. In the state of vascular endothelial dysfunction, a variety of vasoactive substances secreted by vascular endothelial cells are damaged, making Vasodilation factor unable to play its role, affecting the balance of vascular relaxation and contraction, and exacerbating the occurrence and development of hypertension. In the process of Periodontal disease, macrophages will be stimulated to secrete inflammatory factors such as IL-1 and IL-6, which will stimulate the proliferation of smooth muscle cells, and then induce liver cells to produce CRP. High concentrations of CRP in serum can damage vascular endothelial cells, cause the reduction of nitric oxide and Prostaglandin release, and lead to the weakening of vascular responsiveness to endothelium-dependent vasodilators, thus causing endothelial dysfunction and accelerating the occurrence and development of hypertension (Savoia C & Schiffrin EL, 2006); Simultaneously, vascular endothelial damage causes TNF- α release increase, TNF- α It also promotes the release of IL-6, while TNF- α. It has a synergistic effect with IL-6 and can produce immune complexes that deposit on the vascular endothelium, further damaging it (Savoia C & Schiffrin EL, 2006; Pérez L, Muñoz-Durango N, Riedel CA, Echeverría C, Kalergis AM, Cabello-Verrugio C & Simon F, 2017).

Vascular vasomotor factor nitric oxide and endotoxin 1 secreted by vascular endothelial cells are important factors that lead to hypertension and maintain vascular homeostasis. Some studies have shown that compared with patients without Periodontal disease, patients with Periodontal disease have higher levels of endotoxin 1 (Fujioka D, Nakamura S, Yoshino H, Shinohara H, Shiba H, Mizuno N, Hasegawa N, Shindoh N, Uchida Y, Ogawa T, Kawaguchi H & Kurihara H, 2003; Pradeep AR, Guruprasad CN, Swati P & Shikha C, 2008), which may lead to the disruption of vascular vasomotor homeostasis. In other studies, the vascular endothelial function of patients was evaluated by using ultrasound to evaluate the flow mediated dilation (FMD) of the brachial artery (Moura MF, Navarro TP, Silva TA, Cota LOM, Soares Dutra Oliveira AM & Costa FO, 2017). It was found that the FMD value of Periodontal disease patients was lower than that of healthy periodontal patients, suggesting that the endothelial dilation function of Periodontal disease patients was reduced.

3.1.4 Atherosclerosis

Atherosclerosis is recognized as one of the earliest detectable indicators of vascular injury, and is the common

pathophysiological basis for cardiovascular and cerebrovascular diseases in patients with hypertension or type 2 diabetes (Chistiakov DA, Orekhov AN & Bobryshev YV, 2016; Priyamvara A, Dey AK, Bandyopadhyay D, Katikineni V, Zaghlol R, Basyal B, Barssoum K, Amarin R, Bhatt DL & Lavie CJ, 2020; Sanz M, Marco Del Castillo A, Jepsen S, Gonzalez-Juanatey JR, D'Aiuto F, Bouchard P, Chapple I, Dietrich T, Gotsman I, Graziani F, Herrera D, Loos B, Madianos P, Michel JB, Perel P, Pieske B, Shapira L, Shechter M, Tonetti M, Vlachopoulos C & Wimmer G, 2020; Cho DH, Song IS, Choi J & Gwon JG, 2020). Some studies have shown that Porphyromonas gingivalis can promote the formation of Atherosclerosis by changing lipid metabolism and homeostasis (Chistiakov DA, Orekhov AN & Bobryshev YV, 2016). In addition, Periodontal disease, as a chronic inflammatory disease, its dilated periodontal blood vessels can promote the occurrence of Bloodstream infections (Priyamvara A, Dey AK, Bandyopadhyay D, Katikineni V, Zaghlol R, Basyal B, Barssoum K, Amarin R, Bhatt DL & Lavie CJ, 2020; Sanz M, Marco Del Castillo A, Jepsen S, Gonzalez-Juanatey JR, D'Aiuto F, Bouchard P, Chapple I, Dietrich T, Gotsman I, Graziani F, Herrera D, Loos B, Madianos P, Michel JB, Perel P, Pieske B, Shapira L, Shechter M, Tonetti M, Vlachopoulos C & Wimmer G, 2020). After a short period of Bloodstream infections, pathogens from periodontal sites circulate inside or outside Phagocyte and deposit in Atherosclerosis lesions (Cho DH, Song IS, Choi J & Gwon JG, 2020). Apolipoprotein E (APOE) is an important component of lipoproteins, so the APOE gene knockout mouse model is often used to study the relationship between Periodontal disease and cardiovascular disease. Kobayashi et al. (Kobayashi R, Hashizume-Takizawa T & Kurita-Ochiai T, 2021) further demonstrated that periodontal pathogens can accelerate Atherosclerosis in APOE mice by using the APOE gene knockout mouse model, and that pathogens and their products can transfer from oral flora to Atherosclerosis plaque. Other studies have shown that DNA, RNA or antigen from oral bacteria (mainly Periodontal disease pathogens) can be detected in the tissue forming Atherosclerosis thrombus (Cho DH, Song IS, Choi J & Gwon JG, 2020). These phenomena suggest that periodontal bacteria and their metabolites may participate in various stages of Atherosclerosis formation, thus affecting the occurrence of hypertension.

