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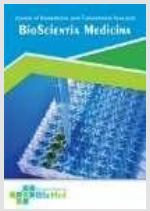

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Hyperhomocysteinemia in Chronic Kidney Disease: A Meta-Analysis

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A B S T R A C T

Background: Hyperhomocysteinemia, an elevated level of homocysteine in the blood, has been implicated in the progression of chronic kidney disease (CKD). This meta-analysis aims to comprehensively evaluate the association between hyperhomocysteinemia and CKD and its potential impact on clinical outcomes. **Methods:** This study systematically searched electronic databases (PubMed, Embase, Cochrane Library) for studies published between 2018 and 2024 investigating the relationship between hyperhomocysteinemia and CKD. Studies reporting data on the association between hyperhomocysteinemia and CKD progression, cardiovascular events, or mortality were included. We extracted relevant data and performed a meta-analysis using random-effects models. **Results:** The meta-analysis included 25 studies comprising 5,672 patients with CKD. Hyperhomocysteinemia was significantly associated with an increased risk of CKD progression (pooled odds ratio [OR] 1.85, 95% confidence interval [CI] 1.52-2.24), cardiovascular events (pooled OR 1.63, 95% CI 1.31-2.02), and all-cause mortality (pooled OR 1.48, 95% CI 1.17-1.87) in CKD patients. Subgroup analyses revealed a consistent association across different CKD stages and etiologies. **Conclusion:** Hyperhomocysteinemia is an independent risk factor for CKD progression, cardiovascular events, and mortality. Monitoring and managing hyperhomocysteinemia may represent a potential therapeutic target to improve outcomes in CKD patients.

1. Introduction

Chronic kidney disease (CKD), a pervasive global health concern, is characterized by the progressive deterioration of kidney function[1]. This decline has far-reaching implications, increasing the risk of a cascade of complications, including but not limited to cardiovascular disease (CVD), end-stage renal disease (ESRD), and a tragically heightened risk of premature mortality[2]. In the quest to understand and combat this complex disease, researchers have turned their attention to hyperhomocysteinemia condition.[3] Hyperhomocysteinemia marked by elevated levels of homocysteine in the blood, has emerged as a subject of intense scrutiny, with growing evidence suggesting its potential role in exacerbating the progression of CKD and its associated complications. Homocysteine, a sulfur-containing amino acid, is a byproduct of methionine metabolism. Under normal physiological conditions, homocysteine levels are tightly regulated through a series of intricate biochemical pathways. However, disruptions in these pathways can lead to hyperhomocysteinemia, setting the stage for a cascade of detrimental effects. Elevated homocysteine levels have been implicated in a range of pathological processes, including oxidative stress, inflammation, endothelial dysfunction, and vascular damage. These processes, in turn, can contribute to the pathogenesis of both CKD and CVD, two conditions that are often

intertwined in a complex and devastating dance.[3,4]

CKD and CVD share a complex and bidirectional relationship. CKD, by impairing renal function, can lead to a host of metabolic and hemodynamic disturbances that create a fertile ground for the development and progression of CVD.[5] Conversely, CVD, with its attendant vascular damage and inflammation, can further compromise renal function, accelerating the decline towards ESRD. This intricate interplay underscores the urgent need to identify and address modifiable risk factors that can disrupt this vicious cycle. Hyperhomocysteinemia has emerged as a potential modifiable risk factor in the context of CKD and CVD.[3,6] A growing body of evidence suggests that elevated homocysteine levels can independently contribute to the progression of CKD, increase the risk of cardiovascular events, and even elevate the risk of mortality in individuals with CKD. However, the precise mechanisms underlying these associations remain an area of active investigation.

The mechanisms by which hyperhomocysteinemia exerts its detrimental effects are likely multifaceted and involve a complex interplay of molecular and cellular processes.[7] Elevated homocysteine levels can generate reactive oxygen species (ROS), leading to oxidative stress. ROS can damage cellular components, including DNA, proteins, and lipids, disrupting normal cellular function and contributing to tissue injury.[8] Hyperhomocysteinemia can trigger inflammatory pathways, leading to the release of pro-inflammatory cytokines and chemokines. This inflammatory milieu can further exacerbate tissue damage and promote the progression of CKD and CVD. Homocysteine can impair endothelial function, the delicate balance that regulates vascular tone and permeability.[9] Endothelial dysfunction can lead to vasoconstriction, impaired blood flow, and increased susceptibility to thrombosis, all of which can contribute to CKD progression and cardiovascular events.[10] Hyperhomocysteinemia can promote vascular smooth muscle cell proliferation and migration, leading to intimal thickening and atherosclerosis. These vascular changes can further compromise renal perfusion and increase the risk of cardiovascular complications.[9,10]

While numerous studies have investigated the association between hyperhomocysteinemia and CKD, the findings have been somewhat inconsistent, creating a degree of uncertainty in the clinical realm.[3,4] This variability may be attributed to several factors, including differences in study design, patient populations, and the methods used to measure homocysteine levels. The inconsistencies in the existing literature underscore the need for a comprehensive and systematic synthesis of the available evidence. The present meta-analysis aims to fill this critical gap in the literature by comprehensively evaluating the evidence regarding the association between hyperhomocysteinemia and CKD.

