Research Journal of Innovative Studies in Medical and Health Sciences
Volume 2, Issue 1, 2025, PP:01-16
www.aytinpublications.com

Research Article

Examination of the Association Between Periodontal Condition and Hypertension in Greek Adults: A Case – Control Study

Nikolaos Andreas Chrysanthakopoulos[1], Theodoros Marinakis[2]

[1] Dental Surgeon (DDSc), Oncologist (MSc), Specialized in Clinical Oncology, Cytology and Histopathology, Dept. of Pathological Anatomy, Medical School, University of Athens, Athens, Greece.
[2]Resident in Maxillofacial and Oral Surgery, 401 General Military Hospital of Athens, Athens, Greece.
PhD in Oncology (cand), Registrar in Dentistry, NHS of Greece.
[2]MD, Cardiologist, Registrar in Medicine, NHS of Greece.

***Corresponding Author:** Nikolaos Andreas Chrysanthakopoulos, Dental Surgeon (DDSc), Oncologist (MSc), Specialized in Clinical Oncology, Cytology and Histopathology, Dept. of Pathological Anatomy, Medical School, University of Athens, Athens, Greece.

Abstract

Background/Aim: It is well known that Periodontal Disease (PD) is a risk factor for diverse systematic diseases and disorders, such as Cardiovascular Disease, Diabetes Mellitus (DM), pulmonary diseases such as Chronic Obstructive Pulmonary Disease, Hypertension (HT), several types of Cancer, etc. The aim of the current case-control study was to examine the possible role of PD indices as risk factors of developing Hypertension in an adult population in Greece.

Material and Method: The research sample consisted of 158 males and 146 females, aged 45 to 75 years. 98 participants suffered from HT-case group, and 196 concerned the healthy ones-control group. PD clinical indices investigated were collected via a modified standardized questionnaire and an oral tissue clinical examination. Periodontal condition comprised the following clinical variables, probing pocket depth (PPD), clinical attachment loss (CAL), plaque index (PlI), and gingival index (GI). Univariate and logistic regression models adjusted for possible confounders were applied for data analysis.

Results: Statistical analysis revealed that advanced age (p= 0.062, OR=1.457, 95% CI=0.8652.314), smoking (p= 0.032, OR= 2.117, 95% CI= 1.022-3.167), increased BMI (p=0.058, OR= 1.429, 95% CI= 0.995-2.518), presence of DM (p=0.000, OR=2.270, 95% CI=1.146-4.231), family history HT presence (p=0.036, OR= 2.076, 95% CI=1.058-3.289), gingival inflammation (GI) (p= 0.049, OR= 1.814, 95% CI= 1.019-3,123), and plaque accumulation (PlI) (p= 0.032, OR= 2.090, 95% CI=1.105-3.583) were statistically significantly associated with the risk of developing HT.

Conclusions: The present case-control study recorded positive associations of advanced age, smoking, increased BMI, presence of DM and HT family history, gingival inflammation (GI), and dental plaque accumulation (PlI) with HT development.

Keywords: Periodontal disease, Blood Pressure, Hypertension, Oral microbiota, Gut microbiota

Article Information

Recieved: 11 April 2025

Accepted: 05 May 2025

Published: 20 May 2025

Cite this article as:

Nikolaos Andreas Chrysanthakopoulos, Theodoros Marinakis. Examination of the Association Between Periodontal Condition and Hypertension in Greek Adults: A Case – Control Study. Research Journal of Innovative Studies in Medical and Health sciences, 2025;2(1); 01.

Introduction

Hypertension (HT) is a worldwide public health, and a significant risk factor for Cardiovascular Disease (CVD), increases all-cause morbidity and mortality [1], and is responsible for 10.4 million deaths each year [2]. A rate of 33% worldwide suffers from HT, and premature deaths attributed to HT increased by 56.1% in the past decade[3]. The American College of Cardiology/ American Heart Association guidelines in 2017 declared that the overall crude prevalence of HT in American adults was assessed to be 45.6% [4]. It is also estimated that more than 30% of the overall population suffers from HT, and this assessment increases with age [5]. A ratio between 15% and 50% of individuals are not aware that are affected by HT [6], whereas many of those with a confirmed diagnosis are not able to control their blood pressure despite their prescribed medications [5]. Raised arterial blood pressure increases the risk of CVD, and complications such as stroke and myocardial infarction [7], as more than 7.6 million deaths accounted for every year and 143 million disability-adjusted life-years [8]. HT also consists a serious problem for social resources and a significant economic burden on society [9].

HT etiology still remains indistinct despite the fact that a large amount of epidemiological and clinical researches have been carried out [10]. It has been detected that gut microbiota consists a critical environmental factor for HT occurrence and progression [11]. However, it remains unclear whether other microbial flora types such as oral microbiota also plays an essential role in HT etiopathogenesis [12]. Inflammation is regarded an important factor of vascular dysfunction and is involved in the HT development and progression [13].

Periodontal Disease (PD) consists a wide spectrum of oral diseases with high prevalence globally [14]. Especially, periodontitis is the 6th most prevalent disease in the world, affecting about 50% of the population [15]. Despite the fact of its high prevalence, periodontitis is not taken seriously enough in an early period, and many patients requesting for treatment are in advanced stages of the disease. Approximately 11% of the world population suffers from severe form of periodontitis [16], whereas almost 750 million individuals, aged 15-99 years, worldwide suffer from moderate to severe periodontitis [17].

Periodontitis as a chronic inflammatory disease caused by a dysbiotic biofilm and affects the periodontal tissues around teeth [18]. In addition, oral dysbiosis is also associated with systemic disease and disorders [19]. To be more specific, the disease is associated with periodontal microbiota dysbiosis [20] and host immune response dysregulation [21]. Periodontal dysbiosis expresses the conversion from a symbiotic to a dysbiotic microbial micro-environment, resulting in the transition from a periodontal healthy status to an inflammatory one [22]. Moreover, genetic and host immunological mechanisms seem to play an essential role in periodontitis pathogenesis [23].Periodontal infection does not affect only oral health but is also associated with a number of systemic diseases and disorders as more than 50 systemic diseases have been linked with PD [24].

Specific periopathogens, such as *Porphyromonas, Treponema, Eubacterium*,*Campylobacter,* and *Tannerella,* have been detected at great levels in periodontitis locations, whereas other species, such as *Actinomyces, Neisseria,Corynebacterium,Veillonella*, and *Rothia,* were highly dominant in the healthy gingival sulcus [25]. *Porphyromonas gingivalis, Treponema denticola, and Tannerella forsythia*, known as the red-complex may play a critical role during the transition from periodontal health to disease [26].

The disease is characterized by a systematic chronic low-grade infection burden. Evidencebased data has recorded that periodontitis is also a risk factor involved in multiple systemic CVDs, such as HT, Diabetes Mellitus (DM), and stroke [27,28]. As mentioned CVDs are the major public health problems in both developed and developing countries [7]. CVD risk is increased in periodontitis patients [16], whereas there is a consistent association between oral health status and CVD [29].

Poor oral hygiene and PD, gingivitis and periodontitis, have been associated with the risk of HT [29-33], and diverse studies have found a significant positive association between PD and HT [34,35]. Moreover, recent evidence suggests a possible causal association between periodontitis and HT [33]. Periodontitis patients often have higher arterial blood pressure values and a ratio between 30% and 70% higher possibility to also suffer from HT [35], especially in case that active gingival inflammation is present, e.g. gingival bleeding [36]. Cross-sectional studies have recorded that PD patients have higher blood pressure, and that more increased blood pressure levels have been detected in patients with more severe PD [37]. In addition, it has been observed that a comprehensive PD treatment decrease blood pressure [10]. To be more specific, blood pressure reduction has been associated with the Probing Pocket Depth (PPD) decrease, as PPD reduction leads to periodontal status improvement, finding that suggests a causal association between PD and HT [33]. On the contrary, similar studies have led to controversial outcomes [35], whereas other studies showed no association [38-40].

The mentioned controversial outcomes could be attributed

to the weakness or non-existence of an association between periodontal status and blood pressure or obvious HT, possible differences between study populations as regards to its characteristics, and variation in how confounders have been controlled for. Smoking is a known confounding factor and a common risk factor for several diseases, such as CVDs [41-43], different types of cancer [44] and oral diseases, PD in particular [45,46]. The fact that smoking is a risk factor for periodontitis and a number of systemic diseases creates problems when examining PD-systemic disease associations. However, large interventional and longitudinal surveys confirming the nature of the mentioned association and the exact pathogenetic mechanisms have not been carried out.

The oral-gut microbial transmission role in systemic diseases has been investigated. Recent data suggested that oral microbes translocate to and then colonize in the intestine and that the oral cavity is considered as an endogenous reservoir for gut micobiota [47]. Moreover, a raised ectopic oral microbes colonization in the gut has been associated with diverse diseases, such as cirrhosis [48], rheumatoid arthritis[49], inflammatory bowel disease [50], and Alzheimer's Disease [51]. However, it is unclear whether oral-gut microbial transmission plays a crucial role in HT development. A possible biological mechanism for the mentioned association is that the inflammatory mediators released into the local periodontal tissues could enter the blood circulation and contribute to a systemic low-grade chronic inflammation which has been associated with an increased risk for CVD [52]. This is mainly attributed to the low-grade systemic chronic inflammation which is characterized by increased levels of interleukin-6 (IL-6), C-reactive protein (CRP), and fibrinogen [53].

In Greece, no previous epidemiological studies have been carried out for examining the possible association between PD indices and risk of HT developing. The aim of the current case-control survey was to investigate the possible relationship between PD variables, and risk of developing HT in a sample of Greek adults.

Materials and Methods

Study Design And Population Sample

The study sample consisted of 294 individuals, 158 males and 136 females, 45 to 75 years old, and was carried out between March and December 2024. The study size was assessed according to HT [54] prevalence and the EPITOOLS guidelines (https://epitools.ausvet.com.au) determined with 95% Confidence Interval (CI) and desired power 0.8. Age group assessment of was based on the World Health Organization (WHO) recommendations for evaluating periodontal status incidence [55]. The sample was consisted of 98 individuals suffered from HT-Cases and 196 healthy ones-Controls.

