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NUTRIEPIGENETIC MODULATION OF HYPERTENSION RISK: A REVIEW OF THE LITERATURE

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ABSTRACT

This review aimed to investigate the interplay between dietary components and epigenetic modulation in the pathogenesis of hypertension. A comprehensive literature search encompassing all published primary and secondary research dating up to March 2024 was carried out on several electronic databases, including MEDLINE, EBSCO-Host, Science Direct, ProQuest, and Google Scholar. Individual genomes and dietary intake exhibit a bidirectional relationship, influencing the hypertension risk. Unhealthy dietary patterns can compromise DNA integrity through DNA methylation and histone acetylation, ultimately affecting both systolic and diastolic blood pressure. Dietary macronutrient composition (carbohydrates, lipids, and proteins) significantly alters the expression of specific microRNAs (miRNAs) known to regulate endothelial function and blood pressure homeostasis. Moreover, micronutrients (vitamin A, D, E, Zinc, Iodine, and Sodium) can exert epigenetic effects on blood pressure via receptor interactions, potentially modifying cardiovascular disease risk. Dietary imbalances in macro and micronutrients can epigenetically influence hypertension development. Addressing these deficiencies through targeted interventions may offer a complementary approach to hypertension treatment.

Keywords: hypertension; nutriepigenetics; risk factor

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INTRODUCTION

Hypertension represents a major global public health burden, constituting the primary etiological factor for cardiovascular disease and premature mortality.1 The prevalence of hypertension has demonstrably increased on a global scale, with a particularly notable rise observed in low- and middle-income countries (LMICs).2 In 2010, estimates indicated that 31.1% of the global adult population (approximately 1.39 billion individuals) were affected by hypertension.3The etiology of hypertension is multifaceted, involving a dynamic interplay between genetic susceptibility and environmental factors that confer disease risk.4 While numerous conventional risk factors for hypertension have been well-defined, a counterintuitive finding has emerged: many identified susceptibility genes do not appear to directly influence these established risk factors.5 Additionally, the complex interplay between

genetic polymorphisms and environmental exposures, which is manifested in macro- and micronutrients status, further complicates the hypertension pathogenesis, posing a significant challenge to the elucidation of the underlying genetic architecture.6

Globally, an estimated 870 million individuals experience some forms of malnutrition, with nearly 97.9% residing in developing nations. The insufficient dietary intake, characterized by limited consumption of fresh fruits, vegetables, and high-quality protein sources, contributes to widespread micronutrient deficiencies in essential amino acids, vitamins, and minerals.7 Study by Yang et al. in 2022 showed that 82.9% hypertensive patients were considered to have malnutrition as evaluated by Naples Prognostic Score (NPS), and was independently associated with cardiovascular mortality (HR=3.30 [95% CI:1.66–6.56]) using the Nutritional Risk Index (NRI) score ($P<0.05$).8 Conversely, a 2023 study by Zhang et al. revealed that individuals categorized as obese-well-nourished also had a substantially elevated risk of hypertension (OR = 1.47, 95% CI: 1.30-1.67) and a significantly higher risk of mortality (HR = 1.31, 95% CI: 1.03-1.69).9 Several novel genes involved in this mechanism include PCSK9, MyBPC3, and DNase1. In addition, microRNAs also play a role in this mechanism; specific miRNAs involved are miR-145-5p, miR-1-3p, and miR-423-5p.9 This findings highlighting the potential detrimental effects of both insufficient and excessive dietary intake on cardiovascular health and also potential novel biomarker for hypertension.

Large-scale epigenome-wide association studies (EWAS), combined with targeted candidate gene analysis and functional experiments in cell lines and animal models, have elucidated the mechanisms by which dietary components and patterns influence the epigenome.10 Notably, risk factors for hypertension and its complications, such as obesity, inflammation, and oxidative stress, have been linked to specific epigenetic alterations: histone acetylation modifications, global DNA hypomethylation (decreased methylation), and telomere shortening.11,12 Dietary imbalances, including excess macronutrients in high-fat diets or deficiencies in micronutrients like folate and B-vitamins, alongside the influence of bioactive food compounds, can modulate the activity of DNA methyltransferases and histone-modifying enzymes, subsequently leads to the occurrence of hypertension.13,14 This review aimed to investigate the link between dietary influences on gene expression and the development of hypertension.