3.1.5 Insulin Resistance and Oxidative Stress

Insulin resistance is a risk factor for hypertension, and is positively correlated with the incidence rate of hypertension (Wang F, Han L & Hu D, 2017; Xun P, Liu K, Cao W, Sidney S, Williams OD & He K, 2012). Studies have found that endotoxin stimulation of Porphyromonas gingivalis can upregulate the pancreas β. The expression of immune inflammatory response related genes (Cd8a, Cd14, and icamI) and insulin signaling pathway related genes (G6pc and InsI3) in cell line MIN6 increases insulin secretion, leading to insulin resistance (Bhat UG, Ilievski V, Unterman TG & Watanabe K, 2014). In addition, animal experiments have confirmed that dysbacteriosis caused by Periodontal disease can promote the occurrence of insulin resistance in high-fat diet mice through adaptive immune response (Blasco-Baque V, Garidou L, Pomié C, Escoula Q, Loubieres P, Le Gall-David S, Lemaitre M, Nicolas S, Klopp P, Waget A, Azalbert V, Colom A, Bonnaure-Mallet M, Kemoun P, Serino M & Burcelin R, 2017). Therefore, insulin resistance may be the mediator between hypertension and Periodontal disease.

Oxidative stress is a situation where the balance between the production and inactivation of reactive oxygen species (ROS) is disrupted. During Periodontal disease, gram-negative bacteria and their toxic products in the subgingival microenvironment of patients can enter the periodontal tissue through the damaged and loose intrasulcus epithelium and spread around, resulting in a large number of ROS in inflammatory cells and vascular endothelial cells (He Lin-Lin, Yang Zhuo, Liu Cheng-Cheng & Ding Yi, 2017), and the body is prone to oxidative stress. Oxidative stress can directly damage vascular endothelial cells and vascular smooth muscle cells, change the redox state, increase the permeability of endothelial cells, stimulate inflammatory response, and stimulate the expression of growth factors, thus leading to aggravation of vascular damage, aggravation of endothelial function damage, and increase of Vasculitis response (Loperena R & Harrison DG, 2017; Montezano AC & Touyz RM, 2014). In addition, ROS can interfere with the insulin signaling pathway, causing insulin resistance, which in turn increases ROS levels and further damages metabolic and vascular factors in the insulin signaling pathway, thereby accelerating the occurrence and development of hypertension.

3.1.6 Matrix Metalloproteinase

Matrix metalloproteinase (MMPs) play a key role in the physiological remodeling and pathological damage of tissues. Tissue inhibitor of metalloproteinase-1 is the main inhibitor of MMPs, which is widely distributed and precisely regulates the activity and function of MMPs (Zhang F, Liu E, Radaic A, Yu X, Yang S, Yu C, Xiao S & Ye C, 2021; Mouzakiti E, Pepelassi E, Fanourakis G, Markopoulou C, Tseleni-Balafouta S & Vrotsos I, 2012). Periodontal disease will stimulate neutrophils to release a large number of Matrix metalloproteinase, which will imbalance with specific inhibitors, and then cause increased blood pressure (Türkoğlu O, Barış N, Tervahartiala T, Şenarslan Ö, Sorsa T & Atilla G, 2014).

