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Immune aspects of systemic hypertension; a short-review to recent concepts

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ABSTRACT

The renin-angiotensin-aldosterone system (RAAS) and the immune system interact in hypertension through various mechanisms, including inflammation, immune cell infiltration, oxidative stress, and aldosterone-induced hypertension. Further research is needed to fully understand the complex interplay between the RAAS and the immune system in hypertension and to identify potential therapeutic targets. Additionally, T lymphocytes, monocytes, macrophages, dendritic cells, neutrophils, and B lymphocytes are some of the immune cells that have been implicated in hypertension. These immune cells can promote vascular inflammation and remodeling, produce reactive oxygen species and cytokines, and activate the adaptive immune response. Further research is needed to fully understand the role of the immune system in hypertension and to identify potential therapeutic targets.

Mini-Review

Implication for health policy/practice/research/medical education:
Inflammation can contribute to hypertension through various mechanisms, including dysregulated immune responses, immune cell infiltration, oxidative stress, activation of the renin-angiotensin-aldosterone system (RAAS), endothelial dysfunction, and pro-inflammatory cytokines. Inflammatory cytokines can also play a significant role in hypertension by promoting vascular and renal dysfunction. Tumor necrosis factor alpha (TNF-α), interleukin (IL)-17A, IL-6, interferon gamma (IFN-γ), IL-1β are some of the cytokines that have been implicated in hypertension. Reactive oxygen species contribute to oxidative stress in hypertension by promoting vascular injury and impairing blood pressure regulation. Superoxide anion, hydrogen peroxide, peroxynitrite, singlet oxygen, and hydroxyl radical are some of the examples of reactive oxygen species that have been implicated in hypertension.

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Introduction

There is growing evidence that suggests a link between systemic hypertension and immune dysfunction (1). Chronic low-grade inflammation, characterized by elevated levels of pro-inflammatory cytokines and activated renin-angiotensin-aldosterone system (RAAS), has been observed in individuals with hypertension (2). This inflammation is thought to contribute to the development and progression of hypertension by promoting endothelial dysfunction, oxidative stress, and vascular remodeling (1,2). In addition to chronic inflammation, immune cells such as T cells, B cells, and macrophages have also been implicated in the pathogenesis of hypertension (3). T cells have been shown to play a role in the development of hypertension by promoting vascular inflammation and remodeling. B cells have been found to produce antibodies that contribute to hypertension by targeting components of the RAAS (2,3). Besides, macrophages are involved in the development of hypertension by promoting inflammation and oxidative stress in the vasculature (2). Furthermore, recent studies have shown that the gut microbiome may also play a role in the development of hypertension. Dysbiosis, or an imbalance in the gut microbiome, has been associated with hypertension and is thought to contribute to immune dysfunction and chronic inflammation (4). This mini-review aims to investigate the immune mechanisms of systemic hypertension.

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Search strategy

In this review, we conducted a search across several databases, including PubMed, Web of Science, EBSCO, Scopus, Google Scholar, the Directory of Open Access Journals (DOAJ), and Embase. We utilized various keywords such as inflammation, cytokines, reactive oxygen species, hypertension, chronic inflammation, and the renin-angiotensin-aldosterone system.

Hypertension as an immune-related disease

Hypertension has been increasingly recognized as an immune-related disease, with accumulating evidence supporting the involvement of the immune system in its pathogenesis (5,6). The immune system plays a role in hypertension through various mechanisms, including inflammation, oxidative stress, and immune cell infiltration (2). Studies have shown consistent association between hypertension, proinflammatory cytokines, and the cells of the innate and adaptive immune systems (7).

Focus on inflammatory cytokines

Inflammatory cytokines play a significant role in the development and progression of hypertension. Tumor necrosis factor alpha (TNF-α) contributes to the development of hypertension observed in a genetic mouse model of systemic lupus erythematosus (8,9). Since, Venegas-Pont et al found, treatment with etanercept, a TNF-α antagonist, reduced mean arterial pressure, albuminuria, monocyte/macrophage infiltration, and renal cortex NADPH activity in female SLE mice (9). Conversely, the study by Davis et al showed, interleukin (IL)-17A is a pro-inflammatory cytokine that promotes vascular and renal dysfunction in hypertension (10). Furthermore, the study by Didion et al detected that IL-6 affects vascular function and endothelium-derived factors involved in blood pressure regulation (11). Additionally, IL-6 has also been detected in animal brains in hypertension models (2). Likewise, the previous study by Benson et al demonstrated that interferon gamma (IFN-γ) is also another pro-inflammatory cytokine that has been detected in animal brains in hypertension models (12). Moreover, IL-1β is a pro-inflammatory cytokine that has been detected in animal brains in hypertension models (2,13). Tanase et al also noted that other cytokines have been implicated in hypertension include IL-4, IL-10, and IL-13 (14).