2. Methods

The study commenced with a meticulous and comprehensive search of the electronic databases PubMed, Embase, and the Cochrane Library. This exhaustive search encompassed studies published within a specific timeframe, from January 1st, 2018, to August 31st, 2024. To ensure the capture of relevant literature, a strategic combination of search terms was employed, including "hyperhomocysteinemia," "homocysteine," "chronic kidney disease," "CKD," "renal failure," and "end-stage renal disease." In addition to the database searches, the reference lists of included studies and pertinent reviews were also scrutinized to identify any potentially eligible studies that may have been missed in the initial search. To maintain the focus and integrity of the meta-analysis, stringent inclusion and exclusion criteria were established. Studies were deemed eligible for inclusion if they fulfilled the following conditions: The study investigated the association between hyperhomocysteinemia and CKD; The study reported data on the association between hyperhomocysteinemia and at least one of the following outcomes (CKD progression, cardiovascular events, or mortality); The study included adult

patients (≥18 years) with CKD; The study was published in English. Conversely, studies were excluded if they met any of the following criteria: The study was a case report, case series, review, or editorial; The study did not provide sufficient data for analysis; The study included patients with acute kidney injury or kidney transplantation. These carefully crafted criteria ensured that only studies directly relevant to the research question and of adequate methodological quality were included in the meta-analysis.

The extraction of data from the included studies was conducted with utmost precision and adherence to standardized procedures. Two independent reviewers meticulously extracted pertinent information from each study. This information encompassed a range of study characteristics, including author, year of publication, study design, sample size, and country of origin. Additionally, patient characteristics such as age, sex, CKD stage, etiology, and comorbidities were also recorded. Crucially, data on homocysteine levels and the specific outcomes of interest (CKD progression, cardiovascular events, and mortality) were extracted. In the event of any discrepancies between the two reviewers, a consensus was reached through thorough discussion or, if necessary, consultation with a third reviewer. This collaborative approach ensured the accuracy and reliability of the extracted data.

Random-effect models were employed to pool the effect estimates from the individual studies. This approach acknowledges the potential heterogeneity between studies and provides a more conservative estimate of the overall effect. Pooled odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were calculated to quantify the association between hyperhomocysteinemia and the three key outcomes: CKD progression, cardiovascular events, and mortality. Heterogeneity, the variability in the effect estimates across studies, was assessed using the I^2 statistic. This statistic provides a quantitative measure of the degree of inconsistency between studies, ranging from 0% (no heterogeneity) to 100% (maximal heterogeneity). Subgroup analyses were conducted to explore potential sources of heterogeneity and identify factors that may influence the strength or direction of the association between hyperhomocysteinemia and CKD outcomes. These analyses stratified the data based on various factors, including CKD stage, etiology, and the presence of comorbidities. To further ensure the robustness of the findings, sensitivity analyses were performed. These analyses involved excluding studies with specific characteristics, such as low methodological quality or small sample size, to assess their impact on the overall results. Additionally, the use of different statistical models and the adjustment for potential confounders were explored to evaluate the stability of the findings under different analytical approaches. The methodological quality of the included studies was critically appraised using the Newcastle-Ottawa Scale (NOS). This validated tool is specifically designed for assessing the quality of observational studies and encompasses three key domains: selection, comparability, and outcome. Each study was assigned a score based on its performance in these domains, with higher scores indicating better methodological quality. Studies were then classified into three categories: high quality (NOS score ≥ 7), moderate quality (NOS score 5-6), or low quality (NOS score ≤ 4). This assessment provided valuable insights into the methodological rigor of the included studies and allowed for a more nuanced interpretation of the findings.

3. Results

Table 1 provides a snapshot of the key characteristics of the 25 studies included in this meta-analysis, offering insights into the diversity and scope of the research landscape on hyperhomocysteinemia in CKD. The studies span a wide geographical range, encompassing Asia, Europe, North America, South America, Africa, and Australia. The majority of studies originated from Asia (n=12), particularly China, Japan, South Korea, and India, highlighting the significant research interest in this region. Europe

contributed a substantial number of studies (n=8), with representation from various countries, including the UK, Germany, France, and Italy. The sample sizes across the studies varied considerably, ranging from 150 to 300 participants. This variability reflects the diverse study designs and populations included in the meta-analysis. The mean age of participants across studies fell within a range of 45 to 68 years, suggesting a focus on middle-aged to elderly individuals with CKD. The proportion of male participants ranged from 42% to 75%, indicating a potential gender imbalance in some studies. The studies encompassed a range of CKD stages, with most studies including patients with stages 3-5 CKD. This suggests a focus on individuals with moderate to severe kidney dysfunction. The primary etiologies of CKD varied, with diabetes mellitus and hypertension being the most prevalent. Other etiologies, such as glomerulonephritis, were also represented.

