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Effects of Hypernatremia on Blood Pressure and Cardiovascular Disease: A Systematic Review and Meta-analysis

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Abstract

Serum sodium (Na) values above 145 mmol/L indicate hypernatremia: drugs, hormone imbalances, water retention, and Na intake cause it. The inability of the body to control salt balance affects infants, older people with neurological or physical impairment, and critically unwell adults. Vital heart function helps critical cardiovascular disease (CVD) patients. Hypernatremia increases blood pressure, risking stroke and heart disease. This study and meta-analysis assessed CVD patients' blood pressure and hypernatremia. The mortality of CVD patients with hypernatremia was also studied. Furthermore, this study explained salt-induced hypertension. The systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations. The included research was published between 2010 and 2022. Several databases were utilized, including PubMed, Scopus, and Science Direct. Ten articles were included in this study. Two studies demonstrated the effects of hypernatremia on blood pressure, five studies demonstrated the effects of hypernatremia on mortality among CVD patients, and three studies demonstrated the mechanisms underlying salt-induced hypertension. The research employs a random effects model represented by Forest plots. The meta-analysis results indicated that hypernatremia significantly increases blood pressure in CVD patients (95% CI: 0.24 to 16.33; p=0.04; OR: 8.29). Hypernatremia also increased mortality in patients with CVD (95% CI, 1.48 to 3.83; p=0.0003; OR, 2.40). Hypernatremia causes arterial wall stiffness and contributes to alterations in blood pressure (95% CI: 1.48–3.83; p=0.02; OR: 0.51). Therefore, managing hypernatremia in patients with CVD may prevent complications, such as mortality and severe hypertension.

Keywords

Hypertension, Blood Pressure, Hypernatremia, Arterial Stiffness

Introduction

Cardiovascular diseases (CVD) encompass a range of pathological conditions affecting the heart and blood vessels and are recognized as a prominent global cause of mortality[1]. High blood pressure is a substantial contributing factor in the pathogenesis of CVD[2]. In bodily functions, sodium (Na) is a crucial electrolyte

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responsible for regulating the equilibrium of water within the body and the fluid volume within blood vessels. Na can be obtained through dietary intake, intravenous fluid administration, and specific medications.

In contrast to individuals with good health, patients with CVD exhibit compromised vascular functions that may hinder their ability to effectively regulate blood pressure fluctuations in the presence of hypernatremia[3]. Moreover, there is still limited understanding regarding the mechanisms through which hypernatremia influences blood pressure. Therefore, additional research is required to tackle these issues effectively.

This research is crucial for investigating the potential impact of hypernatremia on blood pressure in individuals with CVD while also examining the underlying pathophysiological mechanisms that may contribute to these effects. Additionally, this study aims to develop preventive strategies to reduce the morbidity and mortality associated with CVD. Furthermore, this study catalyzes future investigations, offering a contemporary review and enhanced understanding of the subject matter.

Literature Review

Cardiovascular disease

CVDs encompass a range of medical conditions affecting the heart and blood vessels, such as hypertension, and can potentially result in mortality. Additional complications may arise, such as disability and an extended duration of hospitalization. CVD was responsible for an estimated 8.9 million fatalities and 164 million instances of disability in 2015[4]. Nevertheless, there has been a decline in the prevalence of CVD in developed nations during recent decades[5]. It can likely be attributed to the successful implementation of efficacious treatments and preventive strategies. However, it is essential to note that low- and middle-income countries, along with developing countries, have observed an increase in the incidence rates of CVD. It can be attributed to the swift social and economic transformations, which have resulted in exposure to various risk factors associated with CVD. Additionally, the progress made in managing CVD in these regions has been relatively limited[6].