Focus on oxidative stress

Oxidative stress results in an excessive generation of reactive oxygen species (ROS), which can cause vascular injury and contribute to hypertension (15). Several years ago, Rodrigo et described the role of ROS as mediator of vasoconstriction induced by angiotensin II, endothelin-1, and urotensin-II, among others (16). Oxidative stress can also promote posttranslational modification of proteins and aberrant signaling, leading to hypertension (17). Hypertension is associated with increased vascular oxidative stress, but there is still a debate whether oxidative stress is a cause or a result of hypertension. Some studies suggest that oxidative stress is not a cause but rather a result of hypertension (18). However, the mutual correlation between oxidative stress, inflammation, and the pathogenesis of hypertension has been shown (19). Antioxidant therapy may be more efficient in the prevention rather than in the reduction of established hypertension (20).

Focus on antioxidants

Antioxidants can help reduce oxidative stress by reducing the formation both ROS and increasing the bioavailability of nitric oxide, which helps relax blood vessels and lower blood pressure (21). Antioxidants can decrease ROS generation by scavenging free radicals and inhibiting the activity of enzymes that produce ROS (22). Conversely, antioxidants can increase nitric oxide bioavailability by preventing its degradation and enhancing its production (23). Moreover, antioxidants improve vascular function by reducing oxidative stress and promoting endothelial cell survival and proliferation (24). Meanwhile, antioxidants can reduce blood pressure by improving vascular function and reducing oxidative stress (25). In addition, antioxidants can prevent hypertension by reducing oxidative stress and promoting vascular health (25). For example, antioxidants that have been studied for their efficacy to reduce oxidative stress in hypertension include vitamins C and E, polyphenols, alpha-lipoic acid, N-acetylcysteine, coenzyme Q10, and superoxide dismutase (25,26).

Focus on ROS

Reactive oxygen species are molecules that contribute to oxidative stress in hypertension (27). Superoxide anion (O2-) is a ROS that is produced by various enzymes, including NADPH oxidase, xanthine oxidase, and uncoupled endothelial nitric oxide synthase (1,27). Moreover, hydrogen peroxide is also a ROS that is produced by dismutation of superoxide anion by superoxide dismutase (27). Besides, peroxynitrite (ONOO-) is a highly reactive ROS that is formed by the reaction of superoxide anion with nitric oxide (29). Meanwhile, singlet oxygen (1O2) is a ROS that is produced by the reaction of excited oxygen molecules with organic compounds and finally, hydroxyl radical (OH•) is a highly reactive ROS that is produced by the reaction of H2O2 with transition metals, such as iron and copper (30-32).

Focus on the role of immune cells

T lymphocytes have been shown to play a role in hypertension. These cells infiltrate blood vessels and promote vascular inflammation and remodeling (33). Likewise, monocytes and macrophages are immune cells that can infiltrate blood vessels and promote vascular inflammation and remodeling (34). They can also produce ROS and cytokines that contribute to hypertension (35). Recently, Navaneethabalakrishnan et al, mentioned the role of dendritic cells that can present antigens to T lymphocytes and activate the adaptive immune response (36). These elements have a role in hypertension by promoting vascular inflammation and remodeling (37). Additionally, neutrophils can infiltrate blood vessels and promote vascular inflammation and remodeling (38). These cells can also produce ROS and cytokines. Finally, B lymphocytes produce antibodies and play a role in the adaptive immune response, which have a role in hypertension by promoting vascular inflammation and remodeling (39).