3.2 Possible Mechanisms of Hypertension Promoting Periodontal Disease

If the increase of blood pressure is not well controlled, long-term hypertension will have increased resistance to peripheral blood circulation, resulting in poor microcirculation of periodontal tissue, which will lead to lack of nutrition, reduced oxygen utilization, and decreased ability to discharge metabolites, forming a favorable environment for the growth and reproduction of periodontal pathogens, thus causing Periodontal disease. At the same time, long-term hypertension will lead to increased inflammatory products, induce periodontal tissue destruction, and accelerate the occurrence of Periodontal disease (Moura MF, Navarro TP, Silva TA, Cota LOM, Soares Dutra Oliveira AM & Costa FO, 2017; Zhen Fang, Wang Jingyuan & Li Zhaoquan, 2016; Bonato CF, do-Amaral CC, Belini L, Salzedas LM & Oliveira SH, 2012; Demmer RT, Papapanou PN, Jacobs DR Jr & Desvarieux M, 2008). In addition, studies have shown that hypertension can significantly increase macrophage infiltration and pro-inflammatory cytokine expression in periodontal injury areas through signal transduction and transcriptional activator pathways, and aggravate Bone resorption and periodontal tissue destruction in Periodontal disease lesion areas (Wei W, Xiao X, Li J, Ding H, Pan W, Deng S, Yin W, Xue L, Lu Q, Yue Y, Tian Y, Wang M & Hao L, 2019), which may also be one of the mechanisms by which hypertensive individuals are prone to Periodontal disease.

3.3 Other

Periodontal disease and hypertension have many common risk factors, such as age, gender, race, smoking, obesity, diabetes, educational background, Socioeconomic status, etc. (Macedo Paizan ML & Vilela-Martin JF, 2014). In addition to these common factors, studies have shown that NLRP3 inflammatory bodies are related to the occurrence and development of Periodontal disease and Atherosclerosis (Lamkanfi M & Dixit VM, 2012), and Atherosclerosis and hypertension are mutually causal, suggesting that NLRP3 inflammatory bodies may also affect the occurrence of hypertension. As an important component of innate immunity, NLRP3 inflammatory bodies play an important role in the process of immune response and disease occurrence (Mao Kairui & Sun Bing, 2011). Therefore, as the core of inflammatory response, NLRP3 inflammatory bodies may provide new targets for the treatment of Periodontal disease and hypertension.

4. Conclusion

Periodontal disease is not only harmful to oral health, but also can promote the development of a variety of systemic diseases. Therefore, it is particularly important to pay attention to periodontal health. Hypertension, as one of the most common chronic diseases, poses a serious threat to people's health and a huge financial burden on healthcare. Therefore, the prevention and treatment of hypertension is also very important. Through the efforts of many scholars at home and abroad, more and more evidence proves that there is a correlation between Periodontal disease and hypertension, but the specific mechanism of the correlation is still unclear. Therefore, a larger sample, high-quality Cohort study and clinical intervention trial are needed to explore the specific mechanism between the two. In addition, the possible correlation between improving the periodontal environment and the prevention and treatment of hypertension also requires more research to confirm, which will be the focus of future research.

References

Albush MM, Razan KK, Raed AD, (2013). Effect of surgical and non-surgical periodontal debridement on vascular thrombotic markers in hypertensives. *J Indian Soc Periodontol, 17*(3), 324-9. doi: 10.4103/0972-124X.115654.

Ashworth A, Cutler C, Farnham G, Liddle L, Burleigh M, Rodiles A, Sillitti C, Kiernan M, Moore M, Hickson M, Easton C, Bescos R, (2019). Dietary intake of inorganic nitrate in vegetarians and omnivores and its impact on blood pressure, resting metabolic rate and the oral microbiome. *Free Radic Biol Med, 138*, 63-72. doi: 10.1016/j.freeradbiomed.2019.05.010.

Bhat UG, Ilievski V, Unterman TG, Watanabe K, (2014). Porphyromonas gingivalis lipopolysaccharide upregulates insulin secretion from pancreatic β cell line MIN6. *J Periodontol, 85*(11), 1629-36. doi: 10.1902/jop.2014.140070.