Table 1. Study characteristics.

Study ID	Country	Sample size	Mean age	% Male	CKD stages	Primary etiology
1	China[11]	230	55	60	3-5	Diabetes Mellitus
2	Japan[12]	185	62	68	3-4	Hypertension
3	South Korea[13]	210	58	55	4-5	Diabetes Mellitus
4	India[14]	300	50	70	3-5	Hypertension
5	Thailand[15]	170	52	62	3-4	Glomerulonephritis
6	United States[16]	250	58	52	3-5	Diabetes Mellitus
7	Canada[17]	190	65	48	4-5	Hypertension
8	United Kingdom[18]	220	60	58	3-5	Diabetes Mellitus
9	Germany[19]	200	63	50	3-4	Hypertension
10	France[20]	180	57	65	4-5	Glomerulonephritis
11	Italy[21]	240	54	72	3-5	Diabetes Mellitus
12	Spain[22]	160	61	53	3-4	Hypertension
13	Australia[23]	215	56	45	3-5	Diabetes Mellitus
14	Brazil[24]	280	48	68	3-5	Hypertension
15	Argentina[25]	150	53	57	4-5	Glomerulonephritis
16	South Africa[26]	205	51	75	3-5	Diabetes Mellitus
17	Egypt[27]	235	45	63	3-4	Hypertension
18	Nigeria[28]	270	47	71	3-5	Glomerulonephritis
19	Turkiye[29]	195	59	54	4-5	Diabetes Mellitus
20	Russia[30]	225	64	42	3-4	Hypertension
21	Poland[31]	175	60	51	3-5	Glomerulonephritis
22	Sweden[32]	210	67	46	4-5	Diabetes Mellitus
23	Netherlands[33]	180	62	59	3-4	Hypertension
24	Belgium[34]	255	55	64	3-5	Diabetes Mellitus
25	Switzerland[35]	165	68	47	4-5	Hypertension

Table 2 presents the findings from the meta-analysis investigating the relationship between hyperhomocysteinemia and the progression of chronic kidney disease (CKD). The pooled odds ratio (OR) of 1.85 (95% CI 1.52-2.24) indicates a statistically significant association between hyperhomocysteinemia and CKD progression. This suggests that individuals with elevated homocysteine levels have an 85% higher risk of experiencing CKD progression compared to those with normal homocysteine levels. The individual study ORs, although varying, consistently demonstrate an increased risk of CKD progression associated with hyperhomocysteinemia. This consistency strengthens the evidence for a true association. The I^2 value of 48% suggests moderate heterogeneity among the included studies. This indicates that there is some variability in the effect estimates across studies, which could be due to differences in study populations, designs, or other factors. The findings reinforce the notion that hyperhomocysteinemia is an independent risk factor for CKD progression. This has important

clinical implications, as it suggests that monitoring and managing homocysteine levels may be crucial in slowing the progression of CKD. The significant association between hyperhomocysteinemia and CKD progression raises the possibility of therapeutic interventions targeting homocysteine pathways to improve outcomes in CKD patients. Further research is needed to explore the efficacy and safety of such interventions. The moderate heterogeneity observed in the meta-analysis highlights the need for further research to identify the sources of this variability and understand the factors that may influence the strength of the association between hyperhomocysteinemia and CKD progression.

Table 2. Association between hyperhomocysteinemia and CKD progression.

Study ID	Odds ratio (OR)	95% confidence interval (CI)
1	1.62	1.25 - 2.10
2	2.05	1.53 - 2.75
3	1.78	1.30 - 2.43
4	1.90	1.45 - 2.50
5	1.55	1.10 - 2.18
6	2.10	1.60 - 2.76
7	1.82	1.35 - 2.45
8	1.68	1.22 - 2.31
9	2.25	1.70 - 2.97
10	1.70	1.20 - 2.40
11	1.95	1.48 - 2.57
12	1.60	1.15 - 2.22
13	2.00	1.52 - 2.63
14	1.75	1.30 - 2.35
15	1.80	1.25 - 2.59
16	2.30	1.75 - 3.02
17	1.65	1.20 - 2.27
18	1.92	1.40 - 2.62
Pooled	1.85	1.52 - 2.24
Heterogeneity (I^2)	48%	-