High Blood Pressure with Cardiovascular Incidence

The increase in blood pressure observed in the presence of high Na levels can be ascribed to arterial stiffness[7]. The chronic elevation of blood pressure resulting from increased Na levels induces gradual alterations in the arterial wall, specifically in the larger elastic arteries[8]. The alterations described are facilitated by tissue scarring or fibrosis, which initially functions as a reversible form of vascular remodelling in response to vascular injury. A typical elastic artery can undergo dilation and adapt to substantial blood pressure fluctuations during systole while also relaxing during diastole[7,8].

The presence of rigid arteries can lead to an impaired ability of arterial walls to alternate between systole and diastole, resulting in elevated systolic blood pressure, increased workload on the heart, and cardiac hypertrophy. The observed phenomenon of stiffening is commonly ascribed to an imbalance in the ratio of collagen to elastin within the walls of the blood vessels[9]. Collagen deposits within the extracellular matrix of artery walls result from vascular damage and inflammation triggered by hypertension. This process is an integral part of extracellular matrix remodelling, accompanied by elastin fibers' degradation.

Hence, the etiology of elevated blood pressure in individuals with salt sensitivity is attributed to a renal impairment known as a "natriuretic deficit"[10]. Individuals with impaired kidney function cannot effectively eliminate excessive Na from their bodies without an adequate high-pressure level. Therefore, the elimination of excessive Na from the body is contingent upon hypertension and the attainment of adequate renal arterial pressure, which enables the expulsion of the surplus sodium ions (Na^+) from the circulatory system through the kidneys. As mentioned earlier, the condition has resulted in individuals

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sensitive to salt retaining a higher amount of Na^+ in their serum, which is eventually eliminated through the kidneys due to increased blood pressure. Moreover, it has been observed that individuals exhibiting salt sensitivity demonstrate attenuated renin-angiotensin-aldosterone system (RAAS) activity and reduced urinary endothelin levels.

Effects of Hypernatremia on Blood Pressure

One of the risk factors that has been emphasized in the context of CVD is elevated serum Na levels[11]. The walls of arteries are composed of a selectively permeable membrane that facilitates the entry of sodium chloride (NaCl) into the bloodstream[12]. When an excessive amount of NaCl is consumed, the compound can dissolve into its ionic forms[13], namely Na^+ and chloride ions (Cl^-). The phenomenon leads to an elevation in the concentration of solutes within the bloodstream[14], resulting in an augmented osmotic pressure of the blood[15]. The occurrence of these events can stimulate the kidneys to excrete surplus ions from the bloodstream and enhance the retention of water. The increase in water retention leads to elevated blood pressure within the walls of the blood vessels[11,12,15].

The relationship between hypernatremia and blood pressure has been a long-debated topic. However, it is a general belief that hypernatremia exerts a stimulatory effect that induces a rise in blood pressure. Adverse effects of hypernatremia are only partly blood pressure-driven due to the involvement of other systems, such as sympathetic neural activation. In contrast, the harmful effect of hypernatremia continues to be primarily attributed to its impact on blood pressure[1,16]. However, many studies have proven the effect of high Na levels in increasing blood pressure as a significant risk only in hypertensive subjects. Still, they appear to be less of a problem in normotensive subjects[17].

The observed disparities in blood pressure response among individuals can be ascribed to another extensively discussed subject, salt sensitivity. Individuals sensitive to salt exhibit a more significant elevation in blood pressure after being in a state of high sodium concentration than individuals who are resistant to salt[2,12,13,18]. The etiology and pathophysiology of salt sensitivity remain poorly elucidated. Various factors have been suggested as potential contributors to this phenomenon, encompassing genetic mutations, polymorphisms, and metabolic and neuro-endocrine factors pertaining to renal function[18]. These include the renin-angiotensin-aldosterone system, the sympathetic nervous system, and the regulatory system governing natriuretic peptides, insulin, leptin, and other endothelial effectors.