The participants were outpatients of a pathology clinic (50%) and patients of two private practices, one dental (25%) and one medical (25%). This sample selection was applied in order to create a possible representative study sample, without possible selection biases.

Cases and Controls Inclusion and Exclusion Criteria

The selection criteria of the participants comprised a number of more than 15 teeth and periodontitis from stage I to IV, since large numbers of missing teeth could lead to over or underestimate the periodontal status variables and the possible associations that are under examination[56].

The basic criterion for a subject to be selected in the study protocol was the question by a specific pathologist, "Have you ever been told by a medical doctor or other health professional that you suffer from hypertension, also called high blood pressure?"/ "are you now taking prescribed medicine for high blood pressure?" or if they had a high biological measurement value (systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg) [57]. Additional data regarding the participants medical history were collected by their own personal medical files. Exclusion criteria concerned active infectious diseases, such as active tuberculosis, hepatitis, HIV, any confirmed systemic diseases such as cardiovascular, liver, kidney diseases, cancer, or any chronic/systemic medication, pregnant or breastfeeding, and taking non-steroid anti-inflammatory drugs on a regular basis or antibiotics within 3 months of assessment [58]. Moreover, they should not have been cured by a conservative or a surgical process in their periodontal tissues in the last 6 months.

Cases and controls were obtained from the same social environment, friendly and collegial, were resident of the same geographical region, and were presented to routine health follow-up at the mentioned practices. In addition, they were matched for age, gender, and smoking status, as age [59], gender [60], and smoking history [61] have been suggested to be as the main risk factors for Periodontitis, and HT development as covariates according to epidemiological studies [62].

The present case-control study was not an experimental one and was not approved by authorized committees (Health Ministry, Dental Committees, etc.). All participants were informed about the aims/methods and significance of the survey, and gave their written consent to enroll in the study protocol.

Covariates

Before the periodontal tissues examination, all individuals filled a modified Medical Questionnaire [63]. Potential confounding factors for adjustment were age, gender, smoking status (active smokers/non smokers), educational and socio-economic status, Body Mass Index (BMI) and data regarding the general medical history with reference to medication and several chronic systemic disorders.

The age was categorized as 45-50, 51-60, 61-70,71+, socio-economic status as ≤ 1,000 and > 1,000 €/month, educational status as elementary level and graduated from University/College, and cigarette smoking status was categorized as never (individuals who smoked <100 cigarettes during their lifetime), and former (those who smoked at least 100 cigarettes in their lifetime and stated that they now smoke "not at all")/current smokers (those who smoked at least 100 cigarettes in their life-time and stated they now smoke "every day" or "some days"). Body Mass Index (BMI) was classified as normal (<30 Kg/m^2) and high (≥30 Kg/m2), and is regarded as a risk factor for HT development [64].

The intra-examiner variance assessment concerned a sample of 60 (20%) individuals that was chosen randomly and re-examined clinically by the same dentist after three weeks, and no significant differences were observed between the 1st and the 2nd clinical examination *(Cohen's Kappa =0.97*). No oral hygiene instructions were given to the participants for the mentioned period of three weeks.

Periodontal Status assessment

The periodontal status examinations were carried out in the dental practice using a Williams (with a controlled force of 0.2N (DB764R, Aesculap AG &Co. KG,) periodontal probe, mouth mirror, tissue forceps, and dental light source. Remain roots and third molars were excluded from scoring. The periodontal examination focused on periodontal health status and concerned assessment of probing pocket depth (PPD), clinical attachment loss (CAL), plaque index (PlI), and gingival index (GI). All PD indices were recorded at four sites per tooth (mesio-lingual, distolingual, distobuccal, and mesio-buccal) in all quadrants and the worst values of the indices assessed for the nearest 1.0 mm, and coded as dichotomous variables.

PPD was classified as 0-3.00 mm (absence of disease/mild disease) and ≥ 4.0 mm (moderate and severe disease) for mean PPD [65], the severity of attachment loss (CAL) was classified as mild, 1.0-2.0 mm of attachment loss and moderate/severe, ≥ 3.0mm of attachment loss [66].

Gingivitis severity classified as: score 0-normal gingiva/ mild inflammation, slight change in color, slight edema, no bleeding on probing, which corresponds to Löe and Silness [67] classification as score 0 and 1 respectively; score 1-moderate inflammation, edema, redness and glazing, bleeding on probing/severe inflammation, marked edema and redness, ulceration, tendency to spontaneous bleeding, which corresponds to Löe classification as score 2 and 3 respectively [67].

Plaque Index (PlI), by Silness and Löe [68] was recorded by the same probe at the mentioned sites.Dental plaque presence was determined whether it was visualized with naked eye or existed abundance of soft matter within the gingival pocket and/or on the tooth and gingival margin (score 2 and 3, respectively, according to PlI) and regarded as present if at least one site showed the characteristic sign.

Statistical Analysis

The univariate analysis model was applied to estimate the association between the independent indices examined and the HT risk, separately. Categorical data were presented as frequencies and percentages. Cohort-related variables, such as sociodemographic factors (gender, age, socio-economic status, educational level), comorbidities (HT family history, increased BMI, presence of DM, were analyzed using the univariate model (Table 1),whereas the multivariate logistic regression analysis model was applied to estimate the associations between the dependent variable, HT, and independent ones using the Enter method, whereas the Stepwise method was carried out to assess the significant associations among the variables examined.Unadjusted and Adjusted Odds Ratios (OR's) and 95% (Confidence Interval) CI were also assessed (Table 2).

The data analysis was carried out using the statistical package of social sciences (SPSS) ver. 20.0 (SPSS Inc., Chicago, IL, USA), whereas a p-value less than 5% ($p < 0.05$) was regarded to be statistically significant.

Results

The mean age of the study sample was 64.5 ± 3.8 years. Table 1 shows the epidemiological variables of individuals which suffer from HT and healthy individuals after carrying out the univariate analysis model. Advanced age ($p<0.001$), presence of DM ($p<0.001$) and HT family history ($p<0.001$), CAL ≥ 3.0 mm ($p=0.048$), gingival inflammation (GI) ($p<0.001$), and dental plaque accumulation (PlI) ($p<0.001$) were statistically significantly associated with the risk of HT developing. Unadjusted Odds Ratio and 95% Confidence Interval (CI) for each variable examined. Table 2 presents the outcomes after performing the multivariate logistic regression model (step 1[a] and step 7[a], Enter and Wald, respectively). According

Table 1. *Characteristics of overall participants according to hypertension status (Univariate analysis model)*

Variables	Cases	Controls	p-value	Odds Ratio and 95% Confidence Interval
Gender				
Males	55 (56.1)	103 (52.6)	0.563	1.155 (0.709-1.881)
Females	43 (43.9)	93 (47.4)		
Age				
45-49	11 (11.2)	29 (14.8)		
50-59	46 (46.9)	45 (23.0)	**0.000***	_____
60-69	25 (25.5)	82 (41.8)		
70+	16 (16.3)	40 (20.4)		
HT family history				
Absence	36 (36.7)	118 (60.2)	**0.000***	2.605 (1.580-4.298)
Presence	62 (63.3)	78 (39.8)		
Education level				
Low	55 (56.1)	116 (59.2)	0.616	0.882 (0.540-1.440)
High	43 (43.9)	80 (40.8)		
Socio-economic status				
Low	58 (59.2)	112 (57.1)	0.738	1.088 (0.665-1.779)
High	40 (40.8)	84 (42.9)		
Smoking				
No smokers	40 (40.8)	92 (46.9)	0.320	0.780 (0.477-1.274)
Previous/current smokers	58 (59.2)	104 (53.1)		
Body Mass Index				
<30 kg/m^2	42 (42.9)	106 (54.1)	0.070	0.637 (0.391-1.038)
≥30 kg/m^2	56 (57.1)	90 (45.9)		
Diabetes Mellitus				
Yes	60 (61.2)	62 (31.6)	**0.000***	3.413 (2.058-5.659)
No	38 (38.8)	134 (68.4)		
Probing pocket depth				
0-3.00 mm	45 (45.9)	102 (52.0)	0.387	0.782 (0.481-1.272)
≥ 4.0 mm	53 (54.1)	94 (48.0)		
Clinical Attachment Loss				
1.00-2.00 mm	42 (42.9)	108 (55.1)	**0.048***	0.611 (0.375-0.997)
≥ 3.0 mm	56 (57.1)	88 (44.9)		
Gingival Index				
Absence/Mild	35 (35.7)	121 (61.7)	**0.000***	0.344 (0.208-0.570)
Moderate/Severe	63 (64.3)	75 (38.3)		
Plaque Index				
Absence	37 (37.8)	118 (60.2)	**0.000***	0.401 (0.244-0.660)
Presence	61 (62.2)	78 (39.8)		

* p-value statistically significant

to that model, the final step (Wald) showed that advanced age (p=0.062), presence of DM (p<0.001) and HT family history (p= 0.036), smoking (p=0.032), increased BMI (p=0.058), gingival inflammation (GI) (p=0.049), and dental plaque accumulation (PlI) (p=0.032) were statistically significantly associated with the risk of HT developing. Table 2 also presents Unadjusted Odds Ratio and 95% CI for each variable examined.

