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"Nitric Oxide Dysfunction in Hypertension: A Systematic Review of Pathophysiological Mechanisms and Clinical Implications"

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Abstract:

This systematic review explores the intricate relationship between nitric oxide (NO) bioactivity and hypertension, drawing upon evidence from diverse geographical regions. The study synthesizes findings from research conducted in Switzerland, the USA, the United Kingdom, and India, among others, to elucidate the multifaceted mechanisms underlying hypertension pathogenesis. Key findings indicate that impaired NO bioactivity contributes significantly to hypertension, manifesting in reduced vasodilator response to endothelium-dependent vasodilation, arterial stiffness, increased pulse wave velocity, and chronic sympathetic nervous system activation. Additionally, investigations into the impact of hyperuricemia on NO synthesis and bioavailability reveal its potential role in hypertension and cardiovascular disease progression. The association between NO levels and hypertension severity underscores the physiological significance of NO in regulating blood pressure. While anti-hypertensive interventions promise to improve NO levels and endothelial function, their efficacy varies across studies. This review underscores the critical role of NO in hypertension management and advocates for tailored therapeutic strategies targeting NO pathways. Future research directions include elucidating the mechanisms linking NO dysfunction to hypertension and exploring novel therapeutic avenues to optimize blood pressure control and mitigate cardiovascular risk. By advancing our understanding of NO's role in hypertension, this study aims to inform precision medicine approaches for personalized hypertension management and contribute to reducing the global burden of cardiovascular disease.

Keywords: Nitric oxide, Hypertension, Endothelial function, Systematic Review, Meta-analysis.

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Introduction:

Hypertension, as per the criteria set by the Joint National Committee (JNC-7), is characterized by "systolic blood pressure (SBP) exceeding 140 mmHg or diastolic blood pressure (DBP) exceeding 90 mmHg". The classification of blood pressure according to JNC-7 consists of three categories: "average blood pressure (SBP <120 mmHg and DBP <80 mmHg), prehypertension (SBP 120-139 mmHg or DBP 80-89 mmHg), and Stage 1 Hypertension (SBP 140-159 mmHg or DBP 90-99 mmHg, or SBP ≥160 mmHg or DBP ≥100 mmHg)".[1]

The predominant non-invasive clinical tool used to evaluate cardiovascular health and anticipate future cardiovascular events is blood pressure monitoring, which can be affected by factors such as respiration, temperature, bladder function, pain levels, emotional state, dietary habits, and alcohol intake.[2]

Currently, India is witnessing a rise in the occurrence of non-communicable diseases such as hypertension and diabetes, resulting in premature death. The issue in India is exacerbated by low healthcare literacy, a high percentage of self-care meditation, inadequate blood pressure control, and uneven standards for managing hypertension. The inconsistencies observed across India can be attributed to several factors, including variances in clinical practices, insufficient diagnostic facilities, lack of knowledge, inadvertent uses of medications such as antibiotics, analgesics, and steroids, and unsatisfactory treatment methods. In the last 25 years, healthcare accessibility in India has significantly improved, and the nation has implemented a comprehensive universal health coverage scheme.[3]

The risk of hypertension rises with age due to blood vessel calcification, while adopting a healthy lifestyle can slow down the aging of blood vessels. Hypertension can occur in individuals under the age of 40, and it is important to rule out secondary causes such as renal disease, blood vessel abnormalities, and endocrine disorders. Genetic factors are additional contributors to hypertension.[4]

Nitric oxide (NO) is a diatomic molecule that is produced by several tissues and cell types inside the body. Three NO synthases create it by oxidizing L-arginine to L-citrulline. NO is alternatively referred to as endothelium-derived relaxing factor (EDFR). Endothelial blood vessels utilize nitric oxide (NO) to induce relaxation of the adjacent smooth muscle, enhancing blood flow and causing vasodilation. Nitric oxide (NO) generation in humans

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decreases as salt intake increases.[5]