Moreover, salt sensitivity results from a combination of acquired environmental characteristics that lead to changes in various physiological systems responsible for maintaining Na homeostasis[19] and genetic variations that affect the kidneys' response to these changes[20]. However, the sensitivity and resistance to blood pressure in response to salt intake are not mutually exclusive factors but persist throughout an individual's lifespan. The variability in an individual's sensitivity to salt throughout their lifetime can be attributed to various acquired factors, including obesity, diabetes, the aging process, and a diminished capacity for endothelial relaxation[18,21].

Materials and Methods

Study design

The present investigation was conducted as a systematic review and meta-analysis, adhering to the guidelines set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The research was conducted between October 2022 to June 2023. A comprehensive search was performed to identify and evaluate relevant studies. Multiple databases, including PubMed, Scopus, Google Scholar, and Science Direct, were utilized for this purpose.

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Research Question Using the PICO Model

The research question formulation for this systematic review and meta-analysis adhered to the PICO framework. The PICO framework delineates four essential components that should be incorporated when constructing the research question for a systematic review:

What are the effects (O) of hypernatremia (I) on blood pressure in CVD (P)?

The variable denoted by the letter 'P' symbolizes the population that will be measured to assess the impact. The letter 'I' denotes the intervention, prognostic, or diagnostic factor being investigated in the study. The letter 'C' represents the control or comparison group in the study, which serves as an alternative to the intervention group. The letter 'O' in this context represents the outcome or anticipated results that will be assessed as part of the study. The PICOS framework, an alternative and more comprehensive version of the PICO framework, incorporates an additional component denoted by the letter 'S', representing the study design to be employed in the research.

Literature Quality Evaluation and Statistical Analysis

Relevant research and data significant to the topic were extracted and reviewed from reliable electronic resources such as PubMed, ScienceDirect, Google Scholar, and Scopus. Several keywords, such as 'effects of hypernatremia on blood pressure,' 'hypernatremia in CVDs,' and 'serum sodium level in cardiovascular illnesses,' were used to find relevant papers. All collected studies were subjected to a thorough analysis based on multiple inclusion criteria before being included. For meta-analysis, Review Manager (RevMan) was utilized, and Cochrane's Q and I^2 were employed for statistical analysis, with the random effect model adopted.

The Q and I^2 statistics developed by Cochrane were utilized to assess the presence of statistically significant heterogeneity in the study. In the present study, a statistical model incorporating random effects was employed. Subsequently, forest plots were conducted to mitigate any potential bias that might have been inherent in the study. The present meta-analysis was conducted utilizing the Review Manager (RevMan) software, which facilitates the execution of a meta-analysis by utilizing the provided data and presenting the outcomes in a visual format.

Inclusion criteria

The inclusion criteria comprise the specific characteristics of the studies incorporated into this systematic review. The study under consideration must be published between 2010 to 2022 to ensure the inclusion of up-to-date information and data. Furthermore, this study exclusively incorporated published articles that provided readily available full text. Furthermore, it is imperative that the study exclusively focuses on human subjects.

Exclusion criteria

Studies for this systematic review were excluded based on the following criteria. The exclusion criteria encompass studies that present blood pressure not induced by Na^+. In order to ensure the utmost comprehensiveness of the extracted data, the study also excluded literature that was not written in the English language. In addition, any instances of duplicated literature were excluded from the study.

Study selection

The titles and abstracts of each study were examined to determine their relevance. Subsequently, comprehensive evaluations were conducted on the complete texts to ensure compliance with the predetermined criteria for inclusion and exclusion. The final analysis included only those studies that satisfied all the inclusion criteria and did not meet any exclusion criteria. This meta-analysis does not incoorperate with animal model studies.

Data Extraction

The study's progress involved extracting and citing pertinent data from each study that satisfied the specified criteria. The dataset includes publication information, including the authors' names, the year of publication, the journal's name, the volume and issue of the article, and the study design. In addition, an examination was conducted on the mechanisms underlying the changes in blood pressure resulting from hypernatremia in patients with CVD. All the data was extracted to prevent any alteration of their meaning and value throughout the process.