Discussion

After adjustment for confounding factors, individuals with poor oral health or PD, as expressed by GI and PlI showed

Table 2. *Presentation of association between potentially risk factors and HT according to Enter (first step-1a) and Wald (last step 7a) method of multivariate logistic regression analysis model*

Variables in the Equation									
		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	gender	,083	,287	,082	1	,774	1,086	,618	1,907
	Age	,275	,150	3,364	1	**,067***	1,160	,766	1,819
	smok.status	,161	,296	3,146	1	**,051***	1,241	,938	2,046
	socioec.status	,178	,311	4,070	1	**,033***	1,581	,909	2,419
	educ.level	,155	,292	,282	1	,596	1,168	,658	2,071
	BMI	,883	,338	6,841	1	**,079***	1,313	,713	1,801
	diab.mellit	1,343	,324	17,174	1	**,000***	1,961	1,238	3,493
	fam.hist.HT	,749	,337	4,935	1	**,055***	1,514	,992	3,094
	prob.pock.dep	,144	,378	,146	1	,703	1,105	,551	2,124
	clin.att.loss	,017	,380	,002	1	,964	,983	,467	2,068
	ging.index	,768	,334	5,297	1	**,041***	1,656	1,011	3,118
	plaque.index	,720	,308	5,457	1	**,039***	1,954	1,023	3,256
	Constant	,313	,490	,408	1	,523	,731		
Step 7[a]	Age	,288	,149	3,486	1	**,062***	1,457	,865	2,314
	smok.status	,732	,311	5,388	1	**,032***	2,117	1,022	3,167
	BMI	,874	,330	6,599	1	**,058***	1,429	,995	2,518
	diab.mellit	1,408	,315	17,288	1	**,000***	2,270	1,146	4,231
	fam.hist.HT	,792	,322	5,839	1	**,036***	2,076	1,058	3,289
	ging.index	,805	,305	6,813	1	**,049***	1,814	1,019	3,123
	plaque.index	,787	,303	5,936	1	**,032***	2,090	1,055	3,583
	Constant	,417	,582	,423	1	,570	,805		

a. Variable(s) entered on step 1: gender, age, smok.status, socioec.status, educ.level, BMI, diab.mellit, fam.hist.HT, prob.pock. dep, clin.att.loss, ging.index, plaque.index.

* p-value statistically significant

a higher ORs for HT. It was also identified an association between advanced age, increased BMI, smoking, presence of HT family history and DM with an increased risk of HT development. PD as a chronic infectious disease has been associated with diverse systemic diseases and disorders [69,70].

Gender is a known HT risk factor as is overall more common in males [71] , however it is considered as a confounder. The results revealed no association between gender and HT risk, finding that was not in accordance with those from previous reports [28,71-73].

It is also known that older individuals are in a higher risk for HT development [73], however age is also considered as a confounder. It has been suggested that advanced age is an important factor in the pathogeneses of HT [4,28,74,75], finding which was in agreement with that of the current study.

Other crucial confounders are socio-economic status (SES) and educational level, however, it has been proven their possible role in HT development. Individuals with lower education and income status showed higher mortality and incidence rates than the more well-off ones, with a high risk being particularly significant for HT. Low SES is associated with higher blood pressure (BP), and this association is notably evident in the level of education [28,76]. SES is conversely associated with the incidence of HT in mostly developed [77,78], and in developing nations [79].

On the other hand, data from Trinidad and Tobago [80] showed no association between SES and HT, whereas in southwest China a negative association recorded between SES and HT incidence among adults [81]. Similarly, HT and uncontrolled high BP were more prevalent among less-educated older individuals than those with higher educational level [28,82-84]. Those findings suggested that the mentioned association varies in different countries. In the present research no associations were recorded between those variables and HT risk.

The HT family history presence was found to be significantly associated with the HT risk in the current survey, finding that was in accordance with those from previous reports [85-87]. Obesity and increased BMI have been linked with many systemic diseases including HT [28,64, 88,89]. The present research confirmed such an association. In a similar way, smoking is a causal risk factor of diverse systemic diseases. In addition, exposure to tobacco smoke has been associated with mutational or epigenetic alterations in cellular signaling pathways, which may are involved in HT pathogenesis, as it has

been suggested that smoking is another important factor in the pathogenesis of HT [28,30], findings which were in accordance with those of the current study.

Diabetes Mellitus (DM) has been associated with PD [28,90,91]. The current research confirmed that association. PD, and especially periodontitis significantly increases the risk of cardiovascular diseases (CVDs), which makes it a modifiable non classical CV risk factor [92]. Arterial HT and periodontitis often coexist [28], as it has been found that HT occurs in 7-77% of patients with periodontitis (vs 4-70% in general population) [35]. Recent studies have shown significant associations between periodontitis and HT, by increasing the systolic and diastolic BP [35,37, 93-100].

On the contrary, in another prospective cohort of male professionals (dentists, pharmacists, optometrists, etc.) in the United States, there was no significant association between self-reported PD at baseline and the occurrence of HT at 20 years of follow-up (RR= 1.04, 95% CI =0.98-1.10) [38]. In addition, few longitudinal studies have been carried out to date, often with inconsistent results, as reported by Surma et al. [101]. Some researches have recorded a temporal association between periodontitis and the incidence of high BP [102], but others have found no association between periodontitis and any risk factors for CVD [103,104].

The possible explanation for the conflicting results could be attributed to differences in the study samples in relation to age, gender, SES, ethnic background, and health behavior concerning smoking habits, the extent and severity of PD and how PD and elevated BP or apparent HT have been defined. In most cases the confounding effect of smoking has been taken into account applying multivariate regression models with a non-quantitative smoking variable [32,35, 40, 105]. In other similar reports the confounding effect of smoking has been removed by excluding smokers [39,106,107]. Among the PD indices examined, GI was found to be statistically significantly associated with the risk for HT development, finding that was in agreement with that of a previous study [108]. GI expresses the gingival inflammation severity [67], however that index is not frequently used in epidemiological studies despite the fact that assesses the gingival tissue inflammatory load.

Desvarieux et al. also observed that systolic and diastolic BP increased with increasing bacterial load and the subgingival plaque [32]. PlI by Silness and Löe [68] assesses dental plaque accumulation. In a previous study it was found that poor oral hygiene, as reflected in the amount of dental plaque, was associated with increased HT [109]. Moreover, the high bacterial load on tooth surfaces and in gingival pockets over a prolonged time could play a role in its pathogenesis [104]. A significant association between PlI and risk for HT was recorded in the current study, finding that was in agreement with a previous report [108]. HT has also been associated with high level of dental plaque [OR = 1.90, 95% CI = 1.55-2.33], dental calculus [OR =1.18, 95% CI = 1.07-1.29] and gingival inflammation [OR = 1.56, 95% CI= 1.35-1.80], as expressed by MGI (modified GI) and PlI [110]. PPD is an index for assessing PD severity [111], and the outcomes showed that was not statistically significantly associated with the risk for HT development, finding that was in accordance with that of another research which conducted on 376 individuals diagnosed with periodontitis, and most of them did not have HT (240 patients, 63.8%) [112], however the same article showed a statistically significant difference between PPD measurements in individuals with different HT categories (p = 0.016, effect size= 0.009). On the contrary, similar reports showed that deep periodontal pockets were associated with HT development [105,108,113-116].

CAL is another PD crucial index of cumulative tissue destruction, concerning previous PD exacerbations, whereas PPD is an indicator of current disease status inflammation [117]. PPD and CAL concern the chronic inflammation long-term stages including destructive processes signs of a chronic inflammatory response [118]. The outcomes showed no association between CAL and the risk for HT development. However, Yildirim et al. observed that CAL was associated with an increased risk of HT [108], whereas in a similar research was recorded that CAL was 6.24 times (AOR=6.24, 95% CI= 1.99-19.56) higher among hypertensive individuals and the difference was significant (p =0.001) [115], and in another study in the US adult population was found that CAL was associated with raised arterial BP and HT [105].

The biologic mechanisms for the implication of oral health or PD in HT development are not well understood. Several hypotheses have been suggested for the mechanisms resulting in arterial HT. The main hypothesis emphasizes the crucial importance of the peripheral vascular resistance control [119]. It has been suggested that HT and hypertensive end-organ damage are not only mediated by hemodynamic injury but also by a systemic inflammation [13,120-122], such as PD [110]. PD is a chronic inflammation caused by bacterial invasion which results in an irreversible destruction of the periodontal tissues caused by a dysbiotic microflora, which can trigger an exaggerated host response [123]. The influence of local inflammation in individuals with generalized periodontitis may significantly contribute to systemic inflammation [28]. It is possible that periodontitis leads to

an increased systemic immune response in those patients [124]. The principal pathogenetic mechanism responsible for increasing BP in individuals with periodontitis is systemic inflammation and secondary damage to the vascular endothelium [37,125-127]. According to previous researches *P. gingivalis*, *A. actinomycetemcomitans* and *T. forsythia* have been identified as causative factors of PD [128,129]. Bryan et al. showed that the oral microbiome's ability to reduce inorganic nitrate to nitric oxide (NO) and nitrite may provide a possible mechanism linking PD to arterial HT [130] as oral bacteria take part in the NO generation. Pathological alterations in the composition of oral bacteria in individuals with periodontitis may lead to a reduction in the NO generation, which in turn may contribute, to an increase in BP [130-132].

Until now the strongest hypotheses regarding the pathogenetic mechanism underlying the examined association suggested that the relationship could be attributed to a progression of microbial dysbiosis. That event, in turn, supports the development of periodontitis by generating chronic inflammation, disrupting the immune response and increasing the atherogenic potential [133,134]. Interaction between oral-gut microbiome are able to contribute to amplification of inflammation and metabolic alterations [135]. Recent data involves oral bacteria in the nitrate-oxide (NO) pathway and HT pathogenesis [136]. Previous cross-sectional, case-control, and cohort studies suggested that periodontitis is associated with CVD, specifically with atherosclerosis, by mechanisms involving microbial dysbiosis [137], and have been based on the association which involves imbalance (dysbiosis) of the oral microbiome structure, periodontitis, and CVD. Oxidative stress, endothelial dysfunction and systematic inflammation are associated with the HT development [138].

Experimental animal evidence indicates that immune system activation induced by *P.gingivalis* promotes the development of HT, vascular inflammation, and endothelial dysfunction [35].Moreover, neutrophilic enzymes and its dysfunction, white blood cells, and imbalance in T-cell subtypes, are all mechanisms resulting in vascular alterations and endothelial dysfunction [16, 139,140].

