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Review Article

Sodium intake and blood pressure regulation in CKD: a systematic review and meta-analysis

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Abstract

Background and objective: Salt intake is an important factor in blood pressure regulation in chronic kidney disease (CKD). This review assessed the impact of salt intake on blood pressure (BP) among CKD patients taking age and duration of intake into consideration.

Materials and methods: Using PRISMA guidelines, a systematic literature search was carried out on Semantic Scholar, ScienceDirect, and PubMed databases. The inclusion criteria were guided by the PICO framework. A total of 337 studies were gathered, after screening 8 studies met the criteria for quality assessment and data extraction (primary outcomes: systolic and diastolic BP). A random-effects model determined the overall effect sizes and heterogeneity across the studies.

Results: Low sodium intake significantly (p=0.02) reduced systolic blood pressure (SBP) but did not affect the diastolic blood pressure (DBP). High sodium intake had no significant effect on either systolic or diastolic BP. CKD patients aged≤50 years had lower systolic and diastolic blood pressure compared to patients >50 years. Additionally, long-term low salt intake had lower systolic and diastolic BP compared to short-term intake in patients with CKD.

Conclusion: Low dietary sodium intake improves only systolic BP in CKD patients, especially in younger individuals. CKD patients may benefit more from long-term salt reduction than short-term intake.

Introduction

Chronic kidney disease (CKD) is a progressive and degenerative disorder marked by a gradual decline in renal function, which can eventually lead to end-stage renal disease (ESRD). At this advanced stage, the kidneys lose their capacity to function effectively without medical intervention, necessitating either dialysis or a kidney transplant for survival [1]. Globally, CKD affects approximately 10% of the population, with its prevalence increasing with age and among individuals with comorbidities such as diabetes, hypertension, and cardiovascular disease. Furthermore, certain ethnic groups demonstrate a higher susceptibility to CKD, highlighting the complex interaction of genetic, socioeconomic, and environmental factors. The disease advances through five stages, ranging from mild renal impairment (Stage 1) to severe renal

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failure (Stage 5). A particularly insidious aspect of CKD is its asymptomatic nature in the early stages, often resulting in delayed diagnosis and treatment. As CKD progresses, patients may exhibit symptoms such as fatigue, edema (notably in the legs and ankles), shortness of breath, persistent itching, and alterations in urinary patterns. These symptoms reflect the kidneys' declining ability to filter waste products, balance electrolytes, and regulate fluid levels in the body [2].

The progression of CKD is closely linked to chronic conditions such as diabetes, hypertension, and glomerulonephritis, all of which contribute to a gradual decline in the glomerular filtration rate (GFR), a key indicator of kidney function. GFR measures the efficiency with which the kidneys filter blood, and a declining GFR signals worsening renal function. As renal function deteriorates, waste products and fluids accumulate in the body, exacerbating hypertension and creating a vicious cycle of kidney damage and elevated blood pressure [1]. Blood pressure is typically measured by two values: systolic blood pressure (SBP), which indicates the pressure in the arteries during heart contractions, and diastolic blood pressure (DBP), which reflects the arterial pressure when the heart is at rest between beats. In CKD patients, both SBP and DBP are often elevated due to fluid overload and increased peripheral vascular resistance, a condition in which blood vessels constrict, compelling the heart to work harder to pump blood [2].

Salt intake plays a crucial role in managing blood pressure, especially in CKD patients. Excessive salt intake causes water retention, an increase in blood volume, and consequently, higher blood pressure. Conversely, reducing sodium intake can decrease blood volume and lower blood pressure, which is particularly advantageous for CKD patients whose kidneys are often compromised in their ability to excrete sodium [3].

The regulation of sodium and its impact on blood pressure in CKD involves complex molecular mechanisms. One of the central pathways is the renin-angiotensin-aldosterone system (RAAS), which is activated when sodium levels are low. The process initiates with the kidneys releasing renin, an enzyme that catalyzes the conversion of angiotensinogen, a liver-produced protein, into angiotensin I. Angiotensin I is then transformed into angiotensin II by the angiotensin-converting enzyme (ACE), mainly in the lungs. Angiotensin II, a potent vasoconstrictor, narrows blood vessels, increasing blood pressure. Additionally, angiotensin II stimulates the secretion of aldosterone from the adrenal glands, which prompts the kidneys to reabsorb sodium and water, further elevating blood volume and pressure [4].

High sodium intake can also activate the sympathetic nervous system, which controls the "fight or flight" response, increasing heart rate and peripheral vascular resistance. In response to these effects, the heart releases natriuretic peptides in response to increased blood volume and pressure. These peptides promote sodium excretion by the kidneys and cause vasodilation, or the widening of blood vessels, to lower blood pressure [5].

In CKD, the impaired function of nephrons diminishes the kidneys’ ability to excrete sodium effectively. This leads to fluid retention, exacerbating hypertension. Moreover, CKD is often accompanied by elevated levels of inflammatory mediators such as tumor necrosis factor-alpha (TNF-α) and transforming growth factor-beta (TGF-β). These cytokines promote fibrosis, or scarring, in the kidneys, further reducing renal function and worsening the disease [6][7]. Elevated sodium levels also contribute to oxidative stress, an imbalance between the generation of harmful reactive oxygen species (ROS) and the body's ability to neutralize them. ROS can harm renal cells, speed up CKD progression, and lead to inflammation and fibrosis [8].

Hypertension in CKD is further exacerbated by endothelial dysfunction, in which the inner lining of blood vessels fails to function normally. Oxidative stress impairs the production of nitric oxide (NO), a molecule that aids in the relaxation of blood vessels. This impairment leads to vasoconstriction and increases vascular resistance, raising blood pressure. Additionally, changes in vascular smooth muscle cells, induced by angiotensin II and high sodium levels, lead to the proliferation and hypertrophy (enlargement) of these cells, contributing to vascular stiffness and elevated blood pressure [9]. Volume overload from fluid

retention, further increases blood volume and pressure, exacerbating hypertension in CKD patients [10].

Aldosterone stimulates salt and water reabsorption in the kidneys, increasing blood volume and pressure. High salt consumption has a substantial impact on this system because it causes greater water retention, which raises blood pressure even further. (Created by the author with Biorender).

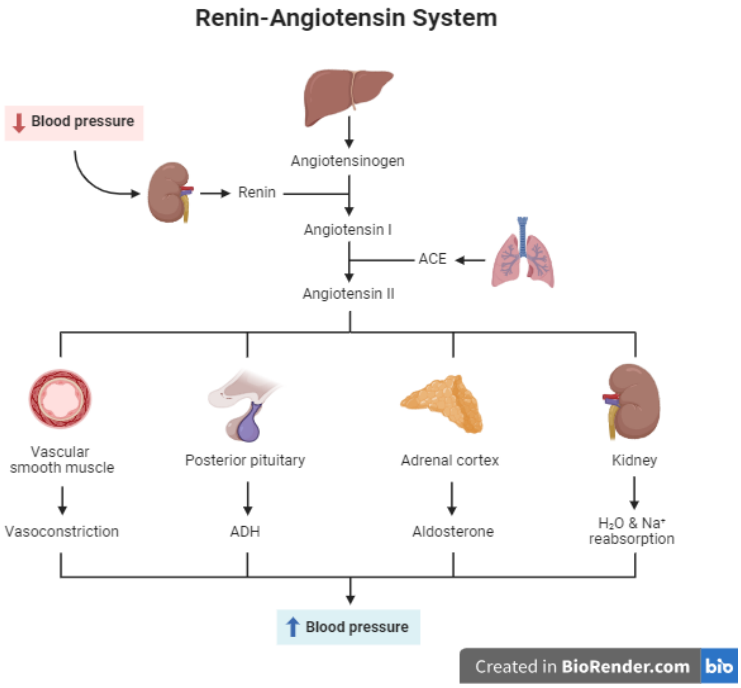

Figure-1: *Depicts the RAAS and its role in blood pressure regulation, emphasizing important components and processes. Low blood pressure causes the kidneys to release renin, which then transforms angiotensinogen from the liver to angiotensin I. ACE from the lungs then transforms angiotensin I to angiotensin II. Angiotensin II causes vasoconstriction, which raises blood pressure and encourages the adrenal cortex to release aldosterone. Diagram self-created by (J112133) using Biorender.*