METHOD

Variable of interest

This review sought to interrogate the potential interplay between dietary interventions and transcriptional regulation, culminating in the development of hypertension.

Eligibility criteria

Type of studies

This comprehensive literature review encompassed all published primary and secondary research endeavors, meticulously examining the potential link between nutriepigenetic modulations and the incidence of hypertension. Conversely, studies falling under the category of commentaries/editorials were excluded.

Outcome of interest

The primary focus of this investigation was to identify genetic elements, such as specific loci or entire genomes, that influence the development of hypertension. Additionally, the research aimed to elucidate the macro- or micronutrients intake that contribute to these epigenetic mechanisms.

Search strategy and study selection

A literature search was carried out from February 25th to March 3rd 2024 on electronic databases including MEDLINE, EBSCO-Host, Science Direct, ProQuest, and Google Scholar to retrieve eligible studies. This was performed by three independent authors. All studies obtained were exported into the Zotero reference manager software, and then checked for duplication, followed by titles and abstracts screening. The assessment was performed separately by the authors and studies were excluded when the title and/or abstract were not appropriate for this review. The selected papers were reviewed in full-text assessment using the aforementioned eligibility criteria. The differences observed were settled among the review team members.

Data collection process

The findings of the included studies were elaborated by all authors. To investigate the epigenetic influence of macro- and micronutrients on blood pressure, the following data were extracted from the reviewed literature: types of nutrients (macro: protein, lipid, carbohydrates), their epigenetic modifications, and their potential impact on blood pressure regulation, alongside with each correspondence studies.

Summary measures

Descriptive results were reported as narrative or tabulative data. All numerical (continuous) data were presented in mean ± standard deviation for normally distributed or median (interquartile range) for non-normally distributed. If applicable, p-value was also included for each item to show the significance of results, with less than 0.05 was considered significant.

RESULT

The Nutrigenetics Basis of Hypertension

A bidirectional interplay exists between individual genomes and dietary intake, influencing a person's susceptibility to hypertension.[15] Genetic framework dictates metabolic response, nutritional state, and propensity towards nutrient-dependent pathologies.[15] Conversely, nutrients modulate gene expression, impacting metabolic pathways at the molecular level. These interactions spurred the emergence of nutrigenetics and nutrigenomics.[16] This review adopted a nutrigenetic perspective to explore the potential for dietary modifications in influencing hypertension risk.A healthy dietary pattern, rich in vegetables, fruits, whole grains, and lean protein sources, with limited processed foods and added sugars, is recommended to promote optimal health.[17] Research suggests that dietary choices can influence various mechanisms related to DNA integrity and stability.[18] An unhealthy eating pattern can disrupt these processes by altering epigenetic mechanisms, including DNA methylation and histone acetylation.[19] These disruptions are believed to contribute to the development of chronic non-communicable diseases (NCDs), such as hypertension.[19]

Diets high in calories may negatively influence gene expression through a decrease in DNA methylation (DNAm) by around 50% within the promoter region of the Zfp423 gene. This phenomenon might be linked to the abundance of CpG sites in this specific region.[20] Conversely, calorie restriction programs that prioritize optimal nutrition alongside weight loss demonstrate protective effects against chronic diseases. This benefit may be attributed to modifications in histone-modifying proteins, such as CREB-binding protein and sirtuins. These proteins play a critical role in epigenetic processes and influence the methylation patterns of various genes within adipose tissue.[21] Adherence to cardioprotective dietary patterns, exemplified by the Mediterranean diet (MedDiet), has been demonstrably associated with alterations in DNA methylation patterns and the expression of genes involved in

inflammation and immune function.[22] A 2024 research by Gimeno et al. called "HELENA study" found a strong negative association between a higher MedDiet score and both systolic and diastolic blood pressure (ß = -0.40, $p < 0.001$ and ß = -0.29, $p = 0.001$, respectively).[23]