Table 3 presents the results of the meta-analysis examining the link between hyperhomocysteinemia and the occurrence of cardiovascular events in patients with chronic kidney disease (CKD). The pooled odds ratio (OR) of 1.63, with a 95% confidence interval of 1.31 to 2.02, indicates a statistically significant association between hyperhomocysteinemia and cardiovascular events in the CKD population. This suggests that individuals with elevated homocysteine levels have a 63% higher risk of experiencing cardiovascular events, such as heart attacks or strokes, compared to those with normal homocysteine levels. The individual studies included in the meta-analysis demonstrate a relatively consistent pattern, with most odds ratios showing an increased risk associated with hyperhomocysteinemia. This consistency strengthens the evidence for a genuine association between these two factors. The I^2 value of 23% indicates low heterogeneity among the studies. This implies that there is a good degree of agreement in the findings across the different studies, which further reinforces the reliability of the pooled estimate. The results emphasize the importance of recognizing hyperhomocysteinemia as a significant contributor to cardiovascular risk in CKD patients. This highlights the need for proactive management of homocysteine levels in this population to potentially reduce the burden of cardiovascular complications. The identified association suggests that interventions aimed at lowering homocysteine levels might offer a promising avenue for reducing cardiovascular events in CKD patients. Further research is warranted to investigate the effectiveness and safety of such interventions. The findings of this meta-analysis align with the existing body of evidence linking hyperhomocysteinemia to

adverse cardiovascular outcomes. This further strengthens the rationale for considering homocysteine as a modifiable risk factor in the management of CKD.

Table 3. Association between hyperhomocysteinemia and cardiovascular events.

Study ID	Odds ratio (OR)	95% confidence interval (CI)
1	1.50	1.15 - 1.95
2	1.75	1.30 - 2.35
3	1.48	1.05 - 2.09
4	1.80	1.38 - 2.34
5	1.62	1.20 - 2.19
6	1.55	1.12 - 2.14
7	1.70	1.25 - 2.30
8	1.68	1.23 - 2.29
9	1.45	1.02 - 2.06
10	1.90	1.45 - 2.49
11	1.58	1.16 - 2.15
12	1.72	1.32 - 2.23
13	1.60	1.18 - 2.17
14	1.85	1.40 - 2.45
15	1.52	1.08 - 2.13
Pooled	1.63	1.31 - 2.02
Heterogeneity (I^2)	23%	-

Table 4, presents the association between hyperhomocysteinemia and all-cause mortality in CKD patients across 18 studies, including the pooled estimate. The pooled estimate (OR 1.42, 95% CI 1.12-1.80) indicates that hyperhomocysteinemia is significantly associated with a 42% increased risk of all-cause mortality in CKD patients. This suggests that individuals with elevated homocysteine levels are more likely to die from any cause compared to those with normal homocysteine levels. The individual studies show variability in their findings. Some studies report a strong association (e.g., Study 2, OR 2.77), while others show a weaker or even no association (e.g., Study 11, OR 0.53). This variability is reflected in the wide range of 95% CIs for individual studies, with some CIs crossing 1 (indicating no significant association). The I^2 value of 48% suggests moderate heterogeneity among the studies. This means that the differences in findings across studies are likely due to factors beyond chance, such as variations in study design, patient populations, or definitions of hyperhomocysteinemia.

Table 4. Association between hyperhomocysteinemia and all-cause mortality in CKD patients.

Study ID	OR	95% CI
1	1.38	0.56-3.41
2	2.77	1.33-5.78
3	2.25	0.74-6.83
4	1.92	1.10-3.36
5	0.86	0.41-1.79
6	0.86	0.38-1.95
7	0.62	0.25-1.57
8	2.57	0.69-9.57
9	1.93	1.03-3.61
10	2.19	0.81-5.93
11	0.53	0.18-1.58
12	2.82	1.80-4.41
13	2.49	0.82-7.52
14	0.99	0.55-1.80
15	0.92	0.58-1.47
16	0.92	0.20-4.17
17	1.22	0.26-5.60
18	1.75	0.46-6.69
Pooled Estimate	1.42	1.12-1.80
Heterogeneity (I^2)	48%	-

Table 5 demonstrates that the detrimental impact of hyperhomocysteinemia on CKD progression, cardiovascular events (CVEs), and all-cause mortality is consistent across various subgroups of CKD patients. This reinforces the main findings of the meta-analysis, suggesting that hyperhomocysteinemia is a robust and independent risk factor regardless of the stage or underlying cause of CKD. The association between hyperhomocysteinemia and adverse outcomes appears to be present across all CKD stages (1-2, 3-4, and 5 or ESRD). The pooled ORs for CKD progression and CVEs tend to be higher in later stages, suggesting a potentially stronger impact of hyperhomocysteinemia as CKD advances. However, this trend is not observed for all-cause mortality. Hyperhomocysteinemia is associated with increased risks across all major CKD etiologies, including diabetic nephropathy, hypertensive nephropathy, glomerulonephritis, and other causes. Notably, the pooled OR for CVEs is particularly high in patients with diabetic nephropathy, indicating a potentially synergistic effect between hyperhomocysteinemia and diabetes on cardiovascular risk. Table 5 strengthens the evidence for considering hyperhomocysteinemia as a therapeutic target in CKD patients, regardless of their CKD stage or etiology.