Previous research on sodium intake in CKD patients has yielded varied results. For instance, a study by Shi et al. (2022) [11] observed that CKD patients who consumed less than 2 grams of sodium per day experienced reductions in both SBP and DBP, with potentially additive effects when combined with antihypertensive medications. This finding suggests that low sodium intake could be an effective strategy for managing blood pressure in chronic kidney disease patients, particularly when used alongside other treatments. Similarly, a meta-analysis conducted by Filippini et al. (2021) [12] supported these findings, indicating that low sodium intake could significantly lower both SBP and DBP, highlighting the importance of dietary sodium restriction in blood pressure management for CKD patients.

Conversely, high sodium intake has been associated with adverse effects on blood pressure in CKD patients. A study by Jaques et al. (2021) [13] reported that consuming more than 4 grams of sodium per day increased both SBP and DBP, along with a higher risk of cardiovascular events. This accentuates the potential dangers of high sodium consumption in CKD patients, who are already at

an increased risk of cardiovascular complications. Similarly, another study by Borrelli et al. (2020) [5] noted that high sodium intake could exacerbate hypertension and proteinuria (the presence of excess protein in the urine), potentially accelerating CKD progression. A meta-analysis by Graudal et al. (2020) [14] further indicated significant increases in SBP and DBP with high sodium intake, reinforcing the link between sodium consumption and blood pressure in CKD patients.

However, several studies have produced conflicting findings. Youssef (2022) [15] proposed that the relationship between sodium intake and blood pressure is not linear, suggesting that moderate sodium intake may be associated with the best cardiovascular outcomes. This finding indicates that both very low and very high sodium intakes might be detrimental and that an optimal range of sodium intake exists. Additionally, another study by Gupta et al. (2023) [16] found no clear benefit of low sodium intake for reducing blood pressure or cardiovascular events in the general population, suggesting that the effects of sodium intake might vary between CKD patients and the wider population. These findings suggest that the relationship between sodium intake and blood pressure is complex and may vary depending on individual patient characteristics.

Furthermore, age-related differences in blood pressure response to sodium intake are also crucial in CKD management. A study by Crawford-Faucher et al. (2017) [17] suggested that older chronic kidney disease patients may experience greater blood pressure reductions with low sodium intake compared to younger patients. This could be due to age-related changes in kidney function and sodium sensitivity, which may render older patients more responsive to sodium reduction. Conversely, younger patients might exhibit more pronounced blood pressure increases with high sodium intake, as reported by Bailey & Dhaun (2024) [18]. A meta-analysis conducted by Stamler et al. (2018) [19] highlighted that age might moderate the blood pressure response to sodium intake, suggesting the need for age-specific guidelines in managing CKD patients.

The duration of sodium intake adjustments can also influence blood pressure outcomes. Huang et al. (2018) indicated that short-term sodium reduction could lead to immediate decreases in SBP and DBP, with more pronounced effects over the long term [20]. This finding suggests that even temporary reductions in sodium intake can benefit chronic kidney disease patients, but sustained reductions may be necessary for long-term blood pressure control. Another study by Cook et al. (2007) [21] demonstrated that long-term sodium reduction was associated with sustained blood pressure control and reduced cardiovascular events, emphasizing the importance of maintaining a low-sodium diet over time for CKD patients.

Despite extensive research, significant gaps remain in understanding the optimal effects of sodium intake on blood pressure in CKD patients. Considering the essential role of sodium intake in blood pressure regulation and the inconsistency in study outcomes, it is clear that additional research is needed to better understand the relationship between sodium intake and blood pressure in this population. This meta-analysis seeks to investigate how varying levels of sodium intake, both low and high, influence systolic and diastolic blood pressure, assesses how these effects differ by age, and compare the blood pressure responses in chronic kidney disease patients to short-term versus long-term low sodium intake. By investigating these variables, this analysis could provide a comprehensive understanding of how sodium intake influences blood pressure in CKD patients, potentially providing more effective dietary guidelines and management strategies. The goal is to improve outcomes for CKD patients by identifying the most effective approaches to managing blood pressure through dietary sodium intake.

Materials and methods

This systematic review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [22]. The review aimed to synthesize the evidence on the effects of sodium intake on blood pressure regulation in patients with chronic kidney disease (CKD).

A comprehensive literature search was conducted using three electronic databases, Semantic Scholar,

ScienceDirect and PubMed', with the use of Boolean operators. The search strategy combined medical subject headings (MeSH), and free-text terms related to 'sodium intake', 'dietary sodium', 'salt intake', 'blood pressure regulation', 'hypertension', and 'chronic kidney disease'. Boolean operators AND, OR, and NOT were used to refine the search, this helped to enhance and optimize search outcomes, furthermore filters were used to ensure the results were specific. The table below provides the exact Boolean functions/queries and filters used for each databases searched.

Table- 1: *Databases for search queries/Boolean functions*

Database	Search query/Boolean function	Filter	Search Date	Outcome
Semantic scholar	("sodium intake" OR "dietary sodium" OR "salt intake") AND ("blood pressure regulation" OR "hypertension") AND ("chronic kidney disease" OR "CKD" OR "renal disease") AND ("primary research" OR "clinical study" OR "clinical trial" OR "randomized controlled trial" + filters	PDF	June/2024	269
ScienceDirect	("sodium intake" OR "dietary sodium" OR "salt intake") AND (hypertension OR "blood pressure") AND "chronic kidney disease" AND ("clinical study" OR "pre-clinical study")	Open Access, Research Articles	June/2024	56
PubMed	Salt INTAKE and hypertension IN CKD	Randomized clinical trial	June/2024	12
Total				**337**

Table-1 showed the databases searched, the queries and Boolean function used in the search, the filters used and number of identified studies. Three databases (sematic scholar, ScienceDirect and PubMed) were searched. Sematic scholar search identification was 269 in June 2024 when the search was made using the exact string and filters provided in the table above, ScienceDirect identified 56 studies in June 2024 when the search on the database was made using the exact string and filters provided in the table above. Finally, 12 studies were identified in PubMed search in June 2024 using the exact string and filters provided in the table above.

Inclusion Criteria: This review included studies that followed the PICO criteria; Population (chronic kidney disease patient), Intervention (varying levels of dietary sodium intake), Comparison (blood pressure level before and after sodium intake), Outcomes (primary outcome: systolic and diastolic blood pressure) and Study Design (randomized controlled trials, RCTs). The studies included were primary studies. In addition, open access articles published in peer-review journals were included to ensure data quality as peer review journals undergo critical manuscript evaluation process by experts in the field prior to publication. To ensure language proficiency, reduce translation costs, and minimize the time required for the review process only studies published in English were included; however, potential language bias is acknowledged.