Macronutrient Epigenetic Modulation in Blood Pressure

Protein and amino acids

Dietary macronutrient intake exhibited a significant interaction effect on the genetic association with long-term changes in systolic blood pressure (SBP). Study by Sun et al. in 2019 found that among participants assigned to a high-protein diet, those with lower SBP-polygenic scores (SBP-PGS) experienced a greater reduction in SBP compared to individuals with higher SBP-PGS at 6, 12, and 24 months, as well as over the entire 2-year intervention. Impressively, this differential response based on SBP-PGS was not observed in the group consuming an average-protein diet.[6] Single nucleotide polymorphisms (SNPs) associated with BP exhibited a particular enrichment for regulatory elements active in vascular endothelial cells.[24] A BP-PGS constructed from 66 BP-related SNPs significantly predicted the development of future damage in target organs, encompassing the heart, brain, and large blood vessels.[25] Furthermore, the observed inverse association between protein intake and BP might be attributable to increased consumption of specific dietary amino acids with vasodilatory properties (e.g., arginine, taurine, and glutamic acid) that contribute to improved vascular function.[26]

Arginine methylation, a post-translational modification, generates homocysteine and asymmetrical dimethylarginine (ADMA). Moreover, methionine metabolism contributes to homocysteine production[27]. Elevated serum homocysteine (>10 μmol/L) and ADMA levels are increasingly recognized as risk factors for essential hypertension (EH) development. In addition to its link with EH, homocysteine has been implicated in vascular dysfunction by promoting the overgrowth of smooth muscle cells in blood vessels. This effect might be mediated by excessive methylation of miR-143, as reported in prior research.[28] Furthermore, homocysteine may downregulate the miR-145/CD40 pathway, potentially contributing to cardiac remodeling.[29]

Lipids

Studies have shown a significant association between saturated, monounsaturated, and trans fats, but not polyunsaturated fatty acids (PUFAs) like omega-3 and omega-6, with the development of EH.[30] Supporting this notion, research using high-fat diet (HFD)-fed rats demonstrated that linoleic acid (an omega-6 PUFA) supplementation resulted in reduced expression of miR-27a, a potential candidate promoting hypertension, and restored expression of miR-143, a miRNA typically downregulated in EH.[31] These findings suggest that PUFAs may hold therapeutic potential against hyperlipidemia-associated EH. Hyperlipidemia could induce alterations in microRNA (miRNA) expression profiles, specifically downregulate miR-10a, miR-139b, miR-206, and miR-222, while conversely upregulating hsa-miR-223-3p, hsa-miR-21-5p, hsa-miR-146a-5p, miR-145-5p, miR-1-3p, and miR-423-5p.[32] Notably, miR-21 exhibits increased expression in lipid-rich environments and further disrupts the remodeling process of vascular smooth muscle cells during EH.[32]Hyperlipidemia also associated to DNA methylation of several genes such as *PCSK9*, *MyBPC3*, and *DNase1*.[32]

Carbohydrates

Dietary patterns characteristic of Western cultures, rich in simple carbohydrates are established risk factor for developing EH.[33] Fructose, in particular, may contribute to EH pathogenesis by altering microRNA (miRNA) expression within the gut liver axis (GLA).[34]

Studies employing high-fructose diets have demonstrated significant changes in the expression levels of specific miRNAs known to regulate endothelial function and blood pressure. Notably, miR-19b and miR-101a are miRNAs with documented anti-atherogenic properties, were downregulated in response to a high-fructose diet. Conversely, fructose overconsumption appears to upregulate miR-145a, a potential prohypertensive miRNA and candidate biomarker for EH diagnosis.[35]