Results

Study Selection

After conducting a thorough screening process based on the predetermined selection criteria, ten articles were ultimately chosen. The quantities of articles involved in each stage of the study selection process are visually represented in a PRISMA flowchart. Forty-nine articles were identified using three databases, namely Scopus, Pubmed, and Science Direct. No instances of duplication were identified in the gathered articles. The titles, publication dates, and abstracts of each article were examined through scanning. A total of 18 articles were excluded from the study based on their inappropriate titles and published dates. The eligibility of the remaining 31 articles was evaluated, resulting in the exclusion of 21 articles. These exclusions were based on the inability to obtain full texts due to accessibility of journal subscription by institution and inappropriate comparison groups including articles on animal model of genetically induced CVD and pregnancy induced hypertension. The total number of articles included in this study is ten.

Mortality rates in cardiovascular patients

Figure 1 compares the mortality rates of individuals with CVD with hypernatremia versus those without, as reported in five distinct studies. The data indicate a statistically significant relationship between hypernatremia and death rates, with an odds ratio (OR) of 2.38 (95% CI, 1.48 to 3.83; p=0.0003). Hence, those with CVD who have hypernatremia have a 2.38 times higher risk of dying from CVD than those who do not have hypernatremia. The results show considerable variability among the investigations, as shown by the high I^2 score of 87%. The findings demonstrated a high level of variability (87%) among the studies included in the analysis.

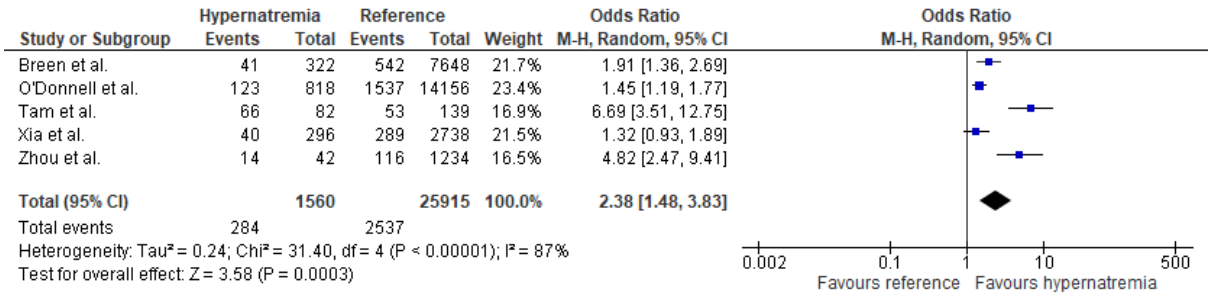

Figure 1: Mortality rates in CVD patients with and without hypernatremia

Vascular stiffness and blood pressure alterations in hypernatremia

Based on the results of the three studies illustrated in Figure 2, it can be predicted that there exists a correlation between heightened blood pressure and augmentation in vascular stiffness among individuals diagnosed with hypernatremia[9,22,23]. The assessment of arterial stiffness was performed utilizing the carotid-femoral pulse wave velocity (m/s), which is widely regarded as the benchmark method for evaluating arterial stiffness[22,23]. The statistical analysis results indicate a noteworthy correlation between hypernatremia and arterial stiffness (MD=0.50; 95% CI, 0.06 to 0.93; p=0.02). Furthermore, there is no indication of variation among the studies (I^2=0%).