Blasco-Baque V, Garidou L, Pomié C, Escoula Q, Loubieres P, Le Gall-David S, Lemaitre M, Nicolas S, Klopp P, Waget A, Azalbert V, Colom A, Bonnaure-Mallet M, Kemoun P, Serino M, Burcelin R, (2017). Periodontitis induced by Porphyromonas gingivalis drives periodontal microbiota dysbiosis and insulin resistance via an impaired adaptive immune response. *Gut, 66*(5), 872-885. doi: 10.1136/gutjnl-2015-309897.

Bonato CF, do-Amaral CC, Belini L, Salzedas LM, Oliveira SH, (2012). Hypertension favors the inflammatory process in rats with experimentally induced periodontitis. *J Periodontal Res, 47*(6), 783-92. doi: 10.1111/j.1600-0765.2012.01496.x.

Chen W, Alshaikh A, Kim S, Kim J, Chun C, Mehrazarin S, Lee J, Lux R, Kim RH, Shin KH, Park NH, Walentin K, Schmidt-Ott KM, Kang MK, (2019). Porphyromonas gingivalis Impairs Oral Epithelial Barrier

through Targeting GRHL2. *J Dent Res, 98*(10), 1150-1158. doi: 10.1177/0022034519865184.

Chistiakov DA, Orekhov AN, Bobryshev YV, (2016). Links between atherosclerotic and periodontal disease. *Exp Mol Pathol, 100*(1), 220-35. doi: 10.1016/j.yexmp.2016.01.006.

Cho DH, Song IS, Choi J, Gwon JG, (2020). Risk of peripheral arterial disease in patients with periodontitis: A nationwide, population-based, matched cohort study. *Atherosclerosis, 297*, 96-101. doi: 10.1016/j.atherosclerosis.2020.02.012.

Czesnikiewicz-Guzik M, Nosalski R, Mikolajczyk TP, Vidler F, Dohnal T, Dembowska E, Graham D, Harrison DG, Guzik TJ, (2019). Th1-type immune responses to Porphyromonas gingivalis antigens exacerbate angiotensin II-dependent hypertension and vascular dysfunction. *Br J Pharmacol, 176*(12), 1922-1931. doi: 10.1111/bph.14536.

Czesnikiewicz-Guzik M, Osmenda G, Siedlinski M, Nosalski R, Pelka P, Nowakowski D, Wilk G, Mikolajczyk TP, Schramm-Luc A, Furtak A, Matusik P, Koziol J, Drozdz M, Munoz-Aguilera E, Tomaszewski M, Evangelou E, Caulfield M, Grodzicki T, D'Aiuto F, Guzik TJ, (2019). Causal association between periodontitis and hypertension: evidence from Mendelian randomization and a randomized controlled trial of non-surgical periodontal therapy. *Eur Heart J, 40*(42), 3459-3470. doi: 10.1093/eurheartj/ehz646.

Darnaud C, Thomas F, Pannier B, Danchin N, Bouchard P, (2015). Oral Health and Blood Pressure: The IPC Cohort. *Am J Hypertens, 28*(10), 1257-61. doi: 10.1093/ajh/hpv025.

Demmer RT, Papapanou PN, Jacobs DR Jr, Desvarieux M, (2008). Bleeding on probing differentially relates to bacterial profiles: the Oral Infections and Vascular Disease Epidemiology Study. *J Clin Periodontol, 35*(6), 479-86.doi: 10.1111/j.1600-051X.2008.01232.x.

Drummond GR, Vinh A, Guzik TJ, Sobey CG, (2019). Immune mechanisms of hypertension. *Nat Rev Immunol, 19*(8), 517-532. doi: 10.1038/s41577-019-0160-5.

Feng Xiping, (2018). Oral Health Status of Chinese Residents: The Fourth National Oral Health Epidemiological Survey in China. Chinese Preventive Dentistry Committee, Chinese Stomatological Association. *Proceedings of the 18th Annual Conference on Preventive Dentistry of the Chinese Stomatological Association*. Chinese Preventive Dentistry Committee, Chinese Stomatological Association, 2.

Fujioka D, Nakamura S, Yoshino H, Shinohara H, Shiba H, Mizuno N, Hasegawa N, Shindoh N, Uchida Y, Ogawa T, Kawaguchi H, Kurihara H, (2003). Expression of endothelins and their receptors in cells from human periodontal tissues. *J Periodontal Res, 38*(3), 269-75. doi: 10.1034/j.1600-0765.2003.00653.x.

