Hypertension

COMMENTARY

Mounting Pressure of Periodontitis

Tomasz J. Guzik, Marta Czesnikiewicz-Guzik

Immune and inflammatory mechanisms modulate blood pressure and play an essential role in the development of hypertension.[1] Activation of T cells, macrophages, and natural killer (NK) cells is essential for their infiltration into the target organs, where they exert prohypertensive effects. The mechanisms of immune activation in hypertension remain, however, unclear.[1] While a generation of neoantigens has been implicated, it is clinically highly plausible, that underlying systemic inflammation may contribute to the development of hypertension. Periodontitis represents one of the most common inflammatory conditions worldwide.[2] An estimated 42% of dentate US adults 30 years or older have periodontitis, with 7.8% having severe periodontitis.[2] Prevalence of periodontitis increases with age, reaching 60% in adults older than 65.[2]This makes periodontitis one of the most common contributor to cardiovascular inflammatory risk.[3] It is also directly associated with the risk of hypertension.

Recent systematic review and metanalysis of 40 observational studies showed that diagnosis of periodontitis increased the likelihood of hypertension with an odds ratio of 1.68 (95% CI, 0.85–3.35) and was associated with higher mean systolic blood pressure (SBP; weighted mean difference of 4.49 mm Hg [95% CI, 2.88–6.11]) and diastolic blood pressure (DBP, 2.03 mm Hg [95% CI, 1.25–2.81]) when compared with subjects without periodontitis.[4] While mounting evidence supports a significant association between periodontitis and hypertension, the nature and mechanisms of this relationship remain unclear (Figure). Mendelian randomization and randomized clinical studies provide important clues. A 2-sample Mendelian randomization analysis, in the ≈750 000 UK-Biobank/International Consortium for Blood Pressure-genome-wide association study participants, using SNPs (single nucleotide polymprphisms) that were GWAS-linked to periodontitis (in *SIGLEC5*, *DEFA1A3*, *MTND1P5*, and *LOC107984137*), demonstrated a significant causal link between periodontitis and blood pressure phenotypes. It is essential to develop genetic tools for these studies further, to strengthen the conclusions of causality in this relationship. Randomized intervention trials also support a causal relationship between periodontitis and hypertension, by showing beneficial effects of treatment of periodontitis on blood pressure. Blood pressure reductions in patients randomized to intensive treatment of periodontitis were related to the improvement of periodontal status and the reduction in systemic inflammation.[5] A recent meta-analysis of interventional studies using periodontal therapy in hypertensive and prehypertensive individuals[6] has demonstrated improved blood pressure control (both SBP and DBP) in patients receiving intensive periodontal care. These changes were accompanied by improvements in vascular function and systemic inflammatory markers, previously implicated in hypertension,[7] such as circulating proinflammatory cytokines such as IFN-γ (interferon-γ) and IL (interleukin)-6 and activated (CD38+) and immunosenescent (CD57+CD28null) CD8+T cells.[5]

Moreover, mediation studies support the contribution of systemic inflammation to the increased prevalence of hypertension in patients with periodontitis. In a recent cross-sectional study, a representative sample of the United States (n=3460; National Health and Nutrition Examination Survey 2009/10) and Korean (n=4539; 2015 Korean National Health and Nutrition Examination Survey VI-3) populations were studied. A clear

Key Words: blood pressure ■ cytokines ■ inflammation ■ macrophages ■ phenotype

The opinions expressed in this Commentary are not necessarily those of the editors or of the American Heart Association.

Correspondence to: Tomasz J. Guzik, Regius Chair of Physiology and Cardiovascular Medicine, Institute of Cardiovascular and Medical Sciences, Glasgow, G12 8LA, United Kingdom. Email tomasz.guzik@glasgow.ac.uk

This article was sent to Meena S. Madhur, Guest Editor, for review by expert referees, editorial decision, and final disposition.

For Sources of Funding and Disclosures, see page 554.