Exclusion Criteria: Studies were excluded if they did not include the population of interest (patients with CKD), the intervention of interest (dietary salt), and primary outcome of interest which is blood pressure. Additionally, reviews, secondary studies, editorials and commentaries, unpublished articles and gray literature, and website and social media publications were excluded. Animal studies and cross-sectional studies were also excluded.

Gray literature was excluded to prioritize peer-reviewed publications that have undergone rigorous quality appraisal and editorial scrutiny. Exclusion was also applied to reduce bias or heterogeneity, since lack of standardized methodologies or reporting guidelines in gray literature can introduce bias, however, we acknowledged that recent advancements in unpublished findings may be omitted, however priority was placed on high-confidence evidence available in peer-reviewed journal articles indexed in reputable repositories.

Data extraction and management: Data extraction was conducted manually, and the data of interest was collated on an Excel sheet. Extracted data included study characteristics (author, year, study design), participant characteristics (sample size, age, CKD stage) intervention details (duration, sodium intake levels), outcome measures (systolic and diastolic blood pressure), study results and conclusions. Zotero, a widely used reference manager [23] was used in the management of the references from the selected studies. The extracted data from the selected studies were saved in Microsoft Excel. These collated secondary data were then used to create the study characteristics table and for subsequent use for descriptive analysis, and meta-analysis.

Quality Assessment: The quality of the included studies was assessed using the Jadad tool for randomized controlled trials (RCTs) [24]. This evaluation is crucial for understanding the methodological rigor and potential biases that could affect the reliability of the study findings. The assessment criteria included randomization (evaluating the method used to generate the randomization sequence), blinding (determining if blinding was applied to participants and personnel) and withdrawals (to know if the research work gave opportunities for participants to withdraw from the work). Each quality assessment criterion had a maximum score of 2 except for withdrawal, such that studies not conforming to the quality parameter assessed scored 0 while partial compliance score 1. Since 3 criteria are being assessed, a study can only have a maximum score of 6. Studies with a score of at least 3 were considered of sufficient quality and included for further analysis.

Table-2: *Quality assessment report using randomized clinical trial using JADAD tool*

Studies	**Randomization**		**Blinding**		**Withdrawal and dropouts**	**Total**
	Was the study randomised?	Was the method appropriate?	Was there blinding?	Was the method appropriate?	Was there a description for withdrawal or dropouts?	
Saran et al. [25]	1	1	1	1	1	**5**
Akdag et al. [26]	1	1	1	1	1	**5**
De Brito-Ashurst et al. [27]	1	1	0	0	1	**3**
Meuleman et al. [28]	1	1	0	0	1	**3**
O'Callaghan et al. [29]	1	1	1	1	1	**5**
Taylor et al. [30]	1	1	0	0	1	**3**
McMahon et al. [31]	1	1	1	1	1	**5**
Slagman et al. [32]	1	1	0	0	1	**3**

Table-2 showed the outcome of quality assessment of each included study using JADAD tool. All studies passed the quality assessment set at a cut-off score of 3. The studies by Saran et al. [25], Akdag et al. [26], O'Callaghan et al. [29] and McMahon et al. [31] had the highest overall quality as they fully complied with randomization, blinding and withdrawal. Studies by De Brito-Ashurst et al. [27],

Meuleman et al. [28], Taylor et al. [30] and Slagman et al. [32] had the lowest met the threshold quality score of 3/5.

Data synthesis and analysis: Data synthesis involved the meta-analysis of the extracted data from the selected studies. RevMan analytical tool was used to pool quantitative data by using the random-effects model to account for variability among studies [33]. Heterogeneity was assessed using the I^2 statistic [34]. Subgroup analyses were performed to descriptively compare the levels of blood pressure (systolic and diastolic) between age groups and duration (short and long term) of low salt intake to understand how age and duration of salt intake affect blood pressure level in CKD patients

Results

From the Figure-2 presented below, a total of 337 studies were Identified, and a final total of 8 studies passed the PRISMA guideline [22] for eligibility for data extraction.

Table-3 shows the characteristics of the included studies. From the table, 8 studies were presented. All presented studies were published between 2012 to 2023 and involved CKD patients, including those on haemodialysis. The sample size of the presented studies was between 12 to 138. All studies were randomised clinical trials (RCT) involving both males and females but with more males than females in all studies with complete data (without missing data). The studies captured participants from a wide group ranging from 18 to 68 years. Each presented study had at least one level of salt intake.