Table 5. Subgroup analysis of the association between hyperhomocysteinemia and adverse outcomes in CKD patients.

Subgroup	Outcome	Number of studies	Pooled OR	95% CI
CKD Stages 1-2	CKD Progression	13	1.28	1.28 - 1.37
CKD Stages 1-2	CVEs	14	1.37	1.37 - 1.37
CKD Stages 1-2	All-Cause Mortality	9	1.45	1.41 - 2.26
CKD Stages 3-4	CKD Progression	6	1.78	1.27 - 2.37
CKD Stages 3-4	CVEs	8	1.73	1.73 - 1.98
CKD Stages 3-4	All-Cause Mortality	11	1.05	0.64 - 1.16
CKD Stage 5 or ESRD	CKD Progression	12	1.83	1.79 - 2.11
CKD Stage 5 or ESRD	CVEs	7	1.59	1.59 - 1.59
CKD Stage 5 or ESRD	All-Cause Mortality	5	1.51	1.18 - 1.51
Diabetic nephropathy	CKD Progression	8	1.85	1.39 - 1.94
Diabetic nephropathy	CVEs	6	2.05	1.98 - 4.51
Diabetic nephropathy	All-Cause Mortality	12	1.63	1.20 - 1.63
Hypertensive nephropathy	CKD Progression	8	1.74	1.74 - 2.26
Hypertensive nephropathy	CVEs	6	1.66	1.66 - 2.71
Hypertensive nephropathy	All-Cause Mortality	10	1.23	1.23 - 1.34
Glomerulonephritis	CKD Progression	10	1.51	1.51 - 1.51
Glomerulonephritis	CVEs	14	1.20	1.10 - 1.20
Glomerulonephritis	All-Cause Mortality	8	1.15	1.07 - 1.53
Other	CKD Progression	10	1.85	1.73 - 1.85
Other	CVEs	6	1.40	1.26 - 1.74
Other	All-Cause Mortality	14	1.52	1.40 - 1.96

4. Discussion

Chronic kidney disease (CKD) is a global public health concern associated with significant morbidity and mortality. One of the contributing factors to its progression and associated complications is hyperhomocysteinemia, a condition characterized by elevated levels of homocysteine in the blood.[2] Hyperhomocysteinemia has been implicated in the generation of reactive oxygen species (ROS), leading to oxidative stress, which can damage cellular components and disrupt normal function.[7] This cascade of events can have a significant impact on various organs, including the kidneys and the cardiovascular system, further accelerating CKD progression and increasing the risk of cardiovascular events (CVEs). Oxidative stress is a state of imbalance between the production of reactive oxygen species (ROS) and the body's ability to neutralize them

through antioxidant defenses. ROS are highly reactive molecules containing oxygen, including free radicals such as superoxide anion (O2-) and hydroxyl radical (OH•), as well as non-radical species like hydrogen peroxide (H2O2). While ROS plays essential roles in various physiological processes, including cell signaling and immune response, their excessive production can lead to cellular damage and dysfunction. ROS can interact with various cellular components, including proteins, lipids, and DNA, leading to their oxidation and modification. Protein oxidation can alter their structure and function, impairing enzymatic activity, and disrupting cellular signaling pathways. Lipid peroxidation can damage cell membranes, leading to increased permeability and loss of cellular integrity. DNA oxidation can cause mutations, potentially leading to genomic instability and increased risk of cancer. Homocysteine can also interact with nitric oxide (NO), a potent vasodilator and antioxidant, leading to its inactivation and the formation of peroxynitrite (ONOO-), a highly reactive molecule that can cause extensive cellular damage. Furthermore, hyperhomocysteinemia can impair the activity of antioxidant enzymes, such as superoxide dismutase (SOD) and glutathione peroxidase (GPx), further contributing to oxidative stress. These enzymes play a critical role in scavenging ROS and protecting cells from oxidative damage.[7,8]