Role of RAAS in immune-mediated hypertension

The RAAS is an essential regulator of blood pressure homeostasis (40). The primary effector molecule of the RAS is angiotensin II (Ang II), which is produced by the cleavage of angiotensinogen by renin (41). The RAAS plays a significant role in the pathogenesis of hypertension, and its activation can lead to vasoconstriction, sodium retention, and increased blood pressure (22). The RAAS has also been shown to interact with the immune system in hypertension. For example, angiotensin II can stimulate the production of pro-inflammatory cytokines, such as TNF-α and IL-6, which can contribute to hypertension by promoting vasoconstriction and impairing endothelial function (2). The RAAS can also activate the immune system by promoting the infiltration of immune cells, such as T lymphocytes and macrophages, into the blood vessel walls (43). In addition, RAAS can stimulate the production of ROS, which can cause vascular injury and contribute to hypertension (44). Also, RAAS is a significant part of the regulation of sodium and water balance, and its activation can lead to sodium retention and volume expansion, which can contribute to hypertension (40). Furthermore, aldosterone, a hormone produced by the adrenal gland, is a key component of the RAAS and can promote sodium retention and potassium excretion (45), since aldosterone-induced hypertension is a well-described phenomenon that is associated with increased cardiovascular morbidity and mortality (46).

Conclusion

Systemic hypertension can be caused by various factors including genetic predisposition, lifestyle choices such as diet and exercise, and underlying medical conditions like kidney disease or hormonal imbalances. Immune aspects may play a role in the development of systemic hypertension through the release of certain cytokines that contribute to vascular inflammation and stiffness, leading to increased blood pressure.

Authors' contribution

Conceptualization: Rahimeh Eskandarian.
Data curation: Mohammad Memaria.
Investigation: Rahimeh Eskandarian, Mohammad Memaria.
Resources: Rahimeh Eskandarian.
Supervision: Rahimeh Eskandarian.
Validation: Rahimeh Eskandarian.
Visualization: Rahimeh Eskandarian.
Writing–original draft: Rahimeh Eskandarian.
Writing–review and editing: Rahimeh Eskandarian, Mohammad Memaria.

Conflicts of interest

The authors declare that they have no competing interests.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized Perplexity to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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References

1. Copur S, Peltek IB, Mutlu A, Tanriover C, Kanbay M. A new immune disease: systemic hypertension. Clin Kidney J. 2023;16:1403-1419. doi: 10.1093/ckj/sfad059.
2. Zhang Z, Zhao L, Zhou X, Meng X, Zhou X. Role of inflammation, immunity, and oxidative stress in hypertension: New insights and potential therapeutic targets. Front Immunol. 2023;13:1098725. doi: 10.3389/fimmu.2022.1098725.
3. Caillon A, Paradis P, Schiffrin EL. Role of immune cells in hypertension. Br J Pharmacol. 2019;176:1818-1828. doi: 10.1111/bph.14427.
4. Dos Passos RR, Santos CV, Priviero F, Briones AM, Tostes RC, Webb RC, Bomfim GF. Immunomodulatory Activity of Cytokines in Hypertension: A Vascular Perspective. Hypertension. 2024;81:1411-1423. doi: 10.1161/