The involvement of miRNAs in fructose-induced EH might additionally be mediated by advanced glycation end (AGE) products.[36,37] Fructose may undergo a non-enzymatic reaction with free amino groups present in proteins, lipids, or nucleic acids called Maillard reaction, leads to the formation of AGEs.[38] The association between AGEs and EH likely arises from the contribution of AGEs to endothelial dysfunction.[39] In a study by Pachoka et al, the rs1799752 polymorphism interacted with dietary carbohydrate intake to serve as a potential genetic moderator of hypertension risk.[40] The DD genotype displayed a propensity for both higher carbohydrate consumption and a heightened susceptibility to hypertension, compared to the ID and II genotypes.[40]

Table 1.
Summary of Macronutrients Epigenetic Modulation in Blood Pressure

Macronutrients	Epigenetic Modulations	Effects on Cardiovascular and Blood Pressure
Protein	• Increased in SNP of *arginine*, *taurine*, and *glutamic acid* amino acids. • Arginine methylation leading to elevated serum homocysteine and ADMA levels.	• Vasodilatation and reduce systemic vascular resistance. • Inhibit NO bioavailability and promote endothelial dysfunction.
Lipid (cholesterol, fatty acid)	• Reduced expression of *miR-27a, miR-10a, miR-139b, miR-206,* and *miR-222*. • Restored expression *of miR-143, hsa-miR-223-3p, hsa-miR-21-5p, hsa-miR-146a-5p, miR-145-5p, miR-1-3p, and miR-423-5p.* • Elevated DNA methylation of *PCSK9*, *MyBPC3*, and *DNase1*	• Decrease vascular integrity and promote oxidative stress. • Disruption of vascular smooth muscle remodelling during EH. • Increase LDL-cholesterol and total cholesterol levels.
Carbohydrates	• Downregulation of anti-atherogenic miRNAs: *miR-19b* and *miR-101a* • Upregulation of prohypertension miRNA: *miR-145a* • Polymorphism of *rs1799752* loci. • Increasing *AGEs*	• Increased systemic vascular resistance • Decreased vascular integrity. • Promote endothelial dysfunction

Micronutrient Epigenetic Modulation in Blood Pressure Vitamin A

Vitamin A acts as a gene expression regulator by interacting with two receptor families: Retinoid Acid Receptors (RARs) and Retinoid X Receptors (RXRs). These receptors play a crucial role in DNA methylation and histone acetylation pathways. Dietary vitamin A deficiency leads to aberrant methylation of the GATA binding protein 4 (GATA-4) gene promoter region, resulting in various developmental defects. Furthermore, vitamin A insufficiency disrupts histone acetylation by impairing the function of CREB-binding protein, a key histone acetyltransferase induced by RAR-α. As a results, the genomic instability caused by epigenetic perturbation could lead to the development of several chronic diseases including hypertension.

A large study in Chinese adult populations found a L-shaped association between dietary vitamin A intake and the development of new hypertension ($p < 0.001$ for non-linearity).[41] Individuals with higher vitamin A intake (≥227.3 μg RE/day) had a significantly lower risk of new hypertension compared to those with lower intake (<227.3 μg RE/day) (adjusted HR = 0.73; 95% CI: 0.63, 0.78). This protective effect was observed for both plant-based (adjusted HR = 0.65; 95% CI: 0.61, 0.70) and animal-derived vitamin A intake (adjusted HR = 0.76; 95% CI: 0.70, 0.82).[41]