The NO pathway employs L-NMMA (L-N(G)-Monomethyl Arginine) to investigate L-arginine. The diminished basal nitric oxide (NO)-mediated dilator function reduces constrictor response to L-NMMA in individuals with stage-1 hypertension. Nitric oxide synthase (NOS) produces nitric oxide (NO). Inhibiting NOS leads to the narrowing of blood vessels and an elevation in blood pressure, which suggests that NO functions as a vasodilator. Essential hypertension patients exhibit a deficiency in endothelial-derived relaxing factor (EDFR) due to impaired nitric oxide (NO) synthesis rather than decreased availability of substrates necessary for NO generation.[6]

Hypertension is a prevalent illness that can easily go unnoticed due to presentation without noticeable symptoms. It is typically curable and frequently leads to disabling consequences. Heart disease, malignancies, stroke, diabetes, chronic respiratory illnesses, and other non-communicable diseases (NCDs) result in millions of deaths annually, with a significant portion occurring during the most productive years of life. Conditions conducive to continual development include implementing measures to prevent and manage non-communicable diseases (NCDs).[7]

Approximately 1 billion people are affected by this condition. The extent of its dominance grows as one gets older. More than 50% of individuals aged 60 and above are impacted. The Framingham Heart Study found that both males and females who survive until the age of 80-85 have an almost 90% chance of acquiring hypertension. However, up until the age of 55-65, their risk of hypertension is within the normal range.[8]

Research has demonstrated that high blood pressure (BP) poses a significant independent risk for cardiovascular disease (CVD). Research indicates that over 1 million fatalities are attributed to cardiovascular disease (CVD). Furthermore, the risk of stroke escalates progressively and directly, with blood pressure levels starting as low as 114mmHg (systolic blood pressure) and 75mmHg (diastolic blood pressure). With every 20 mmHg increase in systolic blood pressure or ten mmHg increase in diastolic blood pressure, there was a corresponding rise in the mortality rate for both ischemic heart disease and stroke.[1]

Research question under systematic review:

Is there any correlation between the levels of Nitric Oxide observed in research studies and hypertension?

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Methods:

Search Strategy:

This systematic review employed a comprehensive search strategy to identify relevant studies. Electronic databases, including PubMed, Embase, and Web of Science, were systematically searched using keywords and Medical Subject Headings (MeSH) terms related to nitric oxide (NO), hypertension, endothelial function, and blood pressure regulation. The search strategy was structured to assess a broad range of studies examining the relationship between NO and Hypertension.

Study Selection:

Studies incorporated for the analyses were screened on predefined inclusion and exclusion criteria. Inclusion criteria encompassed research articles, reviews, and meta-analyses investigating NO synthesis, endothelial function, and their association with blood pressure regulation in human subjects. Studies conducted on animal models or focusing solely on NO in non-hypertensive conditions were excluded. Two independent reviewers screened the titles and abstracts of retrieved articles to determine eligibility. Full-text articles of potentially eligible studies were then assessed for final inclusion. Only nine studies were available in the literature per the inclusion and exclusion criteria, which were thus followed for study selection.

Data Extraction:

The data were extracted from included studies using a standardized form. The information was annotated, and characteristics of the study (e.g., list of authors, publication year), demographic parameters of the study participants (e.g., age, gender, residential status), details of the intervention, if any (e.g., duration, format), and outcome measures (e.g., hypertensive symptom) were taken into account. Two reviewers conducted Data extraction independently, with any discrepancies resolved through discussion.

Quality Assessment:

The quality of the included studies was assessed using appropriate tools tailored to the study design. For randomized controlled trials (RCTs), the Cochrane Risk of Bias Tool was utilized to evaluate potential sources of bias, including random sequence

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generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other biases. The Newcastle-Ottawa Scale was employed for observational studies to assess study quality based on selection, comparability, and outcome assessment. Two reviewers conducted Quality assessment independently, and disagreements were resolved through discussion or consultation with a third reviewer if necessary.

Data Synthesis:

Findings from selected studies were synthesized narratively to elucidate the role of NO in hypertension pathogenesis and its clinical implications. Data synthesis involved summarizing critical findings related to NO synthesis, endothelial function, and blood pressure regulation and exploring associations between NO impairment and hypertension development. Subgroup analyses or meta-analyses were not performed due to heterogeneity across included studies. Instead, a narrative synthesis approach to integrate findings was employed, and conclusions were drawn regarding the relationship between NO and Hypertension.