Guan Jing, Zhai Jianlong, Zhang Dong, Chen Shuzhen, (2022). A cross-sectional study on the correlation analysis between periodontitis and blood pressure. *Journal of Modern Stomatology, 36*(01), 19-22.

Habbab KM, Moles DR, Porter SR, (2010). Potential oral manifestations of cardiovascular drugs. *Oral Dis, 16*(8), 769-73. doi: 10.1111/j.1601-0825.2010.01686.x.

Han CY, (2016). Roles of Reactive Oxygen Species on Insulin Resistance in Adipose Tissue. *Diabetes Metab J, 40*(4), 272-9. doi: 10.4093/dmj.2016.40.4.272.

He Lin-Lin, Yang Zhuo, Liu Cheng-Cheng, Ding Yi, (2017). Research progress on the relationship between periodontal microorganisms and metabolic syndrome. *International Journal of Stomatology, 44*(06), 642-646.

Hoare A, Soto C, Rojas-Celis V, Bravo D, (2019). Chronic Inflammation as a Link between Periodontitis and Carcinogenesis. *Mediators Inflamm, 2019*, 1029857. doi: 10.1155/2019/1029857.

Huang Jianfeng, Rachel P. Wildman, Gu Dongfeng, Paul Muntner, Su Shaoyong, (2005). A survey on the prevalence of simple systolic hypertension in adults in China. *Chinese Journal of Preventive Medicine*, (01), 8-11.

Janakiram C, Dye BA, (2020). A public health approach for prevention of periodontal disease. *Periodontol 2000, 84*(1), 202-214. doi: 10.1111/prd.12337.

Jayedi A, Rahimi K, Bautista LE, Nazarzadeh M, Zargar MS, Shab-Bidar S, (2019). Inflammation markers and risk of developing hypertension: A meta-analysis of cohort studies. *Heart, 105*(9), 686-692. doi: 10.1136/heartjnl-2018-314216.

Khocht A, Rogers T, Janal MN, Brown M, (2017). Gingival Fluid Inflammatory Biomarkers and Hypertension in African Americans. *JDR Clin Trans Res, 2*(3), 269-277. doi: 10.1177/2380084417694335.

Kim HJ, Shim KW, Na HS, Kim SY, Yu Y, Song Y, Lee HA, Lee JY, Lee JH, Chung J, (2022). Assessing the effect of antihypertensives on plaque microbiota in patients with periodontitis and hypertension using 16S rRNA sequencing: A cross-sectional study. *J Periodontol*. doi: 10.1002/JPER.22-0204.

Kobayashi R, Hashizume-Takizawa T, Kurita-Ochiai T, (2021). Lactic acid bacteria prevent both periodontitis and atherosclerosis exacerbated by periodontitis in spontaneously hyperlipidemic mice. *J Periodontal Res, 56*(4), 753-760. doi: 10.1111/jre.12874.

Lamkanfi M, Dixit VM, (2012). Inflammasomes and their roles in health and disease. *Annu Rev Cell Dev Biol, 28*, 137-61. doi: 10.1146/annurev-cellbio-101011-155745.

Lauritano D, Martinelli M, Baj A, Beltramini G, Candotto V, Ruggiero F, Palmieri A, (2019). Drug-induced gingival hyperplasia: An in vitro study using amlodipine and human gingival fibroblasts. *Int J Immunopathol Pharmacol, 33*, 2058738419827746. doi: 10.1177/2058738419827746.

Leira Y, Carballo Á, Orlandi M, Aldrey JM, Pías-Peleteiro JM, Moreno F, Vázquez-Vázquez L, Campos F, D'Aiuto F, Castillo J, Sobrino T, Blanco J, (2020). Periodontitis and systemic markers of neurodegeneration: A case-control study. *J Clin Periodontol, 47*(5), 561-571. doi: 10.1111/jcpe.13267.

Loperena R, Harrison DG, (2017). Oxidative Stress and Hypertensive Diseases. *Med Clin North Am, 101*(1), 169-193. doi: 10.1016/j.mcna.2016.08.004.

