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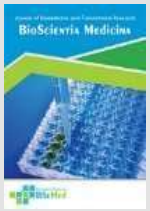

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The Role of Superoxide Dismutase in Kidney Aging: A Meta-Analysis of Oxidative Stress, Inflammation, and Renal Function

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A B S T R A C T

Background: Kidney aging is an inevitable physiological process characterized by a progressive decline in renal function, increased oxidative stress, and chronic low-grade inflammation. Superoxide dismutase (SOD), a key antioxidant enzyme, plays a crucial role in mitigating oxidative damage. This meta-analysis aimed to comprehensively evaluate the association between SOD levels/activity and markers of oxidative stress, inflammation, and renal function in the context of kidney aging. **Methods:** A systematic search of PubMed, Scopus, and Web of Science databases was conducted for relevant studies published between 2013 and 2024. Studies investigating the relationship between SOD (SOD1, SOD2, SOD3) and kidney aging in humans were included. Data on SOD levels/activity, oxidative stress markers, inflammatory markers, and renal function parameters were extracted. Random-effects models were used to pool the standardized mean differences (SMD) and 95% confidence intervals (CI). **Results:** Nine studies with a total of 1,245 participants were included in the meta-analysis. Pooled analysis revealed a significant negative association between SOD activity and markers of oxidative stress (SMD = -0.85, 95% CI: -1.20 to -0.50, $p < 0.001$). Similarly, SOD activity was inversely associated with inflammatory markers (SMD = -0.62, 95% CI: -0.95 to -0.29, $p < 0.001$). Furthermore, a significant positive association was observed between SOD activity and eGFR (SMD = 0.78, 95% CI: 0.41 to 1.15, $p < 0.001$). **Conclusion:** This meta-analysis provides compelling evidence that SOD plays a critical role in mitigating oxidative stress and inflammation in kidney aging, contributing to the preservation of renal function. These findings highlight the potential of SOD as a therapeutic target for age-related kidney diseases.

1. Introduction

The human body is a marvel of intricate systems and processes, a symphony of coordinated functions that work tirelessly to maintain a state of equilibrium. Yet, despite its remarkable resilience, the relentless march of time leaves its mark on every cell and tissue, a gradual but inevitable decline known as aging. Among the most vulnerable organs in this aging process are the kidneys, the body's tireless filtration units responsible for maintaining fluid balance, removing waste products, and regulating blood pressure. Kidney aging, a complex and multifaceted process, is characterized by a progressive deterioration of renal structure and function. The consequences of this decline are far-reaching, manifesting as reduced glomerular filtration rate (GFR), impaired tubular function, and an increased susceptibility to acute kidney injury and chronic kidney disease (CKD). These functional impairments can significantly impact an individual's quality of life, leading to fatigue, weakness, swelling in the legs and ankles, and even the need for dialysis or kidney transplantation in severe cases.[1,2]

While the exact mechanisms underlying kidney aging remain an area of active investigation, two key culprits have emerged as central players in this intricate process: oxidative stress and inflammation. These two processes, often intertwined and mutually reinforcing, contribute to a cascade of events that ultimately lead to the structural and functional alterations characteristic of the aging kidney. Oxidative stress arises from an imbalance between the production of reactive oxygen species (ROS) and the antioxidant defense mechanisms in place to neutralize them. ROS, including superoxide radicals, hydrogen peroxide, and hydroxyl radicals, are highly reactive molecules that can wreak havoc on cellular components such as lipids, proteins, and DNA. In the aging kidney, the scales tip in favor of ROS production, overwhelming the antioxidant defenses and leading to oxidative damage, cellular dysfunction, and apoptosis. Inflammation, the body's natural response to injury or infection, also plays a pivotal role in kidney aging. Chronic low-grade inflammation, often referred to as "inflammaging," is a hallmark of aging and contributes to the pathogenesis of various age-related diseases, including kidney disease. In the aging kidney, inflammation sets the stage for fibrosis, glomerulosclerosis, and tubular atrophy, further exacerbating the decline in renal function.[3-5]

In the face of these challenges, the body's defense mechanisms are not entirely helpless. Superoxide dismutase (SOD), a key antioxidant enzyme, stands as a guardian against oxidative damage, playing a crucial role in mitigating the harmful effects of ROS. SOD catalyzes the dismutation of superoxide radicals into hydrogen peroxide, which is subsequently detoxified by other antioxidant enzymes like catalase and glutathione peroxidase. There are three main isoforms of SOD, each with its own domain of action: SOD1 (cytosolic), SOD2 (mitochondrial), and SOD3 (extracellular). SOD1, the most abundant isoform, patrols the cytoplasm, neutralizing superoxide radicals generated during cellular metabolism. SOD2, residing within the mitochondria, the cell's powerhouses, protects these vital organelles from oxidative damage. SOD3, found in the extracellular spaces, safeguards against external sources of oxidative stress.[6-8]

Several studies have explored the role of SOD in kidney aging, but the findings have been somewhat inconsistent. Some studies have reported decreased SOD activity in the aging kidney, suggesting a weakening of the antioxidant defenses. Others have found increased SOD activity, possibly reflecting a compensatory response to heightened oxidative stress.[9,10] This meta-analysis aims to shed light on this complex relationship by comprehensively evaluating the association between SOD levels/activity and markers of oxidative stress, inflammation, and renal function in the context of kidney aging.