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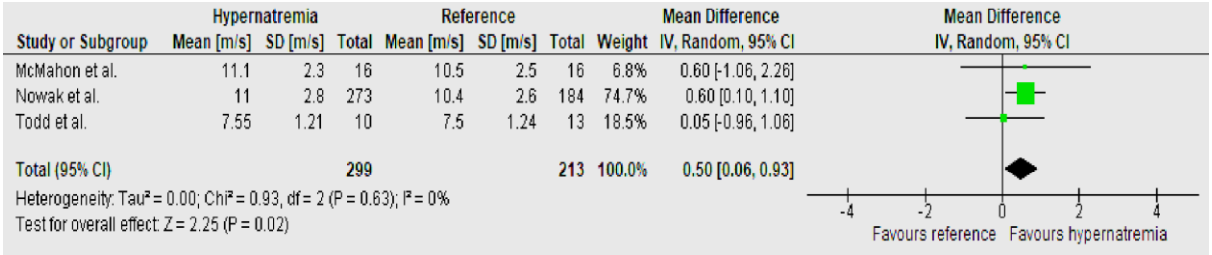

Figure 2: Vascular stiffness and blood pressure alterations in hypernatremia

Hypernatremia effects on Blood Pressure

According to the findings presented in Figure 3, it can be observed that the blood pressure is significantly higher in the group with hypernatremia compared to the group without hypernatremia (mean difference [MD] 8.29; 95% CI, 0.24 to 16.33; p=0.04). Furthermore, there is minimal variation among the studies included in terms of heterogeneity (I^2=12%). Both articles discussed the mean and standard deviation of blood pressure (mm/Hg) in both the hypernatremia and the reference groups. The study's findings indicate that hypernatremia significantly impacts blood pressure in individuals with CVD.

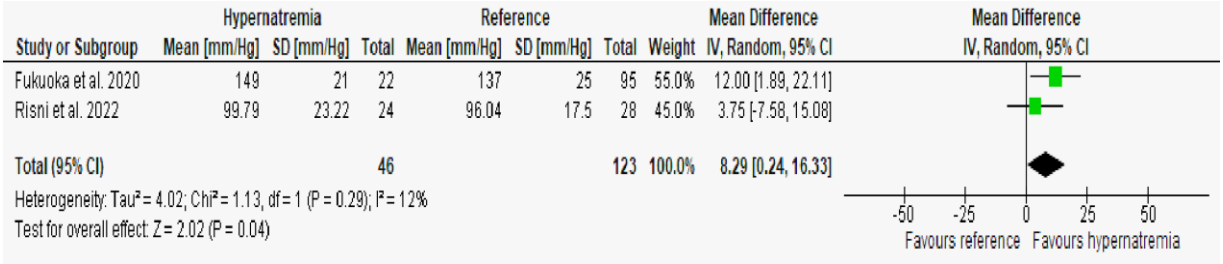

Figure 3: Hypernatremia effects on blood pressure

Discussion

The results of five studies the mortality rates among patients with CVD who had hypernatremia compared to those without hypernatremia[24–28]. The findings suggest a statistically significant association between hypernatremia and mortality rates. Patients with CVD who experience hypernatremia exhibit a 2.38-fold increase in the odds of mortality due to CVD compared to patients without hypernatremia. The findings indicate significant variability among the studies, as evidenced by an I^2 value of 87%.

The findings of the two studies exhibited greater deviations[26,28] from the aggregated results of the pooled studies. The observed discrepancy can be attributed to a smaller sample size in both studies than in the remaining three. Additionally, the meta-analysis did not provide specific details regarding the specific CVD encompassed within the study. Therefore, conducting a subgroup analysis that categorizes CVD based on its types may help address the issue of heterogeneity. Despite this, all empirical studies concur with the findings of this meta-analysis.

This study's findings indicate a positive correlation between hypernatremia and mortality rates in patients with CVD. This analysis is supported by a study noting that hypernatremia is associated with mortality rates ranging from 40% to 60%[29]. Furthermore, patients with hypernatremia upon admission exhibited a mortality rate of 39%, while patients who developed hypernatremia later had a mortality rate of 43%. In contrast, patients without hypernatremia had a lower mortality rate of 24%[30].