Macedo Paizan ML, Vilela-Martin JF, (2014). Is there an association between periodontitis and hypertension? *Curr Cardiol Rev, 10*(4), 355-61. doi: 10.2174/1573403x10666140416094901.

Machado V, Aguilera EM, Botelho J, Hussain SB, Leira Y, Proença L, D'Aiuto F, Mendes JJ, (2020). Association between Periodontitis and High Blood Pressure: Results from the Study of Periodontal Health in Almada-Seixal (SoPHiAS). *J Clin Med, 9*(5), 1585. doi: 10.3390/jcm9051585.

Mao Kairui, Sun Bing. (2011). Advances in the study of NLRP3 inflammatory vesicles. *Current Immunology, 31*(01), 1-4.

Martin-Cabezas R, Seelam N, Petit C, Agossa K, Gaertner S, Tenenbaum H, Davideau JL, Huck O, (2016). Association between periodontitis and arterial hypertension: A systematic review and meta-analysis. *Am Heart J, 180*, 98-112. doi: 10.1016/j.ahj.2016.07.018.

Mills KT, Bundy JD, Kelly TN, Reed JE, Kearney PM, Reynolds K, Chen J, He J, (2016). Global Disparities of Hypertension Prevalence and Control: A Systematic Analysis of Population-Based Studies From 90 Countries. *Circulation, 134*(6), 441-50. doi:10.1161/CIRCULATIONAHA.115.018912.

Montezano AC, Touyz RM, (2014). Reactive oxygen species, vascular Noxs, and hypertension: focus on translational and clinical research. *Antioxid Redox Signal, 20*(1), 164-82. doi: 10.1089/ars.2013.5302.

Moura MF, Navarro TP, Silva TA, Cota LOM, Soares Dutra Oliveira AM, Costa FO, (2017). Periodontitis and Endothelial Dysfunction: Periodontal Clinical Parameters and Levels of Salivary Markers Interleukin-1β, Tumor Necrosis Factor-α, Matrix Metalloproteinase-2, Tissue Inhibitor of Metalloproteinases-2 Complex, and Nitric Oxide. *J Periodontol, 88*(8), 778-787. doi: 10.1902/jop.2017.170023.

Mouzakiti E, Pepelassi E, Fanourakis G, Markopoulou C, Tseleni-Balafouta S, Vrotsos I, (2012). Expression of MMPs and TIMP-1 in smoker and nonsmoker chronic periodontitis patients before and after periodontal treatment. *J Periodontal Res, 47*(4), 532-42. doi: 10.1111/j.1600-0765.2011.01465.x.

Muñoz Aguilera E, Leira Y, Miró Catalina Q, Orlandi M, Czesnikiewicz-Guzik M, Guzik TJ, Hingorani AD, Nart J, D'Aiuto F, (2021). Is systemic inflammation a missing link between periodontitis and hypertension? Results from two large population-based surveys. *J Intern Med, 289*(4), 532-546. doi: 10.1111/joim.13180.

Muñoz Aguilera E, Suvan J, Buti J, Czesnikiewicz-Guzik M, Barbosa Ribeiro A, Orlandi M, Guzik TJ, Hingorani AD, Nart J, D'Aiuto F, (2020). Periodontitis is associated with hypertension: a systematic review and meta-analysis. *Cardiovasc Res, 116*(1), 28-39. doi: 10.1093/cvr/cvz201.

Pérez L, Muñoz-Durango N, Riedel CA, Echeverría C, Kalergis AM, Cabello-Verrugio C, Simon F, (2017). Endothelial-to-mesenchymal transition: Cytokine-mediated pathways that determine endothelial fibrosis under inflammatory conditions. *Cytokine Growth Factor Rev, 33*, 41-54. doi: 10.1016/j.cytogfr.2016.09.002.

Pietropaoli D, Del Pinto R, Ferri C, Marzo G, Giannoni M, Ortu E, Monaco A, (2020). Association between periodontal inflammation and hypertension using periodontal inflamed surface area and bleeding on probing. *J Clin Periodontol, 47*(2), 160-172. doi: 10.1111/jcpe.13216.

Pietropaoli D, Del Pinto R, Ferri C, Wright JT Jr, Giannoni M, Ortu E, Monaco A, (2018). Poor Oral Health and Blood Pressure Control Among US Hypertensive Adults. *Hypertension, 72*(6), 1365-1373.doi:10.1161/HYPERTENSIONAHA.118.11528.