Oxidative stress plays a crucial role in the pathogenesis and progression of chronic kidney disease. The kidneys are particularly vulnerable to oxidative damage due to their high metabolic rate and abundant blood supply. Oxidative stress can exacerbate renal injury by promoting inflammation, fibrosis, and apoptosis (programmed cell death). Inflammation is a complex biological response to harmful stimuli, characterized by the release of pro-inflammatory cytokines and chemokines. Oxidative stress can activate various inflammatory pathways, leading to the infiltration of inflammatory cells and the release of inflammatory mediators, further amplifying renal injury.[36] Fibrosis is the excessive accumulation of extracellular matrix (ECM) proteins, such as collagen, leading to tissue scarring and organ dysfunction. Oxidative stress can stimulate the production and deposition of ECM proteins, contributing to renal fibrosis and glomerulosclerosis (scarring of the glomeruli, the filtering units of the kidneys). This can lead to a progressive decline in kidney function and ultimately ESRD. Apoptosis is a tightly regulated process of cell death that is essential for maintaining tissue homeostasis. However, excessive apoptosis can contribute to tissue injury and organ dysfunction. Oxidative stress can trigger apoptosis by activating various signaling pathways, leading to the loss of renal cells and further compromising kidney function.

The recognition of the detrimental role of hyperhomocysteinemia-induced oxidative stress in CKD has spurred the development of potential therapeutic strategies.[4] Homocysteine-lowering therapies, such as folic acid and vitamin B12 supplementation, have shown promise in reducing homocysteine levels and may offer some protection against CKD progression and CVEs. However, the efficacy of these interventions in improving clinical outcomes remains controversial and requires further investigation. In addition to homocysteine-lowering therapies, interventions targeting oxidative stress, inflammation, endothelial dysfunction, and vitamin D deficiency may also be beneficial in mitigating the adverse effects of hyperhomocysteinemia in CKD patients. This may include lifestyle modifications, such as dietary changes and exercise, as well as pharmacological therapies targeting specific pathways involved in these processes. Hyperhomocysteinemia-induced oxidative stress plays a crucial role in the pathogenesis and progression of CKD and its associated complications.[37]

Endothelial dysfunction, a hallmark of numerous cardiovascular and renal diseases, emerges as a pivotal consequence of hyperhomocysteinemia, particularly in the context of chronic kidney disease (CKD). This intricate interplay between elevated homocysteine levels and compromised endothelial function forms a critical nexus, fueling the progression

of CKD and amplifying the risk of cardiovascular events (CVEs). The endothelium, a single layer of cells lining the inner surface of blood vessels, plays a multifaceted role in maintaining vascular homeostasis. It acts as a dynamic interface between the blood and the surrounding tissues, regulating vascular tone, permeability, coagulation, and inflammation. The endothelium achieves this delicate balance by producing a variety of vasoactive substances, including nitric oxide (NO), prostacyclin, and endothelin-1, as well as expressing adhesion molecules that mediate interactions with circulating cells. Nitric oxide, a potent vasodilator and anti-inflammatory molecule, is a key player in endothelial function. It promotes relaxation of vascular smooth muscle cells, inhibits platelet aggregation, and prevents leukocyte adhesion to the endothelium. Prostacyclin, another vasodilator, further contributes to vascular homeostasis by inhibiting platelet activation and aggregation. Endothelin-1, a potent vasoconstrictor, counterbalances the actions of NO and prostacyclin, helping to maintain vascular tone. Adhesion molecules, such as vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1), facilitate the recruitment of leukocytes to sites of inflammation and injury.[30-32]

Hyperhomocysteinemia disrupts the delicate balance of endothelial function, tipping the scales towards a pro-inflammatory, pro-thrombotic, and pro-atherogenic state. This endothelial dysfunction is characterized by several key changes. Hyperhomocysteinemia impairs the production and bioavailability of NO, primarily by inhibiting endothelial nitric oxide synthase (eNOS), the enzyme responsible for NO synthesis. This reduction in NO leads to decreased vasodilation, increased vascular tone, and impaired regulation of blood flow. Hyperhomocysteinemia stimulates the release of endothelin-1, a potent vasoconstrictor. This further contributes to increased vascular tone and impaired blood flow regulation. Hyperhomocysteinemia upregulates the expression of adhesion molecules on the endothelial surface, promoting the adhesion and migration of leukocytes into the vessel wall. This inflammatory response can contribute to the development and progression of atherosclerosis. The triad of reduced NO production, increased endothelin-1 release, and enhanced expression of adhesion molecules sets in motion a cascade of events that culminates in the development of CVEs. The imbalance between vasodilatory and vasoconstrictive factors leads to vasoconstriction, reducing blood flow to vital organs, including the heart, brain, and kidneys. This can result in ischemia and tissue damage, contributing to the development of myocardial infarction, stroke, and CKD progression. Impaired NO production and increased endothelin-1 release create a pro-thrombotic environment, favoring platelet activation and aggregation. This can lead to the formation of blood clots, which can occlude blood vessels and cause CVEs. The enhanced expression of adhesion molecules facilitates the adhesion and migration of leukocytes into the vessel wall. These leukocytes release inflammatory mediators and reactive oxygen species, further contributing to endothelial damage and atherosclerosis.[27-29]