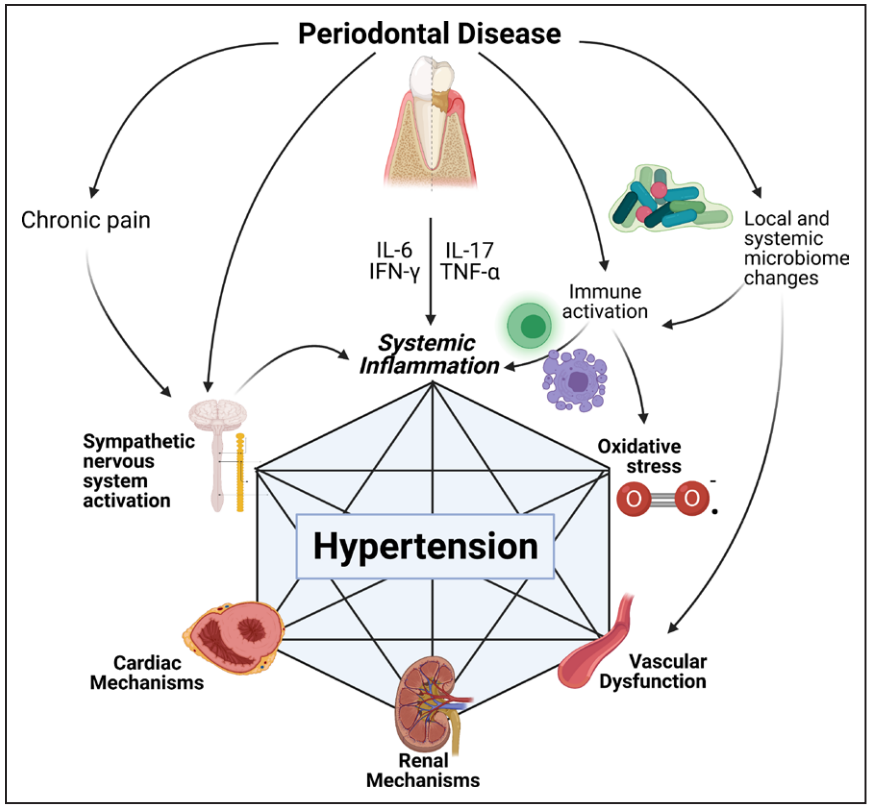

Figure. Potential mechanisms through which periodontal disease can affect blood pressure and hypertension development based on mosaic theory of hypertension. Created with BioRender. IFN-γ indicates interferon γ; IL, interleukin; and TNF - tumor necrosis factor.

association between periodontitis and hypertension was demonstrated, and inflammatory markers, including CRP (C-reactive protein) and white blood cell counts, served as mediators.[8] Importantly, the association between periodontitis and hypertension was independent of age, gender, body mass index, education level, smoking, alcohol consumption, creatinine, physical activity, presence of other comorbidities, or antihypertensive medications.[8] Mediation analyses performed by Muñoz Aguilera et al[8] in these large populations indicated that CRP acted as a mediator in the association between periodontitis and hypertension in both populations. In contrast, white blood cell acted as a mediator in the KNHANES while in the NHANES, its effect was dependent on CRP inclusion in the model.

A recent article in *Hypertension*,[9] from the group of Francesco D'Aiuto, has further extended these observations to a younger population with a median age of 35 (interquartile range, 12), in a nested case-control study of 250 subjects with periodontitis and 250 controls. Such design is important, as previously available data were reported in older populations with a high prevalence of hypertension. In the current study, authors describe that a significant relationship between periodontitis and SBP is observed not only in the context of hypertension, but also in otherwise systemically healthy young individuals. Thus, periodontitis may be also important at early stages of hypertensive pathology, for example in prehypertension. Indeed, previous clinical studies in prehypertensive individuals have confirmed blood pressure–lowering effect of the intensive improvement of periodontal status.[10] Linear regression performed by Muñoz Aguilera et al,[9] confirmed an association between case definition of periodontitis and increased mean SBP and DBP after adjusting for common risk factors. Similarly to previous studies, greater clinical severity of periodontitis was associated with higher mean SBP and DBP. While interpreting these results, we need to emphasize 2 critical aspects of the population studied here. Participants were recruited at the University College London Eastman Dental Institute between 2001 and 2018, making the population unique from the dental perspective. At the same time, while authors emphasize that studied subjects are systemically healthy, about 15% of them exhibited blood pressure values in a hypertensive range. Authors emphasize that, in contrast to their previous studies in 2015 KNHANES,[8] white blood cell counts did not act as a mediator of the association between periodontitis and SBP. They conclude that, in younger individuals, systemic inflammation may not explain the relationship between periodontitis and increased blood pressure. This is certainly possible, and there are several inflammation-independent mechanisms through which periodontitis could affect blood pressure and hypertension (Figure). Before arriving at such conclusions, however, it is crucial to consider that the current study may not be sufficiently powered to robustly address the role of inflammation in mediating effects of periodontitis on hypertension. In the present study,[9] a significantly smaller number of subjects was investigated than in the 2015 KNHANES cohort.[8] Therefore large, sufficiently powered cohort studies are needed, before concluding that inflammation is less critical in younger, systemically healthy patients, as suggested by