Inflammation plays a critical role in the HT development, according to experimental and clinical studies [13]. Chronic inflammation predisposes to the development of pro-hypertensive inflammation, whereas the low-grade chronic inflammation associated with periodontitis has harmful effects on endothelial function, which may lead to HT [140]. A recent study revealed that individuals with periodontitis have increased risks of HT and antihypertensive treatment failure [141, 142].

The presence of periodontal pathogens has been associated with HT in epidemiological studies, as already mentioned [32]. The periodontal inflammation increases the levels of inflammatory biomarkers in the blood circulation. Preclinical evidence originated from experimental animal models, including immunizations with *P. gingivalis* lysate and lipopolysaccharide-endotoxin from other gram-negative bacteria, led to prolonged T-cell activation and resulted in increased levels of CRP, IL-1β, and tumor necrosis factor-α (TNF-α), leading to increased BP [142]. The increased levels of hs-CRP can damage vascular endothelial cells, affect the level of renin-angiotensin pathway, and lead to HT development [143]. Similarly, IL-6 can cause endothelial dysfunction, increase peripheral vascular resistance, deteriorate the occurrence of inflammatory biomarkers, and eventually cause damage to blood vessels [144,145]. It has also been observed a significant association between gingival fluid TNF-α levels and BP, leading to a double inflammatory effect in individuals with both periodontitis and HT [146]. PD seems to attenuate endothelium-dependent vasodilation in rats [35,124,147], observations which could be attributed to increased systemic inflammatory biomarkers, such as CRP, IL-1b, IL-6, and TNF-α [148], increased vascular superoxide free radicals generation, worsening lipid levels, and decreased vascular nitric oxide synthase-3 (NOS-3) expression [147]. It has also been found that the immune response to the periodontal pathogen *P. gingivalis* led directly to an increase in BP, vasculitis, and deteriorated vascular endothelial function [33]. Oral bacteria have been revealed in atherosclerotic plaques [93,149]. It was observed that effective treatment of severe periodontitis improved the vascular endothelium function by reducing systemic inflammation, and decreased pro-inflammatory cytokines and chemokines in individuals with and without other comorbidities such as DM [35,140,150,151]. Moreover, the effective periodontal treatment has improved the periodontal condition and reduced BP in humans [33,152-155].However, data which supports BP reduction following PD therapy is inconclusive [35].

Another mechanism is that periodontal inflammation increases the chemotactic activity of T- and B-lymphocytes, and monocytes, resulting in vascular dysfunction, increased atherosclerosis progression, and increased BP [156,157]. Previous reports have shown the central role of T- cells in the arterial HT development. To be more specific, following hypertensive stimuli, activated T- cells accumulate in the perivascular tissue, where they release cytokines and chemokines, such as IL-6, IL-17, and TNF-α, which, in turn, contribute to the development of HT [158,159].

A special role of diverse lymphocyte sub-types in the HT pathogenesis has been revealed. CD8 T cell senescence is an important characteristic of arterial HT [160]. In a previous study by Czesnikiewicz Guzik et al., it was shown that the periodontitis treatment led to a decrease in the proportion of CD8 and CD28 null CD57+ cells. The same study showed that after the treatment of periodontitis, was observed a decrease in the proportion of IL-6, IL-17A, TNF-α, and interferon gamma (INF-γ), in the blood circulation, whereas it was also observed that Th1 immune responses induced by bacterial antigens derived from *P. gingivalis* increased the sensitivity to suppressor pro-hypertensive attack in mice and provided a mechanistic association between PD associated chronic infection and HT [33]. Another sub-type of lymphocyte which also arrears to be of importance in the periodontitis pathogenesis is Th17 lymphocytes and the dysbiosis-dependent increase in their proportion. It has been found that individuals with natural Th17 deficiency suffered from periodontitis less frequently [161,162].In addition, Th17 lymphocytes seem to play an important role in the impairment of the endothelium, vasodilatory function which by secreting IL-17 lead to an increase in the production of superoxide, which in turn reduce the NO-dependent vasodilation [163]. Regulatory T- cells (Treg) play also a critical role in both diseases. In contrast to Th 17 lymphocytes, Tregs show a protective effect in arterial HT by angiotensin II antagonism and reduction of circulating activated T-cells [164].Tregs also weak the periodontitis severity by increasing the secretion of anti-inflammatory cytokines such as TGF-β and IL-10 [165]. During the course of periodontitis, Tregs proportion may decrease, strengthening the mechanisms resulting in the development of arterial HT [28,35].

A significant potentially causal association between periodontitis-linked single nucleotide polymorphisms (SNPs)and BP phenotypes has been revealed. The identified SNPs included *SIGLEC 5*, *DEFA1A3*, *MTND1P5*, and *LOC107984137* and had been identified using Genome-Wide Association Studies (GWAS) [33].

The present research has certain strengths and limitations. Strengths of the current report concern well-structured cohort design which controlled possible confounders and possible interactions by known risk factors such as age, gender, SES, etc., the follow-up completeness, and the fact that PD status was based on oral clinical examinations and a modified standardized questionnaire and not on self-report questionnaires or non-standardized ones. Consequently, no potent mis-classification of exposure to PD existed, as such a misclassification may result in underestimation of the examined association link between PD and HT risk.

A potential limitation, is the possibility of confounders in estimation of risk caused by unknown confounders. Moreover, among those studies, some environmental variables also seem to act as confounders, such as age, gender, smoking, SES, and educational status, genetic factors, etc., as they have been considered as risk factors for the diseases examined.

Conclusions

The current survey showed that advanced age, smoking, increased BMI, the presence of DM, the presence of HT family history, gingival inflammation (GI), and the presence of dental plaque on tooth surfaces (PlI) were statistically significantly associated with the risk of HT developing.

Those associations remained after controlling for known confounders such as age, gender, smoking, SES, and educational status.

References

1. Oparil S, Acelajado MC, Bakris GL, Berlowitz DR, Cífková R, Anna F, et al. Hypertension. Hypertension Nat Rev Dis Primers. 2018; 4(1).https://doi.org/10.1038/nrdp.2018.14.

2. Global regional et al. and national comparative risk assessment of 84 behaviour environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018. 392(10159):1923-94. doi: 10.1016/S0140-6736(18)32225-6 .

3. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, et al. Heart Disease and Stroke Statistics-2020 up-date: a Report from the American Heart Association. Circulation. 2020;141(9):e139-e596. doi: 10.1161/CIR.0000000000000757.

4. Muntner P, Carey RM, Gidding S, Jones DW, Tale SJ, Wright Jr JT, et al. Potential US Population Impact of the 2017 ACC/AHA high blood pressure Guideline. Circulation. 2018; 137 (2):109-18. doi: 10.1161/CIRCULATIONAHA.117.032582.

5. Mills KT, Bundy JD, Kelly TN, Reed JE, Kearney PM, Reynolds K, et al. Global disparities of hypertension prevalence and control: a systematic analysis of population-based studies from 90 Countries. Circulation. 2016;134:441-50. doi: 10.1161/CIRCULATIONAHA.115.018912.

6. Scholes S, Conolly A, Mindell JS. Income-based inequalities in hypertension and in undiagnosed hypertension: analysis of Health Survey for England data. J Hypertens. 2020; 38:912-24. doi: 10.1097/HJH.0000000000002350.

7. Roth GA, Mensah GA, O Johnson C, Addolorato G, Ammirati E, Baddour LM, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. J Am Coll Cardiol. 2020; 76(25): 2982-3021. doi: 10.1016/j.jacc.2020.11.010.

8. Forouzanfar MH, Afshin A, Alexander LT. GBD 2015 Risk Factors Collaborators Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016 ; 388:1659-724. doi: 10.1016/S0140 S0140-6736(16)31679-8.

9. Song J-J, Ma Z, Wang J, Chen L-X, Zhong J-C. Gender differences in hypertension. J Cardiovasc Transl Res. 2020 ; 13(1):47-54. doi: 10.1007/s12265-019-09888-z .

10. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018 ; 39(33): 3021-104. doi: 10.1093/eurheartj/ehy339.

11. Yang T, Santisteban MM, Rodriguez V, Li E, Ahmari N, Marulanda Carvajal J, et al. Gut dysbiosis is linked to hypertension. Hypertension. 2015 ; 65(6): 1331-40. DOI: 10.1161/ HYPERTENSIONAHA.115.05315.

12. Deo PN, Deshmukh R. Oral microbiome: Unveiling the fundamentals. J Oral Maxillofac Pathol. 2019 ; 23(1):122-8. DOI: 10.4103/jomfp.JOMFP_304_18.

13. Drummond GR, Vinh A, Guzik TJ, Sobey CG. Immune mechanisms of hypertension. Nat Rev Immunol. 2019 ;19:517-32. doi: 10.1038/s41577-019-0160-5.

14. Petersen PE. The World Oral Health Report. 2003: continuous improvement of oral health in the 21st century-the approach of the WHO Global Oral Health Programme. Community Dent Oral Epidemiol. 2003 ; 31 Suppl 1:3-23. doi: 10.1046/j..2003.com122.x.

15. Balta MG, Papathanasiou E, Blix IJ, Dyke TEV. Host Modulation and Treatment of Periodontal Disease. J Dent Res. 2021 ;100(8):798-809. doi: 10.1177/0022034521995157.

16. Sanz M, Marco Del Castillo A, Jepsen S, Gonzalez-Juanatey JR, D'Aiuto F, Bouchard P, et al. Periodontitis and cardiovascular diseases: consensus report. J Clin Periodontol. 2020; 47:268-88. doi: 10.1111/jcpe.13189.

17. Frencken JE, Sharma P, Stenhouse L, Green D, Laverty D, Dietrich R. Global epidemiology of dental caries and severe periodontitis - a comprehensive review. J Clin Periodontol. 2017; 44 (suppl 18):S94-S105. doi: 10.1111/jcpe.12677.