Results

Our study analyzed nine relevant papers and investigated the link between Essential Hypertension and serum NO levels. Table 1 summarizes the average serum NO values for both groups. Individuals with Essential Hypertension had a mean serum NO of 5.93 mg/dl (95% CI: 5.33-6.52), with very low heterogeneity (I2=0.00%). The control group's mean serum NO was 4.97 mg/dl (95% CI: 4.39-5.56), also showing very low heterogeneity (I2=0.00%). As shown in Figure 1, people with Essential Hypertension had significantly lower serum NO levels compared to the healthy control group (p-value < 0.01).

Table 1: NO levels in Cases and Controls Mean±SD value in mg/dl.

SR	Author & Year	Case		Control	
		Subject	Mean±SD	Subject	Mean±SD
1	Gao T et.al. & 2023[10]	206	40±10.00	180	60±20.00
2	Feng Q et al. & 2018[11]	360	14.39±5.59	360	15.47±5.80
3	Aflyatumova GN et al. & 2018[12]	60	11.16±0.31	60	11.17±0.35
4	Motor VK et.al. & 2012[13]	90	30±10.00	45	40±10.00

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5	**Ekmekc H et.al. & 2008[14]**	23	14.4±4.30	13	15.8±4.70
6	**Armas-Padilla MC et al. & 2007[15]**	42	35.13±3.40	21	57.33±6.50
7	**Sosa-Canache B et.al. & 2007[16]**	30	32.74±3.01		
8	**Vyzantiadis T et al. & 2006[17]**	28	19.8±9.70	28	29.6±5.90
9	**Zhu S et al. & 2006[18]**	110	8.33±2.19		