Vitamin D

Vitamin D plays a crucial role in gene regulation through its receptors (VDRs). VDRs partner with retinoid X receptors (RXRs) to form complexes that target specific DNA sequences within the promoter region of genes, influencing processes of histone modification.[42] VDR/RXR interaction can recruit histone acetyltransferases (HATs) and histone deacetylases (HDACs), enzymes that modify histone proteins and DNA methylation (DNAm) to control gene activity.[43] Vitamin D exerts anti-inflammatory effects by regulating the expression of cytokines associated with the nuclear factor kappa-B (NF-κB) pathway.[44] Vitamin D receptor (VDR) signaling, particularly through the 1,25D metabolite and SIRT1 protein, inhibits NF-κB function.[45] This supports the role of 1,25D in deacetylating NF-κB via its interaction with SIRT1.[45] Notably, vitamin D deficiency is associated with decreased mRNA levels of genes crucial for immune function (NF-κB) and aging prevention (IGF1R, p53, and Fgf-23), suggests that this condition may predispose individuals to developing chronic diseases such as hypertension.[46]

The FokI variant of the vitamin D receptor (VDR) encodes a functionally altered protein, constituting a functional polymorphism.[47] Studies have demonstrated that individuals with low circulating levels of 25-hydroxyvitamin D (25(OH)D) and the FokI genotype exhibit increased plasmatic renin activity and RAAS activation.[48] These findings support the physiological role of the active metabolite, 1,25-dihydroxyvitamin D (1,25(OH)2D), in suppressing renin expression in humans. Consequently, insufficient vitamin D status in combination with the FokI polymorphism may elevate cardiovascular disease risk.[49]

Vitamin E

Studies suggest a positive influence of vitamin E on DNA repair mechanisms at non-cytotoxic concentrations.[50] This is evidenced by increased expression of DNA repair genes, MutL homolog 1 (MLH1) and DNMT1, along with a rise in the global DNA methylation marker, long-interspersed element 1 (LINE-1).[50] MLH1, functioning within the mismatch repair (MMR) system, contributes to base excision repair.[51] In the presence of DNA damage, MLH1 can trigger apoptosis through its interaction with SIRT1 and PARP1, NAD+-dependent deacetylases that are also components of DNA methyltransferases (DNMTs).[52] Conversely, dietary insufficiency of vitamin E has been linked to increased lipid peroxidation within cell membranes. This phenomenon may contribute to an elevated risk of cardiovascular diseases, including hypertension.[53]

Zinc

Zinc is a critical cofactor for numerous epigenetic enzymes, including DNA methyltransferases (DNMTs), histone acetyltransferases (HATs), histone deacetylases (HDACs), and histone demethylases.[54] These enzymes often contain binding sites for zinc, and disruptions in zinc homeostasis can consequently lead to epigenetic alterations. Investigations using both in vivo and in vitro models of zinc deficiency (ZnD) unveil a potential mechanism linking ZnD to hypertension, particularly through its influence on

cardiovascular and renal function.[55] These findings highlight the role of Zn^{2+} in blood pressure regulation by modulating renal sodium transport.[56] Notably, the thiazide-sensitive NaCl cotransporter (NCC) in the kidneys appears to be a critical mediator of ZnD-induced hypertension.[57] Furthermore, NCC itself is a Zn^{2+}-regulated transporter exhibiting upregulation under ZnD conditions.[58]

Iodine and Sodium

Despite existing research on micronutrients and hypertension, the link between iodine status and blood pressure risk remains relatively unexplored. Notably, few studies have investigated the combined effect of iodine and dietary sodium, particularly in the context of iodized salt. A study by Menon et al. in India observed an inverse relationship between urinary iodine levels and systolic blood pressure, even after adjusting for age.[59] This finding suggests that therapeutic salt restriction, a common hypertension treatment, might inadvertently lead to insufficient iodine intake.[59] Moreover, genetic variation in the ACE gene, particularly the rs4343 polymorphism, significantly elevates hypertension risk by more than 2.1-fold,[60] especially under high-sodium dietary conditions.