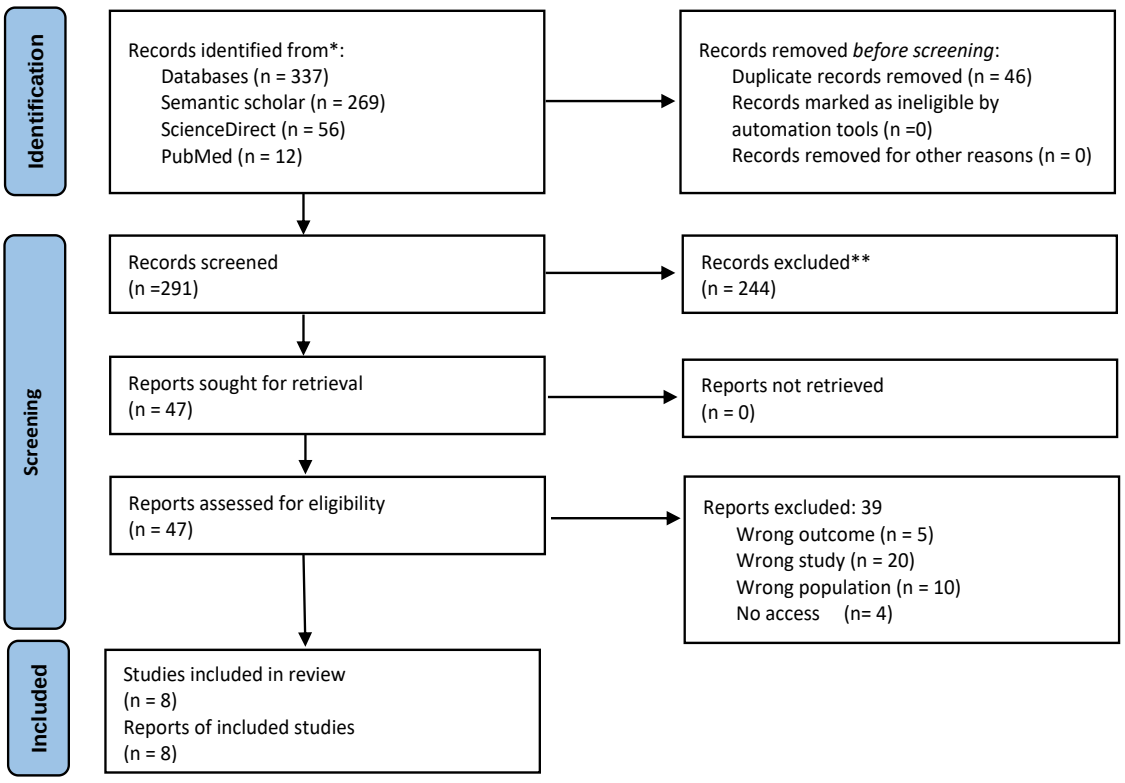

Figure-2: *PRISMA Flowchart*

Table-3: *Study characteristics*

Studies	Year Published	Population	Sample Size	Design	Gender	Mean Age (Yr)	Intervention
Saran et al. [25]	2017	CKD Patients	58	RCT	60% men 40% women	56.2 ±14.0	Sodium diet
Akdag et al. [26]	2015	Hemodialysis patient	22	RCT	13 males 9 females	45.2±2.8	Low sodium dialysate
		Hemodialysis patient	24	RCT	14 males 10 females	43.3±2.6	High sodium dialysate
de Brito-Ashurst et al. [27]	2013	Bangladeshi CKD Patients	48	RCT	Mixed	Adults	Tailored low-salt diet vs. standard low-salt advice
Meuleman et al. [28]	2017	CKD Patients	138	RCT	Male 82 Female 56	18-75	Sodium Restriction
O'Callaghan et al. [29]	2023	CKD	96	RCT	Male: 47 Female: 49	63.3±12.8	Low Oxsalt
Taylor et al. [30]	2018	CKD	12	RCT		18-85	Low salt
							High salt
McMahon et al. [31]	2013	CKD	20	RCT	Male: 15 Female: 5	68.5±11	Low salt
							High salt
Slagman et al. [32]	2012	CKD	32	RCT	Male: 73% Female:27%	50±2	Low salt
							High salt

The forest plot in Figure-3 presents the meta-analysis of the effect of low salt intake on systolic blood pressure in CKD patients, here a total of seven studies were assessed [25-31]. The result revealed a significant reduction in systolic blood pressure in CKD patients following low salt intake, with a pooled difference of 1.47 (95%: C.I [0.25, 2.69], p=0.02, Z= 2.36). Also, the result showed that significant heterogeneity existed among the studies (I^2= 98%, P<0.00001).

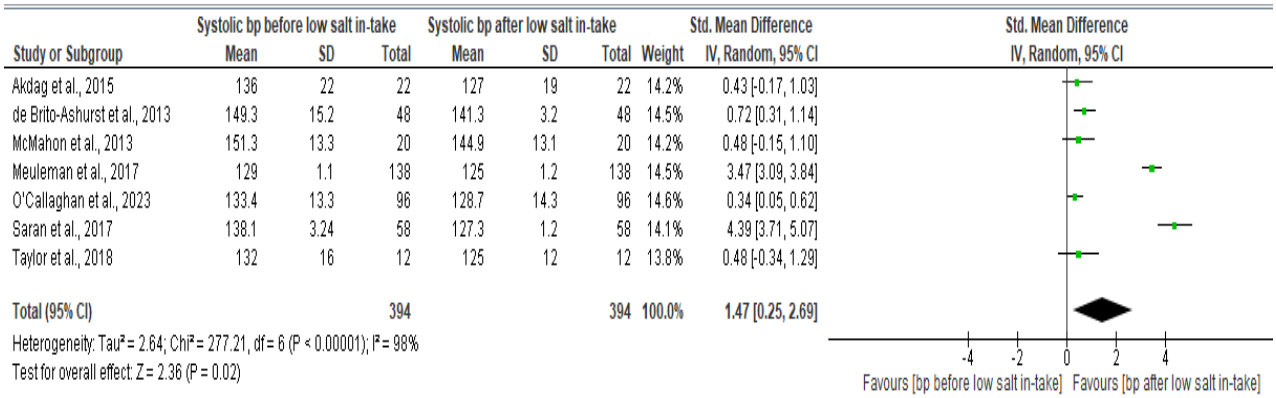

Figure-3: *Forest plot on the effect of low salt intake on systolic blood pressure in CKD patients*

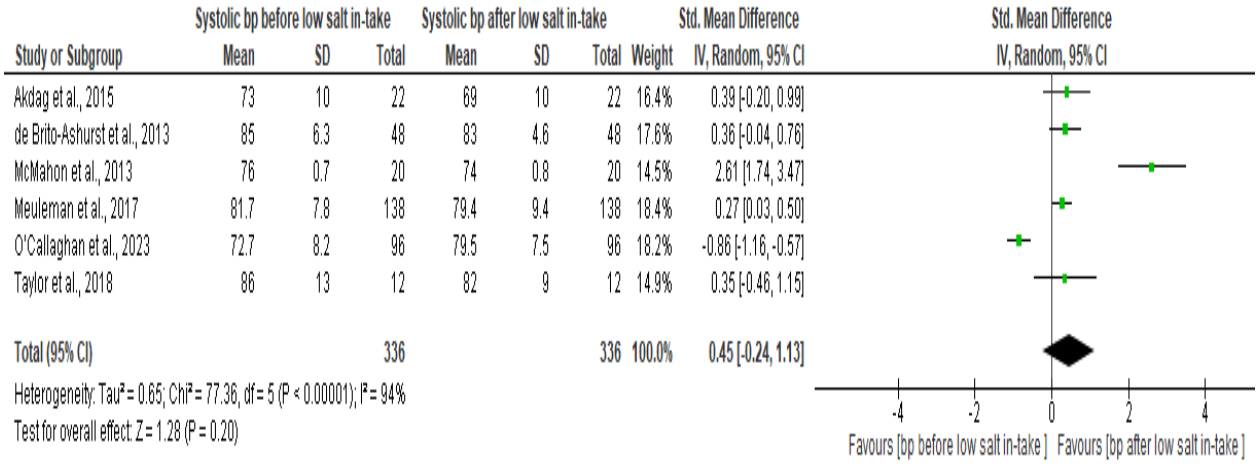

Figure-4: *Forest Plot on the effect of low salt intake on diastolic blood pressure in CKD patients*

The meta-analysis included in Figure-4 indicated that low salt intake had no effect on diastolic blood pressure in CKD patients. with a pooled difference of 0.45 (95%: C.I [-0.24, 1.13], p=0.20, Z= 1.28). Considerable heterogeneity was observed among the studies (I^2= 94%, P<0.00001).

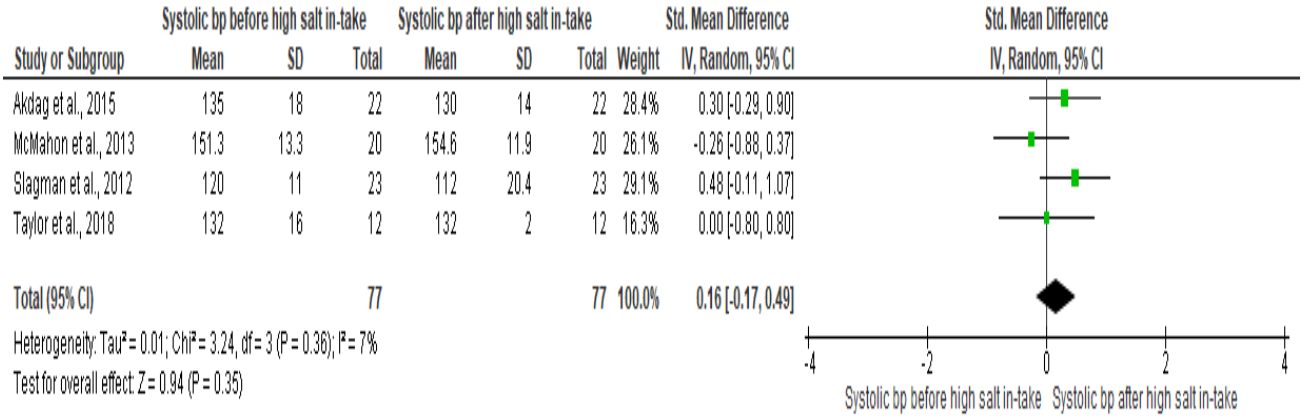

Figure-5: *Forest Plot showing the effect of high salt intake on systolic blood pressure in CKD Patients*

The forest plot in Figure-5 shows the meta-analysis of the effect of high salt intake on systolic blood pressure in CKD patients. The analysis indicated that high salt intake had no significant effect on systolic blood pressure in CKD patients, with a pooled difference of 0.16 (95%: C.I [-0.17, 0.49], p=0.35, Z= 0.94). No significant heterogeneity was observed among the studies (I^2= 7%, P=0.36).