18. Tonetti MS, Greenwell H, Kornman KS. Staging and grading of periodontitis: framework and proposal of a new classification and case definition. J Periodontol. 2018 ; 89(suppl 1): S 159-S172. doi: 10.1002/JPER.18-0006.

19. Hajishengallis G, Chavakis T. Local and systemic mechanisms linking periodontal disease and inflammatory comorbidities. Nat Rev Immunol. 2021 ; 21 (7): 426-40. doi: 10.1038/s 41577-020-00488-6.

20. Sedghi L, Di Massa V, Harrington A, Lynch SV, Kapila YL. The oral microbiome: Role of key organisms and complex networks in oral health and disease. Periodontol 2000. 2021 ; 87(1):107-31. doi: 10.1111/prd.12393.

21. Papapanou PN, Sanz M, Buduneli N, Dietrich T, Feres M, Fine DH, et al. Periodontitis: Consensus report of work- group 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. J Periodontol. 2018 ; 89 Suppl 1: S173-S182. doi: 10.1002/JPER.17-0721.

22. Slazhneva E, Tikhomirova E, Tsarev V, Orekhova L, Loboda E, Atrushkevich V. Candida species detection in patients with chronic periodontitis: A systematic review and meta-analysis. Clin Exp Dent Res. 2022 ;8(6):1354-75. doi: 10.1002/cre2.635.

23. Sedghi LM, Bacino M, Kapila YL. Periodontal Disease: The Good, The Bad, and The Un-known. Front Cell Infect Microbiol. 2021 ;11:766944. doi: 10.3389/ fcimb.2021.766944.

24. Fi C, Wo W. Periodontal disease and systemic diseases: an overview on recent progresses.J Biol Regul Homeost Agents. 2021 ; 35(1 Suppl. 1):1-9.

25. Abusleme L, Hoare A, Hong B-Y, Diaz PI. Microbial signatures of health, gingivitis, and periodontitis. Periodontol 2000. 2021 ; 86(1):57-78. doi: 10.1111/prd.12362.

26. Prucsi Z, Płonczyńska A, Potempa J, Sochalska M. Uncovering the Oral Dysbiotic Microbiota as Masters of Neutrophil Responses in the Pathobiology of Periodontitis. Front Microbiol. 2021 ; 12:729717. doi: 10.3389/fmicb.2021.729717.

27. Thomas RZ, Loos BG, Teeuw W, Kunnen A, van Winkelhoff AJ, Abbas F. Periodontitis and systemic diseases: from science to clinical practice. Ned Tijdschr Tandheelkd. 2015 ;122 (10):542-8. doi: 10.5177/ntvt.2015.10.15134.

28. Del Pinto R, Pietropaoli D, Munoz-Aguilera E, D'Aiuto F, Czesnikiewicz-Guzik M, MonacoA, et al. Periodontitis and Hypertension: Is the Association Causal? High Blood Press Cardiovasc Prev. 2020 ;27(4):281-9. doi: 10.1007/s40292-020-00392-z.

29. Kim J, Jun Kim H, Jeon J, Song T-J. Association between oral health and cardiovascular outcomes in patients with hypertension: a nationwide cohort study. J Hypertens. 2022 ;40(2): 374-81. doi: 10.1097/HJH.0000000000003022.

30. Virdis A, Giannarelli C, Neves MF, Ghiadoni L. Cigarette smoking and hypertension. Curr Pharm Des. 2010 ;16(23):2518-25. doi: 10.2174/138161210792062920.

31. Kim N-H, Lee G-Y, Park S-K, Kim Y-J, Lee M-Y, Kim C-B. Provision of oral hygiene services as a potential method for preventing periodontal disease and control hypertension and diabetes in a community health centre in Korea. Health Soc Care Community. 2018 ;26 (3):e378-385.

32. Desvarieux M, Demmer RT, Jacobs DR Jr, Rundek T, Boden-Albala B, Sacco RL, et al.Periodontal bacteria and hypertension: the oral infections and vascular

disease epidemiology study (INVEST). J Hypertens. 2010;28:1413-21. doi: 10.1097/HJH. 0b013e328338cd36.

33. Czesnikiewicz-Guzik M, Osmenda G, Siedlinski M, Nosalski R, Pelka P, Nowakowski D, et al. Causal association between periodontitis and hypertension: evidence from Mendelian randomization and a randomized controlled trial of non-surgical periodontal therapy. Eur Heart J. 2019; 40(42): 3459-70. doi: 10.1093/eurheartj/ehz646.

34. Shin H-S. Association between the number of teeth and hypertension in a study based on13,561 participants. J Periodontol. 2018 ;89(4):397-406. doi: 10.1002/JPER.17-0413

35. Munoz Aguilera E, Suvan J, Buti J, Czesnikiewicz-Guzik M, Barbosa Ribeiro A, Orlandi M,et al. Periodontitis is associated with hypertension: a systematic review and meta-analysis. Cardiovasc Res. 2020;116:28-39. doi: 10.1093/cvr/cvz201.

36. Pietropaoli D, Monaco A, D'Aiuto F, Muñoz Aguilera E, Ortu E, Giannoni M, et al. Active gingival inflammation is linked to hypertension. J Hypertens. 2020 ; 38: 2018-27. doi:10. 1097/HJH.0000000000002514.

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

38. Rivas-Tumanyan S, Spiegelman D, Curhan GC, Forman JP, Joshipura KJ. Periodontal disease and incidence of hypertension in the health professionals follow-up study. Am J Hypertens. 2012 ; 25(7): 770-6. doi: 10.1038/ajh.2012.32

39. Paddmanabhan P, Gita B, Chandrasekaran SC. Association between chronic periodontitis and hypertension in South Indian population: a cross-sectional study. J Pharm Bioallied Sci. 2015 ; 7(2):543-7. doi: 10.4103/0975-7406.163535.

40. Gordon JH, La Monte M, Genco RJ, Genco RJ, Cimato TR, Hovey KM, et al. Association of periodontal l disease and edentulism with hypertension risk in postmenopausal women. J Periodontol. 2019 ; 89: 1193-202. doi: 10.1093/ajh/hpy164.

41. Messner B, Bernhard D. Smoking and cardiovascular disease: mechanisms of endothelial dysfunction and early atherogenesis. Arterioscler Thromb Vasc Biol. 2014; 34(3) :509-15.doi: 10.1161/ATVBAHA.113.300156.

42. Prochaska JJ, Benowitz NL. Smoking cessation and the cardiovascular patient. Curr OpinCardiol. 2015 ; 30(5):506-11. doi: 10.1097/HCO.0000000000000204.

43. Lee W, Hwang S-H, Choi H, Kim H. The association between smoking or passive smoking and cardiovascular diseases using a Bayesian hierarchical model: based on the 2008-2013Korea Community Health Survey. Epidemiol Health. 2017 ; 22(39):e2017026.doi : 10.4178/ epih. e2017026.

44. Alberg AJ, Brock MV, Ford JG, Samet JM, Spivack SD. Epidemiology of lung cancer: diagnosis and management of lung cancer, 3rd ed: American college of chest physicians evidence-based clinical practice guidelines. Chest. 2013 ;143:e1S-e29S. DOI: 10.1378/ chest. 12-2345

45. Leite FRM, Nascimento GG, Scheutz F, Lopez R. Effect of smoking on periodontitis: a systematic review and meta-regression. Am J Prev Med. 2018 ; 54:831-41. doi : 10.1016 /j. amepre.2018.02.014.

46. Leite FRM, Nascimneto GG, Baake S, Pedersen LD, Scheutz F, López R. Impact of smoking cessation on periodontitis: a systematic review and Meta-analysis of prospective longitudinal observational and interventional studies. Nicotine Tob Res. 2019 ; 21: 1600-8. doi:10.1093/ntr/nty147.

47. Schmidt TSB, Hayward MR, Coelho LP, Li SS, Costea PI, Voigt AY, et al. Extensive transmission of microbes along the gastrointestinal tract. eLife. 2019 ; 8. https://doi.org/10. 7554/eLife.42693.

48. Acharya C, Sahingur SE, Bajaj JS. Microbiota, cirrosis, and the emerging oral-gut- liveraxis. JCI Insight. 2017 ;2(19). https://doi.org/10.1172/jci.insight.94416.

49. du Teil EM, Gabarrini G, Harmsen HJM, Westra J, van Winkelhoff AJ, van Dijl JM. Talk to your gut: the oral-gut microbiome axis and its immunomodulatory role in the etiology of rheumatoid arthritis. FEMS Microbiol Rev. 2019 ;43(1): 1-18. doi: 10.1093/femsre/fuy035.

50. Atarashi K, Suda W, Luo C, Kawaguchi T, Motoo I, Narushima S, et al. Ectopic colonization of oral bacteria in the intestine drives T1 cell induction and inflammation. Science (New York, NY). 2017 ;358 (6361): 359-65. doi: 10.1126/science.aan4526.

51. Narengaowa , Kong W, Lan F, Awan UF, Qing H, Ni J. The Oral-Gut-Brain AXIS: the Influence of Microbes in Alzheimer's Disease. Front Cell Neurosci. 2021 ; 15: 633735. doi: 10. 3389/fncel.2021.633735.

52. Holmlund A, Lampa E, Lind L. Oral health and cardiovascular disease risk in a cohort of periodontitis patients. Atherosclerosis. 2017 ;262:101-6. doi: 10.1016/j. atherosclerosis. 2017.05.009

53. Southerland JH, Taylor GW, Moss K, Beck JD, Offenbacher S. Commonality in chronic inflammatory diseases: periodontitis, diabetes, and coronary artery disease. Periodontol 2000. 2006 ;40:130-143. doi: 10.1111/j.1600-0757.2005.00138.x.

54. Stergiou GS, Menti A, Kalpourtzi N, Gavana M, Vantarakis A, Chlouverakis G, et al. Prevalence, awareness, treatment and control of hypertension in Greece: EMENO national epidemiological study. J Hypertens 2021;39(5):1034-9. doi: 10.1097/HJH. 000000 000 0002714.