Table 2. S
ummary of Micronutrients Epigenetic Modulation in Blood Pressure

Vitamins	Biological forms	Water/fat soluble	Daily doses recommen-dation	Epigenetic Modulatiosn in Blood Pressure
Vitamin A	Retinol, Retinal, Retinoic acid	Fat soluble	700–900 mcg/day	The interaction between Retinoic Acid Receptors (RARs) and Retinoid X Receptors (RXRs) can disrupt histone acetylation, potentially leading to genomic instability and an increased risk of hypertension.
Vitamin D	25-(OH)D, 1, 25 (OH)D	Fat soluble	10 mcg (400 IU)/day	25-hydroxyvitamin D (25(OH)D) deficiency and the FokI genotype synergistically elevate plasmatic renin activity and activate the renin-angiotensin-aldosterone system (RAAS), contributing to hypertension.
Vitamin E	Tocopherol, Tocotrienols	Fat soluble	15 mg/day	Vitamin E deficiency promotes lipid peroxidation in cell membranes, thereby compromising DNA repair mechanisms due to reduced expression of MutL homolog 1 (MLH1) and DNMT1 genes. This dysfunction may contribute to the increased risk of cardiovascular diseases, including hypertension.

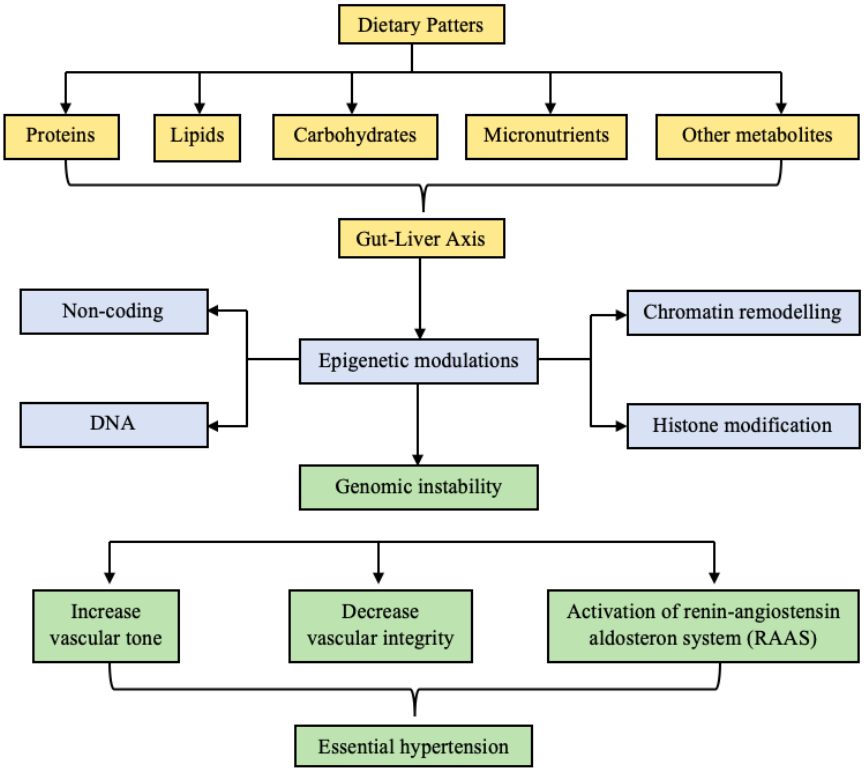

Figure 1. New insights on dietary influences on the gut-liver axis and its epigenetic perturbations which implicated in the development of essential hypertension. *Orange boxes*: Macronutrients (carbohydrates, lipids, and proteins), micronutrients, and other food-derived nutrient metabolites can promote (*blue boxes*): epigenetic perturbations and modulate miRNA signatures, promoting (*green boxes*): increased vascular tone, compromised vascular integrity, and activation of the renin-angiotensin-aldosterone system (RAAS). These factors collectively contribute to the pathogenesis of essential hypertension.

CONCLUSION

Macro and micronutrients significantly influence epigenetic pathways associated with hypertension occurrence. Deficiencies or imbalances in these dietary components relative to recommended daily intakes leads to an altered function of genetic systems, particularly in the genomic levels. Integrating therapeutic strategies to address potential nutritional deficiencies should be considered as a complementary approach within hypertension treatment programs.

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