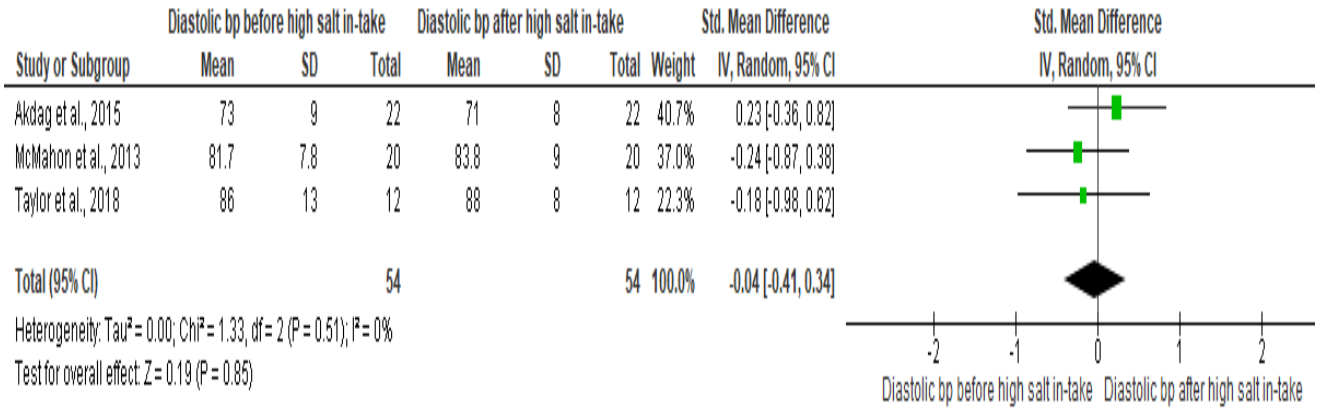

Figure-6: *Forest Plot on the effect of high salt intake on diastolic blood pressure in CKD Patients*

Figure-6 presents the meta-analysis of the effect of high salt intake on diastolic blood pressure in CKD patients. The result showed that there was no significant effect of high salt intake on diastolic blood pressure in CKD patients, with a pooled mean difference of -0.04 (95%: C.I [-0.41, 0.34], p=0.85, Z= 0.19). No significant heterogeneity was observed among the studies (I^2= 0%, P=0.51).

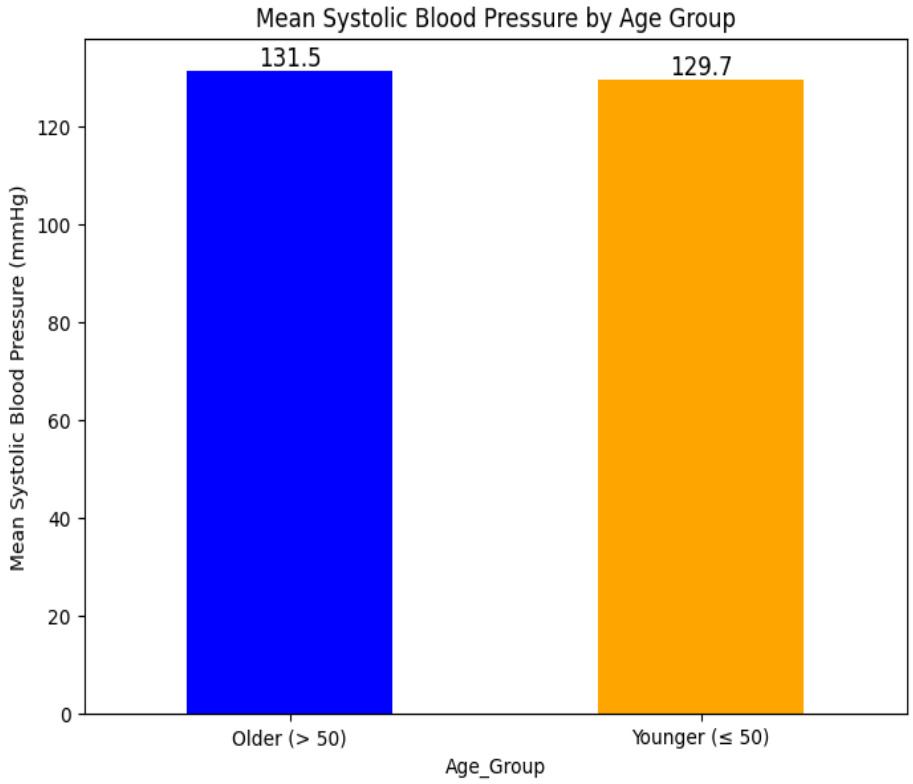

Figure-7: *Age-based difference in systolic blood pressure among CKD Patient on low salt intake*

Figure-7 presents the mean systolic blood pressure between two age groups: patients older than 50 years and those aged 50 years or younger. The chart shows that CKD patients aged 50 years or younger had slightly lower systolic blood pressure compared to CKD patients older than 50 years.

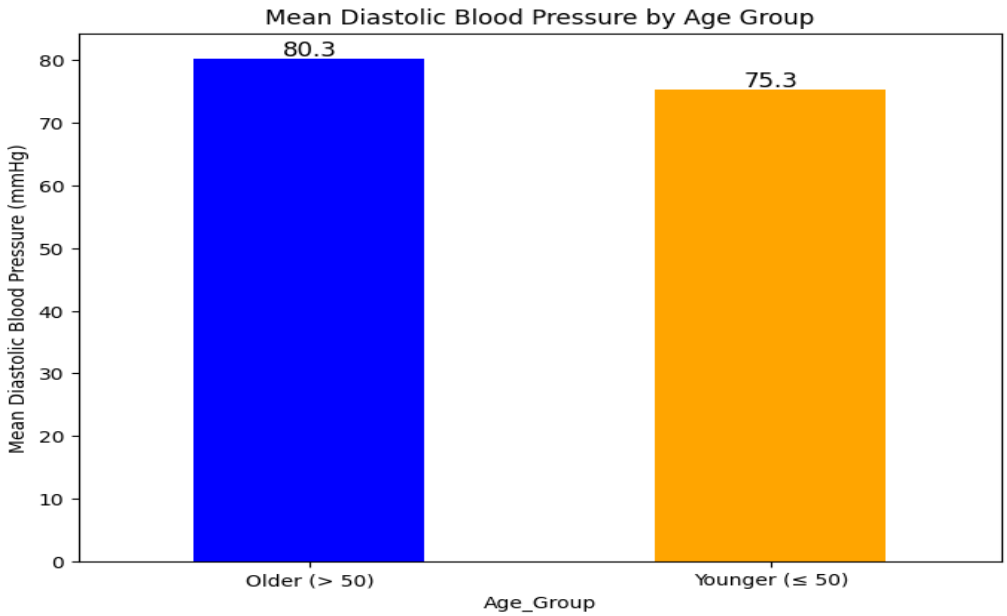

Figure-8: *Age-based difference in diastolic blood pressure among CKD patients on low salt intake*

Figure-8 presents the mean diastolic blood pressure levels in two groups of CKD patients: older than 50 years and those aged 50 years or younger. The results indicate that CKD patients less than or equal to 50 years of age had relatively lower diastolic blood pressure compared to CKD patients older than 50 years of age.