55. World Health Organization. Oral health surveys: basic methods. Geneva: World Health Organization; 1997. https://apps.

who.int/iris/bitstream/handle/10665/41905/9241544937.pdf? sequence=1&isAllowed=y

56. Tonetti MS, Greenwell H, Kornman KS. Staging and grading of periodontitis: framework and proposal of a new classification and case definition. J Clin Periodontol. 2018; 45:S149-S161. doi: 10.1002/JPER.18-0006.

57. Lavstedt S, Bolin A, Henrikson CO. Proximal alveolar bone loss in a longitudinal radiographic investigation. II. A 10-year follow-up study of an epidemiologic material. Acta Odontol Scand. 1986; 44: 199-205. doi: 10.3109/00016358608997721.

58. Reichert S, Stein J, Gautsch A, Schaller HG, Machulla HK. Gender differences in HLA phenotype frequencies found in German patients with generalized aggressive periodontitis and chronic periodontitis. Oral Microbiol Immunol. 2002; 17: 360-8. DOI: 10.1034/j.1399- 302x.2002.170605.x.

59. Tonetti MS, Claffey N. Advances in the progression of periodontitis and proposal of defini tions of a periodontitis case and disease progression for use in risk factor research. Group C consensus report of the 5th European Workshop in Periodontology. J Clin Periodontol. 2005 ; 32: 210-3. doi: 10.1111/j.1600-051X.2005.00822.x.

60. Loos BG, John RP, Laine ML. Identification of genetic risk factors for periodontitis and possible mechanisms of action. J Clin Periodontol. 2005; 32: 159-79. doi: 10.1111/j.1600- 051X.2005.00806.x

61. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, et al. The Seventh Report of the Joint National Committee on Prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. JAMA. 2003; 289(19): 2560-72. doi: 10.1161/01.HYP.0000107251.49515.c2.

62. Muñoz Aguilera E, Suvan J , Orlandi M , Miró Catalina Q , Nart J, D' Aiuto F. Association Between Periodontitis and Blood Pressure Highlighted in Systemically Healthy Individuals. Results From a Nested Case-Control Study. Hypertension. 2021; 77:1765-74. doi: 10.1161/HYPERTENSIONAHA.120.16790.

63. Machuca G, Segura-Egea JJ, Jimenez-Beato G, Lacalle JR, Bullón P. Clinical indicators of periodontal disease in patients with coronary heart disease:A10 years longitudinal study. Med Oral Patol Oral Cir Bucal. 2012; 17: e569-74. doi: 10.4317/medoral.17848.

64. Jiang SZ, Lu W, Zong XF, Ruan HY, Liu Y. Obesity and hypertension. Exp Ther Med. 2016; 12(4): 2395-9. doi: 10.3892/etm.2016.3667.

65. Cutress TW, Ainamo J, Sardo-Infrri J. The community periodontal index of treatment needs (CPITN) procedure for population groups and individuals. Int Dent J. 1987; 37(4): 222-33.

66. Wiebe CB, Putnins EE. The periodontal disease classification system of the American academy of periodontology an update. J Can Dent Assoc. 2000; 66:594-7.

67. Löe H. The Gingival Index, the Plaque Index, and the Retention Index Systems. J Periodontol. 1967; 38(6) Suppl: 610-6. doi: 10.1902/jop.1967.38.6.610.

68. Silness J, Löe H. Periodontal disease in pregnancy. II. Correlation between oral hygiene and periodontal condtion. Acta Odontol Scand. 1964; 22: 121-35. doi: 10.3109/0001635640 8993968.

69. Blaizot A, Vergnes JN, Nuwwareh S, Amar J, Sixou M. Periodontal diseases and cardio vascular events: meta-analysis of observational studies. Int Dent J. 2009;59 (4):197-209.

70. Nazir MA. Prevalence of periodontal disease, its association with systemic diseases and pre- vention. Int J Health Sci. 2017;11(2):72-80.

71. Connelly PJ, Currie G, Delles C. Sex Differences in the Prevalence, Outcomes and Management of Hypertension. Curr Hypertens Rep 2022 ; 24(6):185-92. doi: 10.1007/s 11906-022- 01183-8.

72. Everett B, Zajacova A. Gender Differences in Hypertension and Hypertension Awareness Among Young Adults. Biodemography Soc Biol 2015; 61(1):1-17. doi: 10.1080/194 85565. 2014.929488.

73. Hussainy SA, Shereen S. Blood Pressure in Relation to Age and Gender. J Drug Deliv Therap. 2024; 14(3):39-43 doi: http ://dx. doi.org/10.22270/ jddt. v14i3.6456.

74. Cheng W, Du Y, Zhang Q, Wang X, He C, He J, et al. Age-related changes in the risk of of high blood pressure. Front Cardiovasc Med. 2022 ;9:939103. doi: 10.3389/fcvm. 2022. 939103.

75. Wu J, Han X, Sun D, Zhang J, Li J, Qin G, Deng W, et al. Age-specific association of stage of hypertension at diagnosis with cardiovascular and all-cause mortality among elderly patients with hypertension: a cohort study. BMC Cardiovasc Dis. 2023; 23:270. https://doi.org/10.1186/s12872-023-03250-7.

76. Leng B, Jin Y, Li G, Chen L, Jin N. Socioeconomic status and hypertension: a meta-analysis J Hypertens. 2015;33(2):221-9. doi: 10.1097/HJH.0000000000000428.

77. Neufcourt L, Deguen S, Bayat S, Zins M, Grimaud O. Gender differences in the association between socioeconomic status and hypertension in France: a cross-sectional analysis of the CONSTANCES cohort. PLoS ONE. 2020;15(4):e0231878. doi: 10.1371/journal. pone. 0231 878.

78. James SA, Van Hoewyk J, Belli RF, Strogatz DS, Williams DR, Raghunathan TE. Life-course socioeconomic position and hypertension in African American men: the pitt county study. Am J Public Health. 2006;96(5):812-7. doi: 10.2105/AJPH.2005.076158.

79. Fateh M, Emamian M, Asgari F, Alami A, Fotouhi A. Socioeconomic inequality in hypertension in

Iran. J Hypertens. 2014;32(9):1782-8. doi: 10.1097/HJH.0000000000000260.

80. Gulliford M, Mahabir D, Rocke B. Socioeconomic inequality in blood pressure and its determinants: cross-sectional data from Trinidad and Tobago. J Hum Hypertens. 2004; 18 (1):61-70. doi: 10.1038/sj.jhh.1001638.

81. Luo T, Lin S, Zhang W, Li X, Wang Y, Zhou J, et al. Relationship between socioeconomic status and hypertension incidence among adults in southwest China: a population-based cohort study. BMC Publ Health. 2024; 24:1211. https://doi.org/10.1186/s12889-024-18686-5.

82. Zacher M. Educational Disparities in Hypertension Prevalence and Blood Pressure Percentiles in the Health and Retirement Study. J Gerontol B Psychol Sci Soc Sci. 2023; 78(9): 1535-44. doi: 10.1093/geronb/gbad084.

83. Sun K, Lin D, Li M, Mu Y, Zhao J, Liu C, et al. Association of education levels with the risk of hypertension and hypertension control: a nationwide cohort study in Chinese adults. J Epidemiol Commun Health. 2022;76:451-7. doi: 10.1136/jech-2021-217006.

84. Yu S, Guo X, Li G, Yang H, Zheng L, Sun Y. Low educational status correlates with a high incidence of mortality among hypertensive subjects from Northeast Rural China. Front Public Health 2022;10:951930. doi: 10.3389/fpubh.2022.951930.

85. Kunnas T, Nikkari ST. Family history of hypertension enhances age-dependent rise in blood pressure, a 15-year follow-up, the Tampere adult population cardiovascular risk study. Medicine (Baltimore). 2023;102(39):e35366. doi: 10.1097/MD.0000000000035366.

86. Kanchan KC, Srijana K, Gopal KY, Alisha A, Raj Kumar T, Kumar JS. Family history of hypertension and its relation to other variables in hypertensive patients: a cross-sectional study from a tertiary care hospital. Int J Surgery: Global Health. 2023; 6(5): e0235. doi: 10.1097/GH9.0000000000000235.

87. Li Al, Peng Q, Shao Yq, Fang X, Zhang Y-y.The interaction on hypertension between family history and diabetes and other risk factors. Sci Rep. 2021; 11: 4716. https://doi.org/10.1038/ s41598-021-83589-z.

88. Landi F, Calvani R, Picca A, Tosato M, Martone AM, Ortolani E, et al. Body Mass Index is Strongly Associated with Hypertension: Results from the Longevity Check-up 7+ Study. Nutrients. 2018; 13;10(12): 1976. doi: 10.3390/nu10121976.

89. Kosami K, Kuwabara M, Okayama A, Ae R. Body Mass Index and Weight Change as Predictors of Hypertension Development: A Sex-Specific Analysis. Nutrients. 2025; 17(1): 119; https://doi.org/10.3390/nu17010119.

90. Petrie JR, Guzik TJ, Touyz RM. Diabetes, Hypertension, and Cardiovascular Disease: Cli-nical Insights and Vascular Mechanisms. Can J Cardiol. 2018; 34(5):575-84. doi: 10.1016/ j.cjca.2017.12.005.

91. Kemche B, Saha Foudj BU, Fokou E. Risk Factors of Hypertension among Diabetic Patientsfrom Yaoundé Central Hospital and Etoug-Ebe Baptist Health Centre, Cameroon. J Diab Res.2020; ID 1853516, https://doi.org/10.1155/2020/1853516.

92. Landi L, Grassi G, Sforza MN, Ferri C. Hypertension and periodontitis: an upcoming joint report by the Italian Society of Hypertension (SIIA) and the Italian Society of Periodontology and Implantology (SIdP). High Blood Press Cardiovasc Prev. 2021;28:1-3. https://doi.org/10.1007/s40292-020-00430-w.