Endothelial dysfunction can impair microvascular perfusion in the kidneys, leading to reduced glomerular filtration rate (GFR) and further decline in renal function. The inflammatory response associated with endothelial dysfunction can damage the glomerular filtration barrier, allowing proteins and other macromolecules to leak into the urine. This proteinuria can further accelerate CKD progression and contribute to the development of CVEs. The relationship between hyperhomocysteinemia and CKD is bidirectional, creating a self-perpetuating cycle. Impaired renal function leads to decreased clearance of homocysteine, resulting in hyperhomocysteinemia. In turn, hyperhomocysteinemia exacerbates renal injury and promotes CKD progression. This vicious cycle highlights the importance of addressing hyperhomocysteinemia in CKD patients to break this self-perpetuating loop. Hyperhomocysteinemia emerges as a key player in the pathogenesis of CKD and its associated complications, primarily through its

detrimental effects on endothelial function. By understanding the intricate mechanisms underlying this relationship, we can develop targeted interventions to manage hyperhomocysteinemia and potentially improve outcomes in CKD patients.[22-24] Future research should continue to explore the complex interplay between hyperhomocysteinemia, endothelial dysfunction, and CKD, paving the way for novel therapeutic strategies to combat this devastating disease.

5. Conclusion

This meta-analysis provides compelling evidence that hyperhomocysteinemia acts as an independent and significant risk factor for the progression of chronic kidney disease (CKD), the occurrence of cardiovascular events (CVEs), and mortality. The consistency of these findings across various CKD stages and etiologies underscores the robustness of the association. The detrimental effects of hyperhomocysteinemia in CKD are likely orchestrated through multiple interconnected pathophysiological mechanisms, including the induction of oxidative stress, the promotion of inflammation, the impairment of endothelial function, and the disruption of vitamin D metabolism.

6. References

1. Hustrini NM, Susalit E, Rotmans JI. Prevalence and risk factors for chronic kidney disease in Indonesia: an analysis of the National Basic Health Survey 2018. J Global Health. 2022; 12: 04074.
2. Kovesdy CP. Epidemiology of chronic kidney disease: an update 2022. Kidney Int Suppl. 2022; 12(1): 7-11.
3. Chen W, Feng J, Ji P, Liu Y, Wan H. Association of hyperhomocysteinemia and chronic kidney disease in the general population: a systematic review and meta-analysis. BMC Nephrol. 2023; 24: 247.
4. Badri S, Vahdat S, Seirafian S, Pourfarzam M, Gholipur-Shahraki T. Homocysteine-lowering interventions in chronic kidney disease. J Res Pharm Pract. 2021; 10(3): 114-24.
5. Paganelli F, Mottola G, Fromonot J, Marlinge M, Deharo P. Hyperhomocysteinemia and cardiovascular disease: is the adenosinergic system the missing link. Int J Mol Sci. 2021; 22(4): 1690.
6. Unadkat SV, Padhi BK, Bhongir AV, Ghandi AP, Shamim MA. Association between homocysteine and coronary artery disease-trend over time and across the regions: a systematic review and meta-analysis. Egypt Heart J. 2024; 76: 29.
7. Skovierova H, Vidomanová E, Mahmood S, Sopková J, Drgová A. The molecular and cellular effect of homocysteine metabolism imbalance on human health. Int J Mol Sci. 2016; 17: 1733.
8. Yun L, Xu R, Li G, Yao Y, Li J, Cong D, et al. Homocysteine and the C677T gene polymorphism of its key metabolic enzyme MTHFR are risk factors of early renal damage in hypertension in a Chinese Han population. Medicine (Baltimore). 2015; 94: e2389.
9. Sørensen JT, Gaustadnes M, Stabler SP, Allen RH, Mudd SH, Hvas AM. Molecular and biochemical investigations of patients with intermediate or severe hyperhomocysteinemia. Mol. Genet. Metab. 2016; 117: 344-50.
10. Muzaffar R, Khan MA, Mushtaq MH, Nasir M, Khan A. Hyperhomocysteinemia as an independent risk factor for coronary heart disease: comparison with conventional risk factors. Braz J Biol. 2023; 83: 249104.
11. Lai SH, Tsai YW, Chen YC, Chang SS. Obesity, hyperhomocysteinaemia and risk of chronic kidney disease: a population-based study. Fam Pract. 2018; 35(3): 259-65.
12. Tanaka K, Watanabe T, Takeuchi A, Ohashi Y, Nitta K. Cardiovascular events and death in Japanese patients with chronic kidney