Table-4 below shows the systolic blood pressure across short-term and long-term salt intervention. The results showed that the systolic blood pressure in the short-term salt treatment ranged between 125±12 mmHg to 144.9±13.1 mmHg while in long term salt intervention, the diastolic blood pressure ranged between 125±1.2 mmHg to 141.3 mmHg.

Table- 4: *Systolic blood pressure levels across short term and long-term studies*

Studies	Duration of Treatment	Systolic blood pressure (mmHg)
Short term (≤2months) low sodium on systolic blood pressure		
Saran et al., 2017	4 weeks and 2 weeks crossover diet	127.3
O'Callaghan et al., 2023	1 month	128.7±14.3
Taylor et al., 2018	5 days	125±12
McMahon et al., 2013	6weeks	144.9±13.1
Slagman et al., 2012	6 weeks	137±3
Long term (>2months) low sodium on systolic blood pressure		
Akdag et al., 2015	6 months	127±19
de Brito-Ashurst et al., 2013	6 months	141.3
Meuleman et al., 2017	3 months	125±1.2
Meuleman et al., 2017	6months	128±1.2

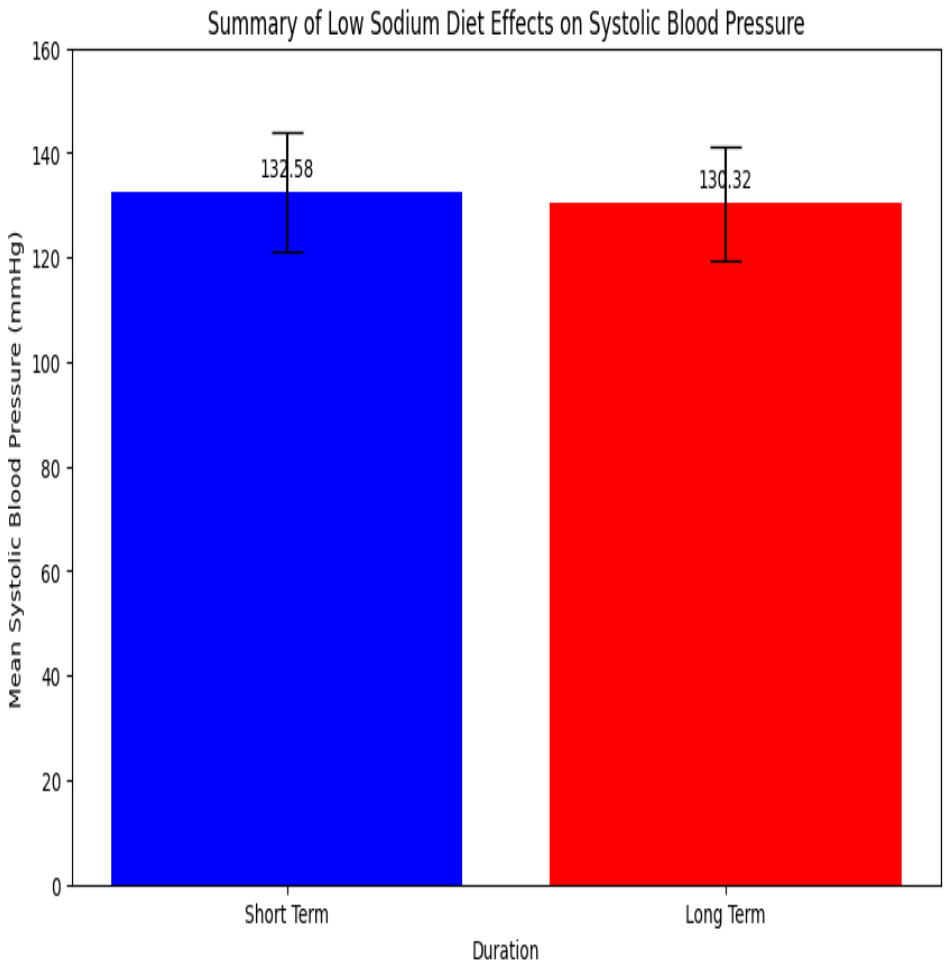

Figure-9: *Comparison of systolic blood pressure between short-term (≤2 months) and long-term (>2 months) low sodium intake in CKD patients*

Figure-9 presents the summary results of short-term (≤2months) and long-term (>2months) low salt intake on systolic blood pressure levels in CKD patients. The results show that studies examining long-term low salt intake reported lower systolic blood pressure averaging 130.32 mmHg, compared to those on short-term low salt intake which reported higher systolic blood pressure, averaging 132.58 mmHg. Table-5 presents the diastolic blood pressure across short-term and long-term salt interventions. The results indicate that the diastolic blood pressure, in the short-term salt treatment ranged between 79.4±9.4 mmHg to 83±1 mmHg, while in long term salt intervention, it ranged between 69±10 mmHg to 83 mmHg.

The summary results of short-term (≤2months) and long-term (>2months) low salt intake on diastolic blood pressure levels was presented in Figure-10. The result showed that studies on long-term low salt intake in CKD patients had lower diastolic blood pressure averaging 75.25 mmHg compared to those on short-term low salt intake which had higher diastolic blood pressure averaging 80.97 mmHg.

Table -5: *Diastolic blood pressure levels across short term and long-term studies*

Studies	Intervention	Duration of Treatment	Diastolic blood pressure (mmHg)
Short term (≤2months) low sodium on diastolic blood pressure			
Saran et al., 2017	Sodium diet	4 weeks and 2 weeks crossover diet	-
O'Callaghan et al., 2023	Low OxSalt	1 month	79.5±7.5
Taylor et al., 2018	Low salt	5 days	82±9
McMahon et al., 2013	Low salt	6weeks	79.4±9.4
Slagman et al., 2012	Low salt	6 weeks	83±1
Long term (>2months) low sodium on diastolic blood pressure			
Akdag et al., 2015	Low sodium dialysate	6 months	69±10
de Brito-Ashurst et al., 2013	Tailored low-salt diet vs. standard low-salt advice	6 months	83
Meuleman et al., 2017	Sodium Restriction	3 months	74±0.8
		6months	75±0.8
Meuleman et al., 2017	Sodium Restriction	6months	75±0.8