Individuals with hypernatremia exhibit higher blood pressure levels compared to those without hypernatremia, with a low degree of heterogeneity observed across the included studies[12,31]. Both articles analyzed the average and variability of blood pressure, measured in mm/Hg, in individuals with

hypernatremia and control groups. The current investigation has arrived at the finding that a correlation exists between hypernatremia and an increase in blood pressure in individuals diagnosed with CVD.

The current study's finding agreed with a cohort study[32], which revealed elevated serum Na levels in hypertensive and myocardial infarction patients compared to individuals without these conditions. Nevertheless, the study did not establish a direct correlation between the serum Na level and blood pressure.

Meanwhile, a cohort study[13] demonstrated a correlation between an elevation in plasma Na concentration and augmentation in blood pressure levels in both normotensive and hypertensive individuals. In addition, the study established a correlation between increased blood pressure and a notable reduction in plasma renin and aldosterone activity.

In addition, in both studies included in this analysis, hypernatremia was induced through oral tolvaptan therapy[12,31]. The potential impact of tolvaptan on blood pressure has been examined in a post-hoc study[33], indicating that it does not demonstrate a significant effect.

Three studies have found a positive correlation between arterial rigidity and elevated blood pressure in individuals with hypernatremia. Carotid-femoral pulse wave velocity in metres per second (m/s) was used to measure arterial stiffness, widely acknowledged as the preferred method for assessing arterial stiffness[22]. Individuals with hypernatremia were found to have a statistically significant association with arterial stiffening, with no observed heterogeneity between studies.

The finding of this study is that hypernatremia may induce arterial rigidity, resulting in increased vascular resistance and elevated blood pressure. Arteries dilate in response to a high serum Na load to accommodate the increased circulating volume, thereby preventing blood pressure increases[34]. This finding is supported by a review[35], indicating that patients with high serum Na burdens produce high reactive oxygen species (ROS)[36]. Furthermore, the production of nitric oxide (NO), a significant vasodilator, is diminished by an increase in ROS.

In addition, decreased NO alters the viscoelasticity of arteries directly. This viscoelasticity is determined by the ratio of elastin to collagen fibres in arterial walls, which is mediated by matrix metalloproteinases (MMPs). The arteries become stiffer as the ratio decreases, and *vice versa*. In the presence of a high Na concentration, MMP2 and MMP9 are activated. This condition stimulated the activity of transforming growth factor beta-1 (TGFß-1), which breaks down elastin filaments and reduces the ratio[35].

However, age may also influence arterial rigidity[37]. Seniors older than 60-65 are more likely to develop stiffer arteries, resulting in elevated systolic and diastolic blood pressure[22]. In this meta-analysis, the average age of participants is 68[38] and 68.5[39] years.

These two investigations[38,39] revealed higher PWV levels than a study[40], in which the average age of participants was 51.8 years. However, all studies support the conclusion of this meta-analysis, with no observed heterogeneity (0%).

There are some limitations to the investigation in this analysis. First, the study data included in this meta-analysis are still insufficient due to the dearth of research conducted on this topic in recent years. Second, no subgroup analyses were performed, such as by patient characteristics or follow-up duration. Therefore, future research could investigate the difference in blood pressure between hypernatremia and controls for the various subcategories of CVDs. In addition, serum sodium levels should be routinely monitored among CVD patients to prevent hypernatremia in clinical settings, and healthcare personnel should be knowledgeable about the management of hypernatremia, particularly in the context of CVD patients.

Conclusion

This meta-analysis concluded that hypernatremia increases blood pressure in CVD patients. This meta-analysis determined that hypernatremia increases the risk of death from cardiovascular disease. This analysis also revealed that arterial rigidity may mediate blood pressure changes in hypernatremia. Therefore, the findings of this meta-analysis may benefit and improve the management of CVD patients with hypernatremia in preventing the risk of mortality and severe hypertension.

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Conflict of Interest Disclosure

None to declare

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