COMMENTARY

Muñoz Aguilera in the current analysis.[9] It is also essential to emphasize that white blood cell, within the normal range, as reported in the current study, do not represent the most optimal marker of systemic inflammation. Immune cells are not only increased in periodontitis but are activated to release soluble mediators, such as IFN-γ, IL-17, IL-6, which affect a wide range of mechanisms regulating blood pressure (Figure).[11] Therefore, the current study does not provide sufficient evidence to exclude the role of low-grade inflammation, even in systemically healthy young subjects. Further detailed mechanistic studies are needed.

Having considered this, the study by Muñoz Aguilera et al,[9] raises key questions regarding the possible mechanisms linking periodontitis and hypertension. These may include chronic pain, sympathetic activation, microbiome changes,[12] local immune, and inflammatory mechanisms (Figure). Recent discoveries of the links between periodontitis and hypertension provide an important clinical and translational context to the inflammatory theory of high blood pressure.[1,13] While the initial evidence for the role of immune mechanisms in hypertension has been obtained primarily in animal models,[1] recent epidemiological and genetic evidence strongly supports this mechanism of hypertension. For example, a positive association between quintiles of lymphocyte, monocyte, or neutrophil counts, with increased SBP, DBP, and pulse pressure was observed in the UK Biobank population.[14] Moreover, Mendelian randomization confirmed a potential causal relationship of lymphocyte count with SBP and DBP. This relationship was estimated as 0.69 mm Hg (95% CI, 0.19–1.20) for SBP and 0.56 mm Hg (95% CI, 0.23–0.90) for DBP increase per 1 SD genetically elevated lymphocyte count.[14] T-lymphocyte activation, with an overproduction of Th1 cytokines, is an important feature of a systemic immune response to periodontitis. In parallel, it exacerbates pressure and vascular responses to low concentrations of angiotensin II in the animal models of hypertension.[15] Such overlap in the immunopathogenesis of both conditions provides important clues for the understanding of a clinical relationship between periodontitis and high blood pressure.

A major question in the field that remains is if treating periodontal disease can prevent hypertension or improve hypertension management. While the proof-of-concept evidence is available, addressing this important issue will require further multicenter randomized trials, which are urgently needed in the light of observational, genetic, and experimental evidence.

ARTICLE INFORMATION

Affiliations

From the Department of Medicine, Jagiellonian University Medical College, Krakow, Poland (T.J.G.). Institute of Cardiovascular and Medical Sciences, University of Glasgow, United Kingdom (T.J.G.); Department of Dental Prophylaxis and Experimental Dentistry, Jagiellonian Medical College, Krakow, Poland (M.C.-G.); and Department of Periodontology and Oral Sciences Research Group, University of Glasgow Dental School, United Kingdom (M.C.-G.).

Sources of Funding

We acknowledge the funding from the European Research Council (ERC-CoG-726318; InflammaTENSION; to T.J. Guzik) and the European Commission (Era-Net CVD; PlaqueFIGHT; funded in Poland by NCBiR).

Disclosures

T.J. Guzik is supported by European Research Council and received support from Merck outside of scope of current text. The other author reports no conflict.