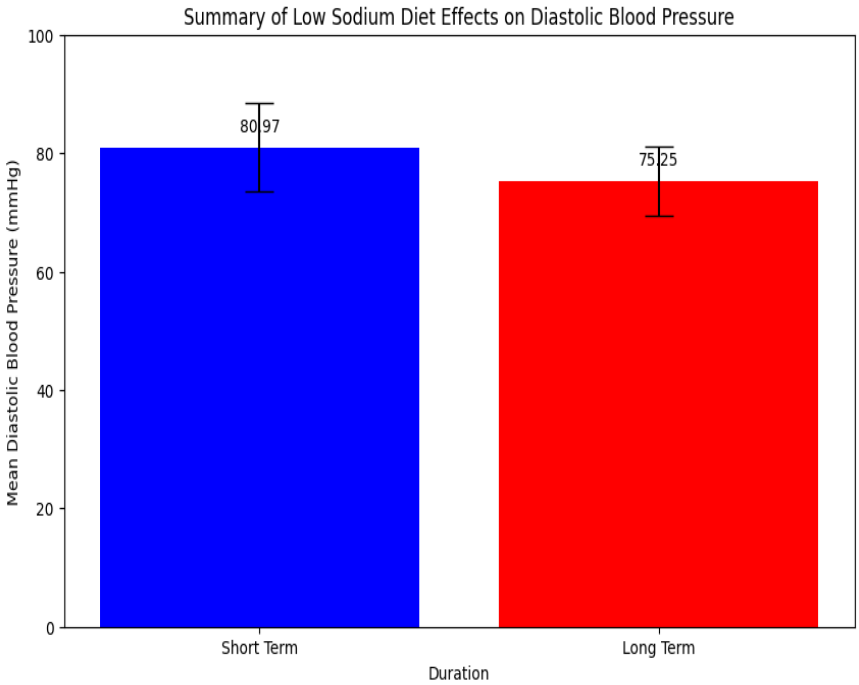

Figure- 10: *Comparison of diastolic blood pressure between short-term (≤2 months) and long-term (>2 months) durations on low sodium intake in CKD patients*

Discussion

The relationship between sodium intake and blood pressure in chronic kidney disease (CKD) patients has been a contentious topic in nephrology and dietary research.

The pooled analysis revealed a statistically significant but clinically modest reduction in systolic blood pressure (−1.47 mmHg) associated with low salt intake across seven studies [25-31]. While this effect size is small, it suggests that even modest dietary sodium restriction may contribute to blood pressure lowering in chronic kidney disease (CKD) patients. Given the cumulative benefits of non-pharmacological interventions in hypertension management, this reduction—though limited—could still support dietary sodium modification as part of a broader therapeutic strategy for CKD patients. Additionally, the consistent finding of SBP reduction across multiple studies highlights the robustness of this association, despite the inherent variability in study designs and populations. This finding aligns with the physiological understanding that lower sodium intake can reduce extracellular fluid volume, cardiac output, and vascular resistance. Sodium restriction may also enhance renal function by reducing glomerular hypertension and hyperfiltration, which are detrimental in chronic kidney disease [35]. The variability in responses to sodium intake suggests the potential for personalized nutrition plans tailored to individual patients' physiological responses. This could involve genetic testing, metabolic profiling, or other advanced diagnostic tools to determine the optimal sodium intake for each patient. Such personalized approaches could significantly enhance the effectiveness of dietary interventions by accounting for individual differences in sodium sensitivity and metabolic pathways.

Conversely, the pooled data from the six studies showed no significant effect of low salt intake on diastolic blood pressure, with a mean difference of 0.45 mmHg [26-31]. This suggests that dietary sodium reduction may not have a meaningful impact on DBP. The mechanisms through which dietary sodium influences systolic blood pressure and diastolic blood pressure may differ, with DBP being more influenced by peripheral vascular resistance and arterial stiffness than systolic blood pressure, which is primarily determined by cardiac output and systemic vascular resistance [36]. However, the significant effect in SBP and the lack of significant effect in DBP must be interpreted cautiously due to the high heterogeneity observed in both outcomes. This high heterogeneity suggests substantial variability across the included studies, possibly stemming from differences in baseline characteristics, variations in the degree of sodium reduction, and differences in intervention duration [37].

This study also reports significant reductions in systolic blood pressure with low sodium intake in CKD patients [11,20,38-40]. A recent Cochrane meta-analysis by Aminde et al. (2023) [41] also found that reducing salt intake by approximately 4.2 grams per day led to a significant decrease in both systolic blood pressure and diastolic blood pressure. While the evidence supporting the effect of low sodium intake on SBP is compelling, the findings regarding DBP are less straightforward, indicating a lack of significant effect and raising questions about the different mechanisms through which dietary sodium influences systolic blood pressure and diastolic blood pressure. Combining dietary sodium restriction with other integrative medicine approaches, such as mindfulness practices, stress reduction techniques, and complementary therapies, could offer synergistic benefits for blood pressure management in CKD patients. These holistic approaches could address the multifaceted nature of hypertension and improve overall well-being, potentially enhancing the effectiveness of dietary interventions.

Contrary to the expected hypertensive effect of high sodium intake, findings from the current study revealed that high sodium intake did not have a significant impact on systolic blood pressure in chronic kidney disease patients. The pooled effect size from four studies was 0.16, indicating no significant change in SBP with high sodium intake [26, 30-32]. Additionally, the low heterogeneity suggests consistent results across different study populations and methodologies. The consistent results highlight the need for a more individualized approach in managing sodium intake in CKD patients, considering the unique pathophysiological context of each patient. One possible explanation

for the non-significant effect of high sodium intake on SBP could be adaptive physiological mechanisms in CKD patients that mitigate the impact of sodium on blood pressure. CKD is often associated with altered sodium handling and volume regulation due to impaired renal function, which might blunt the pressor response to sodium [42]. Furthermore, CKD patients are commonly prescribed antihypertensive medications, which could confound the impact of sodium intake on blood pressure. These medications, depending on their specific mechanisms of action, may mitigate the hypertensive effects of sodium. Some antihypertensive drugs reduce sodium reabsorption in the kidneys, thereby diminishing the potential increase in blood pressure caused by high sodium intake [43]. The inconsistent reporting of antihypertensive medication use in the included studies introduces a variable that could partially account for the observed lack of significant effect.

Similarly, the meta-analysis as deduced from three studies found a non-significant effect of high sodium intake on DBP, with a pooled effect size of -0.04 and no significant heterogeneity [26][30][31]. These findings align with the results for SBP, suggesting a consistent lack of significant impact of high sodium intake on blood pressure parameters in CKD patients. The lack of effect on DBP supports the hypothesis that CKD patients may have an attenuated blood pressure response to sodium [42].

These findings question the traditional view of sodium-induced hypertension, especially within the context of CKD. Despite the well-established link between high sodium intake and hypertension in the general population, CKD patients may exhibit a different response due to their unique pathophysiological state [44]. These results suggest that a one-size-fits-all approach to sodium restriction may not be appropriate for all CKD patients and highlight the importance of personalized dietary recommendations. Other research also challenge these findings, a systematic review by Smyth et al. (2014) [45] and a meta-analysis by Kim et al. (2021) [46] examining the effect of urinary angiotensinogen and high-salt diet on blood pressure in CKD patients found that high sodium intake significantly increased both SBP and DBP.

Furthermore, the examination of age-related differences in blood pressure responses to low salt intake revealed distinct patterns in both SBP and DBP. Analysis of data from eight studies demonstrated age-based variations in how blood pressure is affected by low salt intake. Younger and middle-aged CKD patients (that is, those under 50 years) experienced a slight reduction in SBP and a more pronounced reduced in DBP compared to CKD patients over 50 years. The improved response in younger patients could be attributed to better vascular health and fewer additional health conditions, which enhance their ability to adapt to dietary changes. Older individuals often have more advanced vascular changes and additional health challenges that might reduce the effectiveness of low salt interventions [47].