93. Bui FQ, Almeida-da-Silva CLC, Huynh B, Trinh A, Liu J, Woodward J, et al. Association between periodontal pathogens and systemic disease. Biomed J. 2019;42(1): 27-35. doi: 10. 1016/j.bj.2018.12.001.

94. Arowojolu M, Oladapo O, Opeodu O, Nwhator S. An evaluation of the possible relationship between chronic periodontitis and hypertension. J West Afr Coll Surg. 2016;6:20-38.

95. Carra MC, Fessi S, Detzen L, Darnaud C, Julia C, Hercberg S, et al. Self-reported periodon tal health and incident hypertension: longitudinal evidence from the NutriNet-Santé e-cohort. J Hypertens. 2021; 39(12): 2422-30. doi: 10.1097/HJH.0000000000002941.

96. Lee J-H, Oh J-Y, Youk T-M, Jeong S-N, Kim Y-T, Choi S-H. Association between periodontal disease and non-communicable diseases: a 12-year longitudinal health-examinee cohort study in South Korea. Med (Baltim). 2017;96(26):e7398. doi: 10.1097/MD.0000000000007398.

97. Martin-Cabezas R, Seelam N, Petit C, Agossa K, Gaertner S, Tenenbaum H, et al. Association between periodontitis and arterial hypertension: a systematic review and meta-analysis. Am Heart J. 2016;180:98-112. https://doi.org/10.1016/j.ahj.2016.07.018.

98. Zhan Y, Jiao J, Jing W, Feng X, Tai B, Hu D, et al. Association between periodontitis and hypertension: cross-sectional survey from the Fourth National Oral Health Survey of China (2015-2016). BMJ Open 2023;13:e068724. doi:10.1136/ bmjopen-2022-068724.

99. Messing M, de Souza LC, Cavalla F, Kookal KK, Rizzo G, Walji M, et al. Investigatin potential correlations between endodontic pathology and cardiovascular diseases using epidemiological and genetic approaches. J Endod. 2019; 45:104-10. doi: 10.1016/j.joen. 2018.10.014.

100. Muñoz Aguilera E, Suvan J, Orlandi M, Miró Catalina Q, Nart J, D'Aiuto, F. AssociationAssociation Between Periodontitis and Blood Pressure Highlighted in Systemically Healthy Individuals. Hypertension. 2021; 77: 1765-74. doi: 10.1161/HYPERTENSIONAHA.120.16790.

101. Surma S, Romanczyk M, Witalinska-Łabuzek J, Czerniuk MR, Łabuzek K, Filipiak KJ. Periodontitis, blood pressure, and the risk and control of arterial hypertension: epidemiological, clinical, and pathophysiological aspects-review of the literature and clinical trials. Curr Hypertens Rep. 2021; 23:1-14. doi: 10.1007/s11906-021-01140-x.

102. Kawabata Y, Ekuni D, Miyai H, Kataoka K, Yamane M, Mizutani S, et al. Relationship between prehypertension/ hypertension and periodontal disease: a prospective cohort study. Am J Hypertens. 2016; 29:388-96. doi: 10.1093/ajh/ hpv117.

103. Hujoel PP, Drangsholt M, Spiekerman C, DeRouen TA. Periodontal disease and coronary heart disease risk. JAMA. 2000; 284:1406-10. doi: 10.1001/jama.284.11.1406.

104. Holmlund A, Lampa E, Lind L. Oral health and cardiovascular disease risk in a cohort of periodontitis patients. Atherosclerosis. 2017; 262:101-6. doi: 10.1016/j. atherosclerosis.2017. 05.009.

105. Pietropaoli D, Del Pinto R, Ferri C, Ortu E, Monaco A. Definition of hypertension-associa ted oral pathogens in NHANES. J Periodontol. 2019; 90: 866-76. doi: 10.1002/ JPER.19- 0046.

106. Franek E, Napora M, Blach A, Budlewski T, Gozdowski D, Jedynasty K, et al. Blood pressure and left ventricular mass in subjects with type 2 diabetes and gingivitis or chronic periodontitis. J Clin Periodontol. 2010;37:875-80. doi: 10.1111/j.1600-051X.2010.01613.x.

107. Ollikainen E, Saxlin T, Tervonen T, Suominen LA, Knuuttila M, Jula A, et al. Association between periodontal condition and hypertension in a non-smoking population aged 30-49 years: results of the health 2000 Survey in Finland. J Clin Periodontol. 2014;41:1132-8.doi: 10.1111/ jcpe.12316

108. Yildirim BG, Aksit C, Mutlu M, Ainola M, Eklund KK, Leskelä J, et al. Severity and progression rate of periodontitis are associated with an increased risk of hypertension of patients attending a university clinic. BMC Oral Health**.** 2022; 22: 627. https://doi.org/10.1186/ s12903-022-02637-w.

109. Li Y, Yuan X, Zheng Q, Mo F, Zhu S, Shen T, et al. The association of periodontal disease and oral health with hypertension, NHANES 2009-2018. BMC Public Health. 2023; 23(1): 1122. doi: 10.1186/s12889-023-16012-z.

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

111. Papapanou PN. Periodontal diseases: epidemiology. Ann Periodontol. 1996;1(1):1-36. doi:10.1902/ annals.1996.1.1.1.

112. Saleh Yousef Al-H, Riham Omar I, Mai Z. Association between periodontitis and hypertension among a sample of adult Egyptian patients: A hospital-based cross-sectional study. J Int Oral Health. 2023; 15(6):558-64. doi: 10.4103/ jioh.jioh_184_23.

113. Engström S, Gahnberg L, Högberg H, Svärdsudd K. Association between high blood pressure and deep periodontal pockets: a nested case-referent study. Upsula J Med Sci. 2007; 112(1): 95-103. doi: 10.3109/2000-1967-099.

114. Morita T, Yamazaki Y, Mita A, Takada K, Seto M, Nishinoue N. A cohort study on the association between periodontal disease and the development of metabolic syndrome. J Periodontol. 2010; 81(4): 512-9. https://doi.org/10.1902/jop.2010.090594.

115. Gatarayiha A, Brookes Z, Rulisa S, Andegiorgish AK, Mutesa L. Association between Periodontitis and Hypertension among Adult Population in Rwanda. J Clin Med. 2024; 13 (16):4722. https://doi.org/10.3390/ jcm13164722.

116. Del Pinto R, Pietropaoli D, Monaco A, D'Aiuto F, Aguilera EM, Ortu E, et al. Gingival bleeding: A possible indicator of high blood pressure ? J Hypert. 2021; 39 (Supl.1): e288. doi: 10.1097/01.hjh.0000747768.30823.cb.

117. Burt B. Position paper: Epidemiology of Periodontal Diseases. J Periodontol. 2005;76(8):1406-19. doi: 10.1902/ jop.2005.76.8.1406.

118. Miskiewicz A, Szparecki G, Durlik M, Rydzewska G, Ziobrowski I, Górska R. The corre lation between pancreatic dysfunction markers and selected indices of periodontitis. AdvClin Experim Med. 2018;27(3):313-9. doi: 10.17219/ acem/64937.

119. Beevers G, Lip GY, O' Brien E. The pathophysiology of hypertension. BMJ. 2001;322 (7291):912-6. doi: 10.1136/ bmj.322.7291.912.

120. Norlander AE, Madhur MS, Harrison DG. The immunology of hypertension. J Exp Med. 2018;215(1): 21-33. doi: 10.1084/jem.20171773.

121. Wenzel U, Turner JE, Krebs C, Kurts C, Harrison DG, Ehmke H. Immune mechanisms in arterial hypertension. J Am Soc Nephrol. 2016; 27(3):677-86. doi: 10.1681/ASN. 20150505 62.

122. Wenzel UO, Ehmke H, Bode M. Immune mechanisms in arterial hypertension. Rec Adv Cell Tissue Res. 2021;385(2):393-404. doi: 10.1007/s00441-020-03409-0.

123. Könönen E, Gursoy M, Gursoy UK. Periodontitis: a multifaceted disease of tooth- supporting tissues. J Clin Med. 2019;8(8):1135. doi: 10.3390/jcm8081135.

124. Gomes MS, Blattner TC, Sant'Ana Filho M, Grecca FS, Hugo FN, Fouad AF, et al. Can apical periodontitis modify systemic levels of inflammatory markers? A systematic review and meta-analysis. J Endod. 2013;39(10):1205-17. doi: 10.1016/j.joen.2013.06.014.

125. Leong X, Ng C, Badiah B, Das S. Association between hypertension and periodontitis :possible mechanisms. Sci World J. 2014; 2014: 768237. https://doi.org/ 10.1155/ 2014/768237.

126. Macedo Paizan ML, Vilela-Martin JF. Is there an association between periodontitis and hypertension? Curr Cardiol Rev. 2014;10(4):355-61. doi: 10.2174/1573403x106661404 16 094901.

127. Herrera D, Molina A, Buhlin K, Klinge B. Periodontal diseases and association with atherosclerotic disease. Periodontol 2000 . 2020; 83(1):66-89. doi: 10.1111/ prd.12302.

128. Silva N, Abusleme L, Bravo D, Dutzan N, Garcia-Sesnich J, Vernal R, et al. Host response mechanisms in periodontal diseases. J Appl Oral Sci. 2015; 23:329-55. doi: 10.1590/1678-1678-775720140259.

129. Cekici A, Kantarci A, Hasturk H, Van Dyke TE. Inflammatory and immune pathways in the pathogenesis of periodontal disease. J Periodontol. 2014; 64(1): 57-80. doi:10.1111/ prd. 12002.

130. Bryan NS, Tribble G, Angelov N. Oral microbiome and nitric oxide: the missing link in the management of blood pressure. Curr Hypertens Rep. 2017;19(4):1-8. doi: 10.1007/s11906-017-0725-2.

131. Pignatelli P, Fabietti B, Ricci A, Piattelli A, Curia M. How periodontal disease and presence of nitric oxide reducing oral bacteria can affect blood pressure. Int J Mol Sci. 2020;21:7538.doi: 10.3390/ijms21207538.