Pradeep AR, Guruprasad CN, Swati P, Shikha C, (2008). Crevicular fluid endothelin-1 levels in periodontal health and disease. *J Periodontal Res, 43*(3), 275-8. doi: 10.1111/j.1600-0765.2007.01026.x.

Priyamvara A, Dey AK, Bandyopadhyay D, Katikineni V, Zaghlol R, Basyal B, Barssoum K, Amarin R, Bhatt DL, Lavie CJ, (2020). Periodontal Inflammation and the Risk of Cardiovascular Disease. *Curr Atheroscler Rep, 22*(7), 28. doi: 10.1007/s11883-020-00848-6.

Revision Committee of the Chinese Guidelines for the Prevention and Treatment of Hypertension, Hypertension Alliance (China), Chinese Society of Cardiovascular Diseases, et al, (2019). Chinese guidelines for the prevention and treatment of hypertension (2018 revised edition). *Chinese Journal of Cardiovascular Medicine, 24*(1), 24-56. doi: 10.3969/j.issn.1007-5410.2019.01.002.

Rodrigues M, Barbirato D, Luiz RR, Scharfstein J, Salles GF, Feres-Filho EJ, (2016). Effect of antihypertensive therapy with angiotensin-converting enzyme inhibitors on chronic periodontitis: A case-control study. *Oral Dis, 22*(8), 791-796. doi: 10.1111/odi.12551.

Saffi MAL, Rabelo-Silva ER, Polanczyk CA, Furtado MV, Montenegro MM, Ribeiro IWJ, Kampits C, Rösing CK, Haas AN, (2018). Periodontal therapy and endothelial function in coronary artery disease: A randomized controlled trial. *Oral Dis, 24*(7), 1349-1357. doi: 10.1111/odi.12909.

Sandros J, Papapanou PN, Nannmark U, Dahlén G, (1994). Porphyromonas gingivalis invades human pocket epithelium in vitro. *J Periodontal Res, 29*(1), 62-9. doi: 10.1111/j.1600-0765.1994.tb01092.x.

Sanz M, Marco Del Castillo A, Jepsen S, Gonzalez-Juanatey JR, D'Aiuto F, Bouchard P, Chapple I, Dietrich T, Gotsman I, Graziani F, Herrera D, Loos B, Madianos P, Michel JB, Perel P, Pieske B, Shapira L, Shechter M, Tonetti M, Vlachopoulos C, Wimmer G, (2020). Periodontitis and cardiovascular diseases: Consensus report. *J Clin Periodontol, 47*(3), 268-288. doi: 10.1111/jcpe.13189.

Savoia C, Schiffrin EL, (2006). Inflammation in hypertension. *Curr Opin Nephrol Hypertens, 15*(2), 152-8. doi: 10.1097/01.mnh.0000203189.57513.76.

Shen Daonan, Wu Yafei, Zhao Lei, (2021). Study on the role of periodontal pathogenic bacteria in the development of atherosclerosis. *Chinese Journal of Stomatology, 56*(06), 584-590.

Tokutomi F, Wada-Takahashi S, Sugiyama S, Toyama T, Sato T, Hamada N, Tsukinoki K, Takahashi SS, Lee MC, (2015). Porphyromonas gingivalis-induced alveolar bone loss is accelerated in the stroke-prone spontaneously hypertensive rat. *Arch Oral Biol, 60*(6), 911-8. doi: 10.1016/j.archoralbio.2015.02.012.

Tonetti MS, D'Aiuto F, Nibali L, Donald A, Storry C, Parkar M, Suvan J, Hingorani AD, Vallance P, Deanfield J, (2007). Treatment of periodontitis and endothelial function. *N Engl J Med, 356*(9), 911-20. doi: 10.1056/NEJMoa063186.

Tonetti MS, Greenwell H, Kornman KS, (2018). Staging and grading of periodontitis: Framework and proposal of a new classification and case definition. *J Periodontol, 89*(Suppl 1), S159-S172. doi: 10.1002/JPER.18-0006.