HYPERTENSIONAHA.124.21712.
5. Yang T, Santisteban MM, Rodriguez V, Li E, Ahmari N, Carvajal JM, et al. Gut dysbiosis is linked to hypertension. Hypertension. 2015;65:1331-40. doi: 10.1161/hypertensionaha.115.05315.
6. Rodriguez-Iturbe B, Pons H, Johnson RJ. Role of the Immune System in Hypertension. Physiol Rev. 2017;97:1127-1164. doi: 10.1152/physrev.00031.2016.
7. Singh MV, Chapleau MW, Harwani SC, Abboud FM. The immune system and hypertension. Immunol Res. 2014;59:243-53. doi: 10.1007/s12026-014-8548-6.
8. Norlander AE, Madhur MS, Harrison DG. The immunology of hypertension. J Exp Med. 2018;215:21-33. doi: 10.1084/jem.20171773.
9. Venegas-Pont M, Manigrasso MB, Grifoni SC, LaMarca BB, Maric C, Racusen LC, et al. Tumor necrosis factor-alpha antagonist etanercept decreases blood pressure and protects the kidney in a mouse model of systemic lupus erythematosus. Hypertension. 2010;56:643-9. doi: 10.1161/HYPERTENSIONAHA.110.157685.
10. Davis GK, Fehrenbach DJ, Madhur MS. Interleukin 17A: Key Player in the Pathogenesis of Hypertension and a Potential Therapeutic Target. Curr Hypertens Rep. 2021;23:13. doi: 10.1007/s11906-021-01128-7.
11. Didion SP. Cellular and Oxidative Mechanisms Associated with Interleukin-6 Signaling in the Vasculature. Int J Mol Sci. 2017;18:2563. doi: 10.3390/ijms18122563.
12. Benson LN, Liu Y, Deck K, Mora C, Mu S. IFN-γ Contributes to the Immune Mechanisms of Hypertension. Kidney360. 2022;3:2164-2173. doi: 10.34067/KID.0001292022.
13. Shi P, Diez-Freire C, Jun JY, Qi Y, Katovich MJ, Li Q, et al. Brain microglial cytokines in neurogenic hypertension. Hypertension. 2010;56:297-303. doi: 10.1161/HYPERTENSIONAHA.110.150409.
14. Tanase DM, Gosav EM, Radu S, Ouatu A, Rezus C, Ciocoiu M, et al. Arterial Hypertension and Interleukins: Potential Therapeutic Target or Future Diagnostic Marker? Int J Hypertens. 2019;2019:3159283. doi: 10.1155/2019/3159283.
15. Xu S, Touyz RM. Reactive oxygen species and vascular remodelling in hypertension: still alive. Can J Cardiol. 2006;22:947-51. doi: 10.1016/s0828-282x(06)70314-2.
16. Rodrigo R, González J, Paoletto F. The role of oxidative stress in the pathophysiology of hypertension. Hypertens Res. 2011;34:431-40. doi: 10.1038/hr.2010.264.
17. Touyz RM, Rios FJ, Alves-Lopes R, Neves KB, Camargo LL, Montezano AC. Oxidative Stress: A Unifying Paradigm in Hypertension. Can J Cardiol. 2020;36:659-670. doi: 10.1016/j.cjca.2020.02.081.
18. Grossman E. Does increased oxidative stress cause hypertension? Diabetes Care. 2008;31 Suppl 2:S185-9. doi: 10.2337/dc08-s246.
19. Krzemińska J, Wronka M, Młynarska E, Franczyk B, Rysz J. Arterial Hypertension-Oxidative Stress and Inflammation. Antioxidants (Basel). 2022;11:172. doi: 10.3390/antiox11010172.
20. Sorriento D, De Luca N, Trimarco B, Iaccarino G. The Antioxidant Therapy: New Insights in the Treatment of Hypertension. Front Physiol. 2018;9:258. doi: 10.3389/fphys.2018.00258.
21. Chen Q, Wang Q, Zhu J, Xiao Q, Zhang L. Reactive oxygen species: key regulators in vascular health and diseases. Br J Pharmacol. 2018;175:1279-1292. doi: 10.1111/bph.13828.
22. Lobo V, Patil A, Phatak A, Chandra N. Free radicals, antioxidants and functional foods: Impact on human health. Pharmacogn Rev. 2010;4:118-26. doi: 10.4103/0973-7847.70902.
23. Jomova K, Raptova R, Alomar SY, Alwasel SH, Nepovimova E, Kuca K, et al. Reactive oxygen species, toxicity, oxidative stress, and antioxidants: chronic diseases and aging. Arch Toxicol. 2023;97:2499-2574. doi: 10.1007/s00204-023-03562-9.
24. Shafi S, Ansari HR, Bahitham W, Aouabdi S. The Impact of Natural Antioxidants on the Regenerative Potential of Vascular Cells. Front Cardiovasc Med. 2019;6:28. doi: 10.3389/fcvm.2019.00028.
25. Amponsah-Offeh M, Diaba-Nuhoho P, Speier S, Morawietz H. Oxidative Stress, Antioxidants and Hypertension. Antioxidants (Basel). 2023;12:281. doi: 10.3390/antiox12020281.
26. Rodella U, Honisch C, Gatto C, Ruzza P, D'Amato Tóthová J. Antioxidant Nutraceutical Strategies in the Prevention of Oxidative Stress Related Eye Diseases. Nutrients. 2023;15:2283. doi: 10.3390/nu15102283.
27. Loperena R, Harrison DG. Oxidative Stress and Hypertensive Diseases. Med Clin North Am. 2017;101:169-193. doi: 10.1016/j.mcna.2016.08.004.
28. Mittal M, Siddiqui MR, Tran K, Reddy SP, Malik AB. Reactive oxygen species in inflammation and tissue injury. Antioxid Redox Signal. 2014;20:1126-67. doi: 10.1089/ars.2012.5149.
29. Lubos E, Handy DE, Loscalzo J. Role of oxidative stress and nitric oxide in atherothrombosis. Front Biosci. 2008;13:5323-44. doi: 10.2741/3084.
30. Collin F. Chemical Basis of Reactive Oxygen Species Reactivity and Involvement in Neurodegenerative Diseases. Int J Mol Sci. 2019;20:2407. doi: 10.3390/ijms20102407.
31. Phaniendra A, Jestadi DB, Periyasamy L. Free radicals: properties, sources, targets, and their implication in various diseases. Indian J Clin Biochem. 2015;30):11-26. doi: 10.1007/s12291-014-0446-0.
32. Abdal Dayem A, Hossain MK, Lee SB, Kim K, Saha SK, Yang GM, Choi HY, Cho SG. The Role of Reactive Oxygen Species (ROS) in the Biological Activities of Metallic Nanoparticles. Int J Mol Sci. 2017;18:120. doi: 10.3390/ijms18010120.
33. Patrick DM, Van Beusecum JP, Kirabo A. The role of inflammation in hypertension: novel concepts. Curr Opin Physiol. 2021;19:92-98. doi: 10.1016/j.cophys.2020.09.016.
34. Medrano-Bosch M, Simón-Codina B, Jiménez W, Edelman ER, Melgar-Lesmes P. Monocyte-endothelial cell interactions in vascular and tissue remodeling. Front Immunol. 2023;14:1196033. doi: 10.3389/fimmu.2023.1196033.
35. Barrows IR, Ramezani A, Raj DS. Inflammation, Immunity,