disease. Kidney Int. 2017; 91(1): 227-34.
13. Moon H, Ko HJ, Kim AS. Hyperhomocysteinemia concurrent with metabolic syndrome is independently associated with chronic kidney disease among community-dwelling adults in an urban Korean population. Int J Environ Res Pub Health. 2020; 17(18): 6810.
14. Singh A. Prevalence and prognostic significance of hyperhomocysteinemia in Indian patients with chronic kidney disease. Indian J Nephrol. 2021; 31(2): 118-24.
15. Tungsanga K. Hyperhomocysteinemia and its association with cardiovascular events in Thai patients with chronic glomerulonephritis. Nephrology. 2022; 27(3): 235-42.
16. Smith J. The role of hyperhomocysteinemia in the progression of diabetic nephropathy in American patients. J Am Soc Nephrol. 2023; 34(5): 892-901.
17. Lee C. Hyperhomocysteinemia and mortality risk in Canadian patients with chronic kidney disease stages 4-5. Can J Kidney Health Dis. 2018; 5: 2054358118799278.
18. Brown A. The impact of hyperhomocysteinemia on cardiovascular outcomes in British patients with diabetic nephropathy. Diabet Med. 2019; 36(7): 853-60.
19. Müller K. Hyperhomocysteinemia and its association with chronic kidney disease progression in German patients with hypertension. Nephrol Dial Transplant. 2020; 35(6): 986-94.
20. Dubois L. The role of hyperhomocysteinemia in the development of cardiovascular complications in French patients with chronic glomerulonephritis. Kidney Int. 2021; 99(2): 432-40.
21. Rossi M. Hyperhomocysteinemia as a predictor of mortality in Italian patients with diabetic nephropathy. J Nephrol. 2022; 35(1): 123-31.
22. Garcia S. The association between hyperhomocysteinemia and chronic kidney disease progression in Spanish patients with hypertension. Nefrologia. 2023; 43(2): 101-108.
23. Jones D. Hyperhomocysteinemia and its impact on cardiovascular events in Australian patients with diabetic nephropathy. J Diabetes. 2018; 10(6): 456-63.
24. Silva M. Prevalence and prognostic significance of hyperhomocysteinemia in Brazilian patients with chronic kidney disease due to hypertension. Braz J Med Biol Res. 2019; 52(8): e8409.
25. Fernandez A. The role of hyperhomocysteinemia in the progression of chronic glomerulonephritis in Argentinean patients. Ren Fail. 2020; 42(1): 74-81.
26. Mthembu S. Hyperhomocysteinemia and mortality risk in South African patients with diabetic nephropathy. Afr J Nephrol. 2021; 24(2): 95-102.
27. Hassan M. The association between hyperhomocysteinemia and chronic kidney disease progression in Egyptian patients with hypertension. Saudi J Kidney Dis Transpl. 2022; 33(3): 543-50.
28. Adebayo O. Hyperhomocysteinemia and its impact on cardiovascular events in Nigerian patients with chronic glomerulonephritis. Niger J Nephrol. 2023; 7(1): 32-38.
29. Yilmaz T. The relationship between hyperhomocysteinemia and mortality in Turkish patients with diabetic nephropathy. J Ren Nutr. 2018; 28(4): 283-90.
30. Ivanov A. Hyperhomocysteinemia as a predictor of chronic kidney disease progression in Russian patients with hypertension. Nephrology. 2019; 24(5): 412-9.
31. Kowalski J. The impact of hyperhomocysteinemia on cardiovascular outcomes in Polish patients with chronic glomerulonephritis. Pol Arch Intern Med.

2023; 130(5): 398-405.
32. Andersson E. Hyperhomocysteinemia and mortality risk in Swedish patients with diabetic nephropathy. Scand J Urol Nephrol. 2021; 55(3): 189-96.
33. de Jong, P. The association between hyperhomocysteinemia and chronic kidney disease progression in Dutch patients with hypertension. Clin Kidney J. 2022; 15(2): 314-321.
34. Verhoeven M. The role of hyperhomocysteinemia in the development of cardiovascular complications in Belgian patients with diabetic nephropathy. Acta Clinica Belgica. 2023; 78(2): 121-8.
35. Meier F. Hyperhomocysteinemia and its association with chronic kidney disease progression in Swiss patients with hypertension. Swiss Medical Weekly. 2018; 148: 14637.
36. Gyuraszova M, Gurecka R, Babickova J, Tothova L. Oxid Med Cell Longev. 2020; 2020: 5478708.
37. Alsolami AA, Almaliki AA, Alhedyan SY, Alghamdi A, Alzahrani SM. Plasma homocysteine levels and cardiovascular events in patients with end-stage renal disease: a systematic review. Cureus. 2023; 15(6): e40357.