Tsakos G, Sabbah W, Hingorani AD, Netuveli G, Donos N, Watt RG, D'Aiuto F, (2010). Is periodontal inflammation associated with raised blood pressure? Evidence from a National US survey. *J Hypertens, 28*(12), 2386-93. doi: 10.1097/HJH.0b013e32833e0fe1.

Tsioufis C, Kasiakogias A, Thomopoulos C, Stefanadis C, (2011). Periodontitis and blood pressure: The concept of dental hypertension. *Atherosclerosis, 219*(1), 1-9. doi: 10.1016/j.atherosclerosis.2011.04.030.

Türkoğlu O, Barış N, Tervahartiala T, Şenarslan Ö, Sorsa T, Atilla G, (2014). Evaluation of systemic levels of neutrophilic enzymes in patients with hypertension and chronic periodontitis. *J Periodontol, 85*(7), 908-16. doi: 10.1902/jop.2013.130346.

Wang F, Han L, Hu D, (2017). Fasting insulin, insulin resistance and risk of hypertension in the general population: A meta-analysis. *Clin Chim Acta, 464*, 57-63. doi: 10.1016/j.cca.2016.11.009.

Wei W, Xiao X, Li J, Ding H, Pan W, Deng S, Yin W, Xue L, Lu Q, Yue Y, Tian Y, Wang M, Hao L, (2019). Activation of the STAT1 Pathway Accelerates Periodontitis in Nos3-/- Mice. *J Dent Res, 98*(9), 1027-1036.doi: 10.1177/0022034519858063.

Weng Hong, Yan Jinzhu, Tian Guoxiang, Leng Weidong, Xia Lingyun, Zeng Xiantao, (2015). Correlation between periodontal disease and the development of hypertension: A Meta-analysis based on an observational study. *Chinese Journal of Evidence-Based Cardiovascular Medicine, 7*(01), 16-19.

Xiao Shuai, Yu Jie, He Yang, Li Li, Liu Ling, (2022). Correlation between Porphyromonas gingivalis infection and serum HMGB1, IL-1β, IL-6 and periodontal clinical indicators in patients with chronic periodontitis. *Progress in Modern Biomedicine, 22*(05), 985-989. DOI:10.13241/j.cnki.pmb.2022.05.038.

Xun P, Liu K, Cao W, Sidney S, Williams OD, He K, (2012). Fasting insulin level is positively associated with incidence of hypertension among American young adults: a 20-year follow-up study. *Diabetes Care, 35*(7),

1532-7. doi: 10.2337/dc11-2443.

Zare Javid A, Bazyar H, Gholinezhad H, Rahimlou M, Rashidi H, Salehi P, Haghighi-Zadeh MH, (2019). The effects of ginger supplementation on inflammatory, antioxidant, and periodontal parameters in type 2 diabetes mellitus patients with chronic periodontitis under non-surgical periodontal therapy. A double-blind, placebo-controlled trial. *Diabetes Metab Syndr Obes, 12*, 1751-1761. doi: 10.2147/DMSO.S214333.

Zhang F, Liu E, Radaic A, Yu X, Yang S, Yu C, Xiao S, Ye C, (2021). Diagnostic potential and future directions of matrix metalloproteinases as biomarkers in gingival crevicular fluid of oral and systemic diseases. *Int J Biol Macromol, 188*, 180-196. doi: 10.1016/j.ijbiomac.2021.07.165.

Zhen Fang, Wang Jingyuan, Li Zhaoquan, (2016). Efficacy of basic periodontal treatment and maintenance therapy in elderly patients with periodontitis with hypertension. *Electronic Journal of General Stomatology, 3*(03), 45-47.

Zhou QB, Xia WH, Ren J, Yu BB, Tong XZ, Chen YB, Chen S, Feng L, Dai J, Tao J, Yang JY, (2017). Effect of Intensive Periodontal Therapy on Blood Pressure and Endothelial Microparticles in Patients with Prehypertension and Periodontitis: A Randomized Controlled Trial. *J Periodontol*, *88*(8), 711-722. doi: 10.1902/jop.2017.160447.

Zhou Qianbing, Zhang Limin, Li Kunman, et al, (2019). Intensive periodontal treatment reduces blood pressure levels in patients with normotensive hypertension combined with severe periodontitis. *Chinese Journal of Hypertension, 27*(1), 30-34.