Similarly, reductions in DBP are more significant among younger and middle-aged patients. The trends observed in DBP align with those seen in SBP, indicating that younger patients benefit more from low salt intake. These findings suggest consistent physiological mechanisms, driving these improvements across both types of blood pressure measurements. However, it is important to consider that the benefits observed in younger patients may not directly translate to older populations, where different therapeutic strategies might be required to achieve similar blood pressure control. Further research is needed to explore how age-specific factors such as hormone levels, sodium sensitivity, and medication interactions influence the response to dietary sodium interventions in CKD patients. Considerable variability is observed across the studies for both SBP and DBP.

The effects of low salt intake on blood pressure vary significantly between short-term (≤2 months) and long-term (>2 months) interventions. Short-term interventions typically produce SBP values ranging from 125±12 mmHg to 144.9±13.1 mmHg. McMahon et al. (2012) [31] and Taylor et al. (2018) [32] reported particularly high values (144.9±13.1 mmHg and 137±3 mmHg, respectively), suggesting that short-term low salt intake may not be sufficient to achieve significant and sustained reductions in SBP. In contrast, long-term interventions generally result in lower and more stable SBP values. Research by Akdag et al. (2015) [26] and Meuleman et al. (2017) [28] showed SBP values of 140±14 mmHg and 130.3±2.3 mmHg, respectively. This indicates that prolonged adherence to a low-salt diet can yield

more substantial and lasting reductions in SBP. The distinction between short-term and long-term effects is critical in understanding the full impact of sodium reduction on blood pressure. While short-term interventions might capture the initial, acute responses to sodium reduction, including diuresis and changes in vascular tone, long-term interventions likely reflect more stable physiological adaptations, such as improved arterial compliance and better volume control, which are necessary for sustained blood pressure reductions. Moreover, long-term adherence to dietary sodium restriction could lead to behavioral and lifestyle changes that reinforce the positive effects on blood pressure, contributing to overall cardiovascular health.

Short-term low-salt intake interventions showed DBP values ranging from 79.8±0.8 mmHg to 89.9±2.8mmHg. Notably, studies by McMahon et al. (2012) [31] and Taylor et al. (2018) [32] report DBP values of 87.9±1.4 mmHg and 89.9±2.8 mmHg, respectively, indicating limited impact of short-term dietary changes. Conversely, long-term interventions generally result in lower and more stable DBP values, ranging from 76.2±1.2 mmHg to 81.6±9.5 mmHg. Research by Akdag et al. (2015) [26] and Meuleman et al. (2017) [28] showed DBP values of 80±6 mmHg and 81.6±9.5 mmHg, respectively, indicating more substantial reductions in DBP with prolonged adherence to a low-salt diet. These findings suggest that the benefits of sodium reduction on DBP may take longer to manifest compared to SBP, possibly due to the different physiological processes involved. The more gradual improvement in DBP with long-term sodium restriction highlights the importance of patient persistence and support in maintaining dietary changes, as the full benefits may not be immediately apparent. While short-term interventions can produce rapid but modest improvements in SBP and DBP, these changes often lack stability [39]. This could be due to the body's initial adaptive responses to sodium reduction, such as diuresis and natriuresis, which may not sustain long-term benefits. Long-term adherence to a low-salt diet leads to more significant and stable reductions in both SBP and DBP. Prolonged dietary changes may result in better regulation of extracellular fluid volume, sustained improvements in vascular resistance, and enhanced renal function, contributing to lasting blood pressure control [11][48]. The enduring impact of long-term sodium reduction on blood pressure, particularly in the context of CKD, underpins the importance of sustained dietary interventions as part of a comprehensive management plan for these patients. Continued research is needed to identify the most effective strategies for promoting long-term adherence to sodium restriction, as well as to further elucidate the underlying mechanisms that drive these beneficial effects.

Recommendations

Based on the findings of this systematic review and meta-analysis, several recommendations can be made for clinical practice and future research. Healthcare providers should consider recommending low sodium intake as part of dietary management for CKD patients to achieve better SBP control. Given the greater benefit observed in younger and middle-aged patients, personalized dietary recommendations based on age and other patient characteristics may enhance effectiveness. Long-term dietary interventions should be emphasized over short-term changes. Sustained reduction in sodium intake is more likely to result in significant and consistent blood pressure improvements. Clinical guidelines should be updated to reflect the evidence supporting the benefits of low sodium intake for SBP reduction in CKD patients. Clear thresholds for low sodium intake and detailed recommendations on the duration of dietary interventions should be provided. Additional research is required to investigate the mechanisms behind the differing effects of sodium intake on SBP and DBP. Understanding these mechanisms can help tailor dietary recommendations more effectively. More high-quality, randomized controlled trials with standardized protocols for sodium reduction and blood pressure measurement are essential to reduce heterogeneity and improve the reliability of findings. Research should also investigate the long-term effects of sodium reduction on cardiovascular outcomes in CKD patients, as well as the role of concurrent pharmacotherapy and other lifestyle modifications in enhancing the benefits of dietary sodium reduction.

Limitation

Several constraints should be considered when interpreting these results. Firstly, the high heterogeneity observed in the analysis of low sodium intake on SBP (I^2 = 98%) and DBP (I^2 = 94%) suggests substantial variability among the included studies. This variability could stem from differences in study design, baseline characteristics, degree of sodium reduction, and duration of interventions. The included studies exhibited varying methodological quality, with potential biases such as lack of blinding and randomization influencing the outcomes. Additionally, data availability and consistency were additional challenges. Not all studies provided detailed information on the baseline characteristics of participants, and there were inconsistencies in how blood pressure was measured and reported. The factors could affect the reliability of pooled estimates and the generalizability of the findings to the broader CKD population.

Conclusion

This systematic review and meta-analysis explored the effects of sodium intake on blood pressure in patients with chronic kidney disease. Findings suggest that a reduced sodium intake significantly lowers SBP. This supports the hypothesis that reducing sodium intake can have beneficial effects on blood pressure management in CKD patients. The reduction in SBP can be attributed to the physiological mechanisms of decreased extracellular fluid volume, reduced cardiac output, and lower vascular resistance. However, the impact on DBP was not significant, suggesting that diastolic pressure may not be as responsive to sodium reduction.

Contrarily, high sodium intake did not show a significant effect on SBP or DBP in CKD patients challenging the conventional understanding of sodium-induced hypertension, particularly in the CKD context. Adaptive physiological mechanisms in CKD, such as altered sodium handling and volume regulation, might mitigate the expected hypertensive response. The lack of significant effect on DBP with both low and high sodium intake further underlines the complexity of blood pressure regulation in CKD.

Age-based analysis revealed that younger and middle-aged CKD patients benefit more from low sodium intake compared to older patients, indicating that age-related vascular changes and comorbidities may influence the effectiveness of dietary interventions. Additionally, long-term sodium reduction (over two months) proved more effective in reducing both SBP and DBP compared to short-term interventions, highlighting the importance of sustained dietary changes for optimal blood pressure control.

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Author's contributions

WTT developed the manuscript. CFA performed the meta-analysis and other statistics.

Conflict of interest

Authors declared no conflict of interest.

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Ethical Considerations

As this study involved the analysis of previously published data, no ethical approval was required. However, ethical considerations for conducting and reporting systematic reviews were strictly followed to ensure transparency, accuracy, and reproducibility of the findings. On the other hand, all data obtained from the published works were duly cited as required in academic and research writing.

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