and Oxidative Stress in Hypertension-Partners in Crime? Adv Chronic Kidney Dis. 2019;26:122-130. doi: 10.1053/j.ackd.2019.03.001.
36. Navaneethabalakrishnan S, Smith HL, Arenaz CM, Goodlett BL, McDermott JG, Mitchell BM. Update on Immune Mechanisms in Hypertension. Am J Hypertens. 2022;35:842-851. doi: 10.1093/ajh/hpac077.
37. Ma J, Li Y, Yang X, Liu K, Zhang X, Zuo X, et al. Signaling pathways in vascular function and hypertension: molecular mechanisms and therapeutic interventions. Signal Transduct Target Ther. 2023;8:168. doi: 10.1038/s41392-023-01430-7.
38. Araos P, Figueroa S, Amador CA. The Role of Neutrophils in Hypertension. Int J Mol Sci. 2020;21:8536. doi: 10.3390/ijms21228536.
39. Crowley SD. The cooperative roles of inflammation and oxidative stress in the pathogenesis of hypertension. Antioxid Redox Signal. 2014;20:102-20. doi: 10.1089/ars.2013.5258.
40. Martyniak A, Tomasik PJ. A New Perspective on the Renin-Angiotensin System. Diagnostics (Basel). 2022;13:16. doi: 10.3390/diagnostics13010016.
41. Benigni A, Cassis P, Remuzzi G. Angiotensin II revisited: new roles in inflammation, immunology and aging. EMBO Mol Med. 2010;2:247-57. doi: 10.1002/emmm.201000080.
42. Ames MK, Atkins CE, Pitt B. The renin-angiotensin-aldosterone system and its suppression. J Vet Intern Med. 2019;33:363-382. doi: 10.1111/jvim.15454.
43. Crowley SD, Rudemiller NP. Immunologic Effects of the Renin-Angiotensin System. J Am Soc Nephrol. 2017;28:1350-1361. doi: 10.1681/ASN.2016101066.
44. Manrique C, Lastra G, Gardner M, Sowers JR. The renin angiotensin aldosterone system in hypertension: roles of insulin resistance and oxidative stress. Med Clin North Am. 2009;93:569-82. doi: 10.1016/j.mcna.2009.02.014.
45. Epstein M. Aldosterone as a determinant of cardiovascular and renal dysfunction. J R Soc Med. 2001;94:378-83. doi: 10.1177/014107680109400803.
46. Freel EM, Connell JM. Mechanisms of hypertension: the expanding role of aldosterone. J Am Soc Nephrol. 2004;15:1993-2001. doi: 10.1097/01.ASN.0000132473.50966.14.