REFERENCES

1. Drummond GR, Vinh A, Guzik TJ, Sobey CG. Immune mechanisms of hypertension. *Nat Rev Immunol.* 2019;19:517–532. doi: 10.1038/s41577-019-0160-5
2. Eke PI, Lu H, Zhang X, Thornton-Evans G, Borgnakke WS, Holt JB, Croft JB. Geospatial distribution of periodontists and US adults with severe periodontitis. *J Am Dent Assoc.* 2019;150:103–110. doi: 10.1016/j.adaj.2018.09.021
3. Czesnikiewicz-Guzik M, Górska R. Oral health in childhood as a predictor of future cardiovascular risk. *Cardiovasc Res.* 2020;116:e98–e100. doi: 10.1093/cvr/cvz335
4. Muñoz Aguilera E, Suvan J, Buti J, Czesnikiewicz-Guzik M, Barbosa Ribeiro A, Orlandi M, Guzik TJ, Hingorani AD, Nart J, D'Aiuto F. Periodontitis is associated with hypertension: a systematic review and meta-analysis. *Cardiovasc Res.* 2020;116:28–39. doi: 10.1093/cvr/cvz201
5. Czesnikiewicz-Guzik M, Osmenda G, Siedlinski M, Nosalski R, Pelka P, Nowakowski D, Wilk G, Mikolajczyk TP, Schramm-Luc A, Furtak A, 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;40:3459–3470. doi: 10.1093/eurheartj/ehz646
6. Sharma S, Sridhar S, McIntosh A, Messow CM, Aguilera EM, Del Pinto R, Pietropaoli D, Gorska R, Siedlinski M, Maffia P, 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
7. Kreutz R, Algharably EAE, Azizi M, Dobrowolski P, Guzik T, Januszewicz A, Persu A, Prejbisz A, Riemer TG, Wang JG, et al. Hypertension, the renin-angiotensin system, and the risk of lower respiratory tract infections and lung injury: implications for COVID-19. *Cardiovasc Res.* 2020;116:1688–1699. doi: 10.1093/cvr/cvaa097
8. Muñoz Aguilera E, Leira Y, Miró Catalina Q, Orlandi M, Czesnikiewicz-Guzik M, Guzik TJ, Hingorani AD, Nart J, D'Aiuto F. Is systemic inflammation a missing link between periodontitis and hypertension? Results from two large population-based surveys. *J Intern Med.* 2021;289:532–546. doi: 10.1111/joim.13180
9. 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;77:1765–1774. doi: 10.1161/HYPERTENSIONAHA.120.16790
10. Zhou QB, Xia WH, Ren J, Yu BB, Tong XZ, Chen YB, Chen S, Feng L, Dai J, Tao J, et al. Effect of intensive periodontal therapy on blood pressure and endothelial microparticles in patients with prehypertension and periodontitis: a randomized controlled trial. *J Periodontol.* 2017;88:711–722. doi: 10.1902/jop.2017.160447
11. Nosalski R, Siedlinski M, Denby L, McGinnigle E, Nowak M, Cat AND, Medina-Ruiz L, Cantini M, Skiba D, Wilk G, et al. T-cell-derived miRNA-214 mediates perivascular fibrosis in hypertension. *Circ Res.* 2020;126:988–1003. doi: 10.1161/CIRCRESAHA.119.315428
12. Jama HA, Beale A, Shihata WA, Marques FZ. The effect of diet on hypertensive pathology: is there a link via gut microbiota-driven immunometabolism? *Cardiovasc Res.* 2019;115:1435–1447. doi: 10.1093/cvr/cvz091
13. Van Beusecum JP, Harrison DG. New insight sheds light as to how nitrite might reduce blood pressure height: is this alright? *Cardiovasc Res.* 2020;116:1–3. doi: 10.1093/cvr/cvz248
14. Siedlinski M, Jozefczuk E, Xu X, Teumer A, Evangelou E, Schnabel RB, Welsh P, Maffia P, Erdmann J, Tomaszewski M, et al. White blood cells and blood pressure: a mendelian randomization study. *Circulation.* 2020;141:1307–1317. doi: 10.1161/CIRCULATIONAHA.119.045102
15. Czesnikiewicz-Guzik M, Nosalski R, Mikolajczyk TP, Vidler F, Dohnal T, Dembowska E, Graham D, Harrison DG, Guzik TJ. Th1-type immune responses to Porphyromonas gingivalis antigens exacerbate angiotensin II-dependent hypertension and vascular dysfunction. *Br J Pharmacol.* 2019;176:1922–1931. doi: 10.1111/bph.14536