132. Alzahrani HS, Jackson KG, Hobbs DA, Lovegrove JA. The role of dietary nitrate and the oral microbiome on blood pressure and vascular tone. Nutr Res Rev. 2020:1-18. https://doi.org/10.1017/S0954422420000281.

133. Paul O, Arora P, Mayer M, Chatterjee S. Inflammation in periodontal disease: possible link to vascular disease. Front Physiol. 2021; 11:1818. doi: 10.3389/fphys.2020.609614.

134. Hajishengallis G. Periodontitis: from microbial immune subversion to systemic inflammation. Nat Rev Immunol. 2015; 15:30-44. doi: 10.1038/nri3785.

135. Arimatsu K, Yamada H, Miyazawa H, Minagawa T, Nakajima M, Ryder MI, et al. Oral pathobiont induces systemic inflammation and metabolic changes associated with alteration of gut microbiota. Sci Rep. 2014;4:4828. doi: 10.1038/srep04828.

136. Goh CE, Trinh P, Colombo PC, Genkinger JM, Mathema B, Uhlemann AC, et al. Association between nitrate reducing oral bacteria and cardiometabolic outcomes: results from ORIGINS. J Am Heart Assoc. 2019;8:e013324. doi: 10.1161/JAHA.119.013324.

137. Friedewald VE, Kornman KS, Beck JD, Genco R, Goldfine A, Libby P, et al. The American Journal of Cardiology and Journal of Periodontology editors' consensus: periodontitis and atherosclerotic cardiovascular disease. J Periodontol. 2009; 80:1021-32. doi: 10.1902/jop. 2009.097001.

138. Czopek A, Moorhouse R, Guyonnet L, Farrah T, Lenoir O, Owen E, et al. A novel role for myeloid endothelin-B receptors in hypertension. Eur Heart J. 2019;40:768-84. doi: 10.1093/ eurheartj/ehy881.

139. Czesnikiewicz-Guzik M, Nosalski R, Mikolajczyk TP, Vidler F, Dohnal T, Dembowska E, et al. Th1-type immune responses to Porphyromonas gingivalis antigens exacerbate angiotensin II-dependent hypertension and vascular dysfunction. Br J Pharmacol. 2019;176:1922- 31. doi: 10.1111/bph.14536.

140. Tonetti MS, D'Aiuto F, Nibali L, Donald A, Storry C, Parkar M, et al. Treatment of periodontitis and endothelial function. N Engl J Med. 2007;356:911-20. doi: 10.1056/ NEJMoa 063186.

141. Pietropaoli D, Del Pinto R, Ferri C, Wright Jr JT, Giannoni M, Ortu E, et al. Poor oral health and blood pressure control among US hypertensive adults. Hypertension. 2018;72:1365-73.doi: 10.1161/HYPERTENSIONAHA.118.11528.

142. Libby P, Loscalzo J, Ridker PM, Farkouh ME, Hsue PY, Fuster V, et al. Inflammation, immunity, and infection in atherothrombosis: JACC review topic of the week. J Am Coll Cardiol. 2018;72:2071-81. doi: 10.1016/j. jacc.2018.08.1043.

143. Takeguchi A, Miyazawa K, Sato T, Tabuchi M, Muramatsu R, Maeda H, et al. Effects of a β2- adrenergic receptor blocker onexperimental periodontitis in spontaneously hypertensive rats. Life Sci. 2021; 277:119593. https://doi. org/10.1016/j.lfs.2021.119593.

144. Chrysohoou C, Pitsavos C, Panagiotakos DB, Skoumas J, Stefanadis C. Association between prehypertension status and inflammatory markers related to atherosclerotic disease: the ATTICA study. Am J Hypert. 2004; 17(7): 568-73. doi: 10.1016/j.amjhyper. 2004. 03. 675.

145. Yan LJ, Wang SB, Wang XQ, Cao XM. Protective effect and mechanism of curcumin on aorta in rats with metabolic syndrome. Chin J Chin Mat Med. 2019; 44(21): 4685-90. doi: 10.19540/j.cnki.cjcmm.20190701.401.

146. Khocht A, Rogers T, Janal MN, Brown M. Gingival Fluid inflammatory biomarkers and hypertension in African Americans. JDR Clin Trans Res. 2017;2(3): 269-77. doi: 10.1177/ 2380084417694335.

147. Brito LCW, DalBó S, Striechen TM, Farias JM, Olchanheski LR, Mendes RT, et al. Experimental periodontitis promotes transient vascular inflammation and endothelial dysfunction. Arch Oral Biol. 2013;58(9):1187-98. doi: 10.1016/j. archoralbio.2013.03.009.

148. Garlet GP. Destructive and protective roles of cytokines in periodontitis: a re-appraisal from host defense and tissue destruction viewpoints. J Dent Res. 2010;89:1349-63. doi: 10.1177/ 0022034510376402.

149. Figuero E, Sánchez-Beltrán M, Cuesta-Frechoso S, Tejerina JM, del Castro JA, Gutiérrez JM, et al. Detection of periodontal bacteria in atheromatous plaque by nested polymerase chain reaction. J Periodontol. 2011; 82: 1469-77. doi: 10.1902/jop.2011.100719.

150. D'Aiuto F, Gkranias N, Bhowruth D, Khan T, Orlandi M, Suvan J, et al. Systemic effects of periodontitis treatment in patients with type 2 diabetes: a 12 month, single-centre, investigator-masked, randomized trial. Lancet Diabetes Endocrinol. 2018; 6: 954-65. doi: 10.1016/ S2213-8587(18)30038-X.

151. Czesnikiewicz-Guzik M, D'Aiuto F, Deanfield JE. Understanding residual inflammatory risk sheds new light on the clinical importance of periodontitis in cardiovascular disease. Eur Heart J. 2020; 41:818-9.doi: 10.1093/eurheartj/ehaa107.

152. Sharma S, Sridhar S, McIntosh A, Messow C-M, Munoz Aguilera E, Del Pinto R, et al. Periodontal therapy and treatment of hypertension-alternative to the pharmacological approach. A systematic review and meta-analysis. Pharmacol Res. 2021; 166: 105511, doi: 10.1016/ j.phrs.2021.105511.

153. Vidal F, Cordovil I, Figueredo CM, Guimarães Fischer R. Non-surgical periodontal treatment reduces cardiovascular risk in refractory hypertensive patients: a pilot study. J Clin Periodontol. 2013; 40(7): 681-7, doi: 10.1111/jcpe.12110.

154. D' Aiuto F, Orlandi M, Gunsolley JC. Evidence that periodontal treatment improves biobiomarkers and CVD outcomes. J Clin Periodontol. 2013; 40 Suppl 14(4 Suppl): S85-105, doi: 10.1111/jcpe.12061.

155. Zhou Q-B, Xia W-H, Ren J, Yu B-B, Tong X-Z, Chen Y-B, et al. Effect of Intensive Periodontal Therapy on Blood Pressure and Endothelial Microparticles in Patients with Prehy pertension and Periodontitis: A Randomized Controlled Trial. J Periodontol. 2017; 88: 711-22. doi: 10.1902/jop.2017.160447.

156. Guzik TJ, Skiba DS, Touyz RM, Harrison DG. The role of infiltrating immune cells in dys-functional adipose tissue. Cardiovasc Res. 2017;113:1009-23. doi: 10.1093/cvr/cvx108.

157. Mikolajczyk TP, Nosalski R, Szczepaniak P, Budzyn K, Osmenda G, Skiba D, et al. Role of chemokine RANTES in the regulation of perivascular inflammation, T-cell accumulation, and vascular dysfunction in hypertension. FASEB J. 2016;30:1987-99. doi: 10.1096/fj. 201 500088R.

158. Harrison DG, Guzik TJ, Lob HE, Madhur MS, Marvar PJ, Thabet SR, et al. Inflammation, immunity, and hypertension. Hypertension. 2011; 57: 132-40. doi: 10.1161/HYPERTEN- SION AHA.110.163576.

159. Madhur MS, Lob HE, McCann LA, Iwakura Y, Blinder Y, Guzik TJ, et al. Interleukin 17 promotes angiotensin II-induced hypertension and vascular r dysfunction. Hypertension. 2010;55:500-7. doi: 10.1161/HYPERTENSIONAHA.109.145094.

160. Youn J-C, Yu HT, Lim BJ, Koh MJ, Lee J, Chang DY, et al. Immunosenescent CD8 T Cells and C-X-C chemokine receptor type 3 chemokines are increased in human hypertension. Hypertension. 2013;62:126-33. doi: 10.1161/HYPERTENSIONAHA.113.00689.

161. Dutzan N, Kajikawa T, Abusleme L, Greenwell-Wild T, Zuazo CE, Ikeuchi T, et al. A dysbiotic microbiome triggers T17 cells to mediate oral mucosal immunopathology in mice and humans. Sci Transl Med. 2018;10: eaat0797. doi: 10.1126/scitranslmed.aat0797.

162. Dutzan N, Abusleme L. T helper 17 cells as pathogenic drivers of periodontitis. Adv Exp Med Biol. 2019; 1197: 107-17. doi: 10.1007/978-3-030-28524-1_9.

163. Kao C-Y, Huang F, Chen Y, Thai P, Wachi S, Kim C, et al. Upregulation of CC chemokine ligand 20 expression in human airway epithelium by IL-17 through a JAK-independent but MEK/NF-kappaB - dependent signaling pathway. J Immunol. 2005; 175: 6676-85. doi: 10. 4049/jimmunol.175.10.6676.

164. Kvakan H, Kleinewietfeld M, Qadri F, Park JK, Fischer R, Schwarz I, et al. Regulatory T cells ameliorate angiotensin II induced cardiac damage. Circulation. 2009;119:2904-12. doi: 10.1161/CIRCULATIONAHA.108.832782.

165. Kobayashi R, Kono T, Bolerjack BA, Fukuyama Y, Gilbert RS, Fujihashi K, et al. Induction of IL-10-producing CD4 T-cells in chronic periodontitis. J Dent Res. 2011;90:653-8.