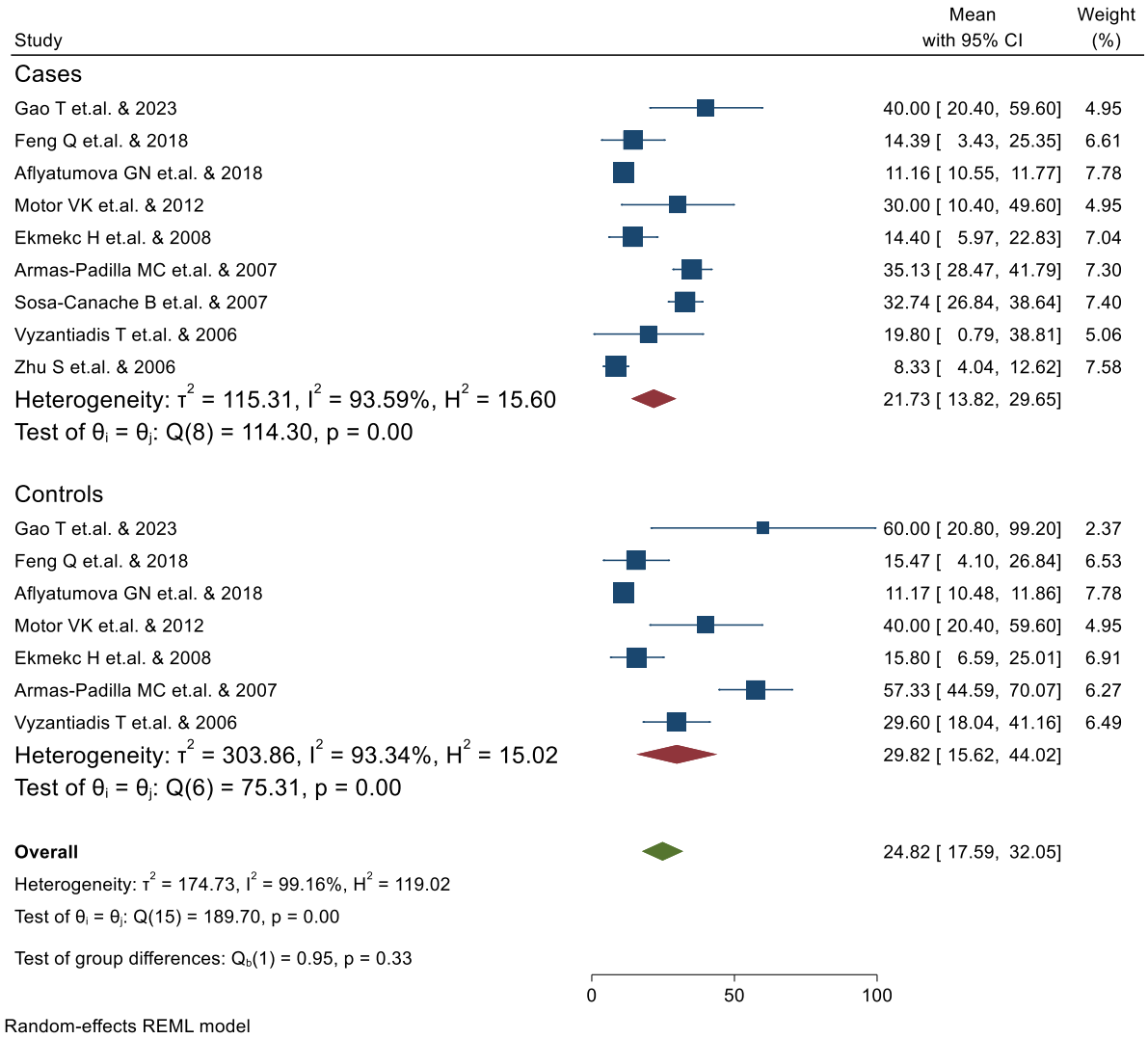

Figure 1: Forest plot for Serum NO levels in mg/dl, in Essential Hypertensive cases and control group.

Discussion:

The findings of this systematic review highlight the intricate relationship between nitric oxide (NO) bioactivity and hypertension, shedding light on the multifaceted mechanisms underlying hypertension pathogenesis. Our analysis synthesizes evidence from diverse geographical regions, emphasizing the global significance of

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understanding NO's role in blood pressure regulation.

The relationship between poor nitric oxide (NO) bioactivity and hypertension is intricate, as individuals with hypertension exhibit a diminished ability to dilate blood vessels in response to endothelium-dependent vasodilation, which may contribute to the development of hypertension.19 Reduced NO bioactivity notably impacts arterial stiffness, elevated pulse wave velocity, and perhaps chronic sympathetic nervous system activation. Research conducted in both the United States and China has discovered a correlation between hyperuricemia and cardiovascular disease (CVD) in individuals with hypertension, as well as increased risk of all-cause mortality and diabetes. However, there is no observed correlation between hyperuricemia and stroke. Additionally, hyperuricemia hinders nitric oxide (NO) production and availability. [20-22]

A study conducted in Lucknow, India, discovered a notable decrease in the concentration of Nitric Oxide among individuals with stage 1 HTN compared to the group of healthy individuals serving as controls. Adding additional anti-hypertensive medicines and antioxidants increased NO levels; however, this increase was not substantial. A 1997 study in London revealed that the impedance of endothelium-dependent relaxation may be the underlying cause of high blood pressure rather than the consequence. [23-25]

A prior investigation conducted in Odisha, India, revealed that the majority of individuals with hypertension belong to the age bracket of 40-55. Furthermore, nitric oxide (NO) levels were notably lower in the affected individuals compared to the control group. Monotherapy with anti-hypertensive medicines did not yield significant results in patients with essential hypertension. However, a combination of anti-hypertensive drugs and vitamin E demonstrated some improvement. [26]

The review highlights the crucial role of age in the development of hypertension, with a substantial number of individuals with high blood pressure belonging to the 40-55 age range. The correlation between nitric oxide (NO) and the severity of hypertension highlights the importance of NO in maintaining the baseline tone of blood vessels and controlling blood pressure.

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Conclusion:

This systematic review consolidates existing evidence on the complex interplay between NO bioactivity and hypertension, providing valuable insights for clinicians and researchers alike. Future studies should focus on elucidating the specific mechanisms linking NO dysfunction to hypertension and exploring novel therapeutic avenues to optimize blood pressure control and mitigate cardiovascular risk. By deepening our understanding of NO's role in hypertension, we can advance precision medicine approaches for personalized hypertension management and ultimately reduce the global burden of cardiovascular disease.

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