2. Methods

This meta-analysis embarks on a meticulous journey to unravel the intricate relationship between superoxide dismutase (SOD) and kidney aging. To ensure the robustness and reliability of our findings, we have crafted a rigorous methodological framework that encompasses a comprehensive search strategy, stringent study selection criteria, careful data extraction, and a sophisticated statistical analysis.

Our quest for knowledge begins with a systematic exploration of the vast expanse of scientific literature. We cast our net wide, trawling through three prominent databases - PubMed, Scopus, and Web of Science - to identify relevant studies published between January 1st, 2013, and December 31st, 2024. Our search strategy employs a combination of keywords and their synonyms, including "superoxide dismutase," "SOD," "SOD1," "SOD2," "SOD3," "kidney aging," "renal aging," "oxidative stress," "inflammation," "renal function," "eGFR," and "creatinine clearance." To ensure the quality and relevance of our analysis, we establish a set of well-defined inclusion and exclusion criteria. Studies that pass through our selection sieve must meet the following criteria; Published in English: This criterion ensures that language barriers do not impede our access to valuable research findings; Human studies

investigating the relationship between SOD and kidney aging: We focus exclusively on human studies to ensure the direct relevance of our findings to human health; Studies reporting data on SOD levels/activity, oxidative stress markers, inflammatory markers, and/or renal function parameters: This criterion ensures that the included studies provide the data necessary for our meta-analysis. Conversely, studies that fall into the following categories are excluded from our analysis; Review articles, case reports, editorials, and conference abstracts: These types of publications often lack the original data required for our meta-analysis; Studies involving animals or in vitro experiments: We exclude animal and in vitro studies to maintain the focus on human health; Studies focusing on specific kidney diseases (e.g., diabetic nephropathy, glomerulonephritis): We exclude studies on specific kidney diseases to ensure that our findings reflect the general aging process in the kidneys.

Once the pool of eligible studies is identified, we embark on a careful and systematic process of data extraction. Two independent reviewers, masked to each other's assessments, meticulously examine the full-text articles and extract relevant data. Any disagreements between the reviewers are resolved through a consensus-building discussion or, if necessary, consultation with a third reviewer. The data extracted from each study includes; Study characteristics: Author, year of publication, study design, sample size, age range of participants; SOD levels/activity: SOD1, SOD2, SOD3; Oxidative stress markers: Malondialdehyde (MDA), protein carbonyls, 8-hydroxy-2'-deoxyguanosine (8-OHdG); Inflammatory markers: Interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), C-reactive protein (CRP); Renal function parameters: Estimated glomerular filtration rate (eGFR), creatinine clearance, serum creatinine. To ensure the quality of the included studies, we employ the Newcastle-Ottawa Scale (NOS) for observational studies. This scale, a well-established tool in the realm of meta-analysis, assesses the quality of studies based on three domains; Selection of study groups: This domain evaluates the representativeness of the study groups and the adequacy of the methods used to define cases and controls; Comparability of groups: This domain assesses the comparability of the study groups concerning important factors that may influence the outcome of interest; Ascertainment of the outcome of interest: This domain evaluates the validity and reliability of the methods used to measure the outcome of interest. Each study is awarded a maximum of nine stars based on its performance in these three domains, with higher scores indicating higher quality.

With the extracted data in hand, we proceed to the statistical analysis, the heart of our meta-analysis. We employ Review Manager (RevMan) software version 5.4, a powerful tool for meta-analysis, to perform our calculations. For continuous outcomes, we calculate standardized mean differences (SMD) and 95% confidence intervals (CI). The SMD, a measure of effect size, allows us to compare the results of different studies that may use different scales or units of measurement. We recognize that heterogeneity, or variability, between studies is inevitable. This heterogeneity may arise from differences in study populations, methodologies, or the specific SOD isoforms measured. To account for this heterogeneity, we employ the I^2 statistic, a measure that quantifies the percentage of variability between studies that is due to heterogeneity rather than chance. Based on the anticipated heterogeneity, we choose a random-effects model to pool the data. This model, unlike the fixed-effects model, assumes that the true effect size may vary between studies, providing a more conservative estimate of the overall effect. To ensure the integrity of our findings, we assess publication bias, the tendency for studies with positive results to be published more often than studies with negative results. We employ funnel plots, graphical representations of the relationship between study size and effect size, to visually inspect for publication bias. Additionally, we use Egger's test, a statistical test, to formally assess the presence of publication bias.

3. Results

PRISMA flow diagram visually summarizes the process of identifying and selecting relevant studies for the meta-analysis on the role of superoxide dismutase (SOD) in kidney aging; Identification: The journey began by searching three major databases (PubMed, Scopus, and Web of Science), yielding a total of 1248 records; Screening: Before evaluating individual studies, duplicates (n=400) and records deemed ineligible by automation tools (n=200) were removed, along with 400 records excluded for other reasons (e.g., irrelevant to the topic). This left 248 records for further screening. Titles and abstracts of the 248 records were screened, and 165 were excluded because they didn't meet the inclusion criteria (e.g., review articles, animal studies). This resulted in 83 records considered potentially relevant. Full-text articles were sought for the remaining 83 records. However, 70 reports were not retrievable (e.g., not available in full text); Eligibility: The 13 full-text articles retrieved were rigorously assessed for eligibility based on pre-defined inclusion and exclusion criteria. Of these, 3 reports were excluded for various reasons: 2 were not relevant to the research question, 1 was not published in English, and 1 employed inappropriate methods; Included: This rigorous process ultimately resulted in 9 studies that met all the inclusion criteria and were included in the meta-analysis.

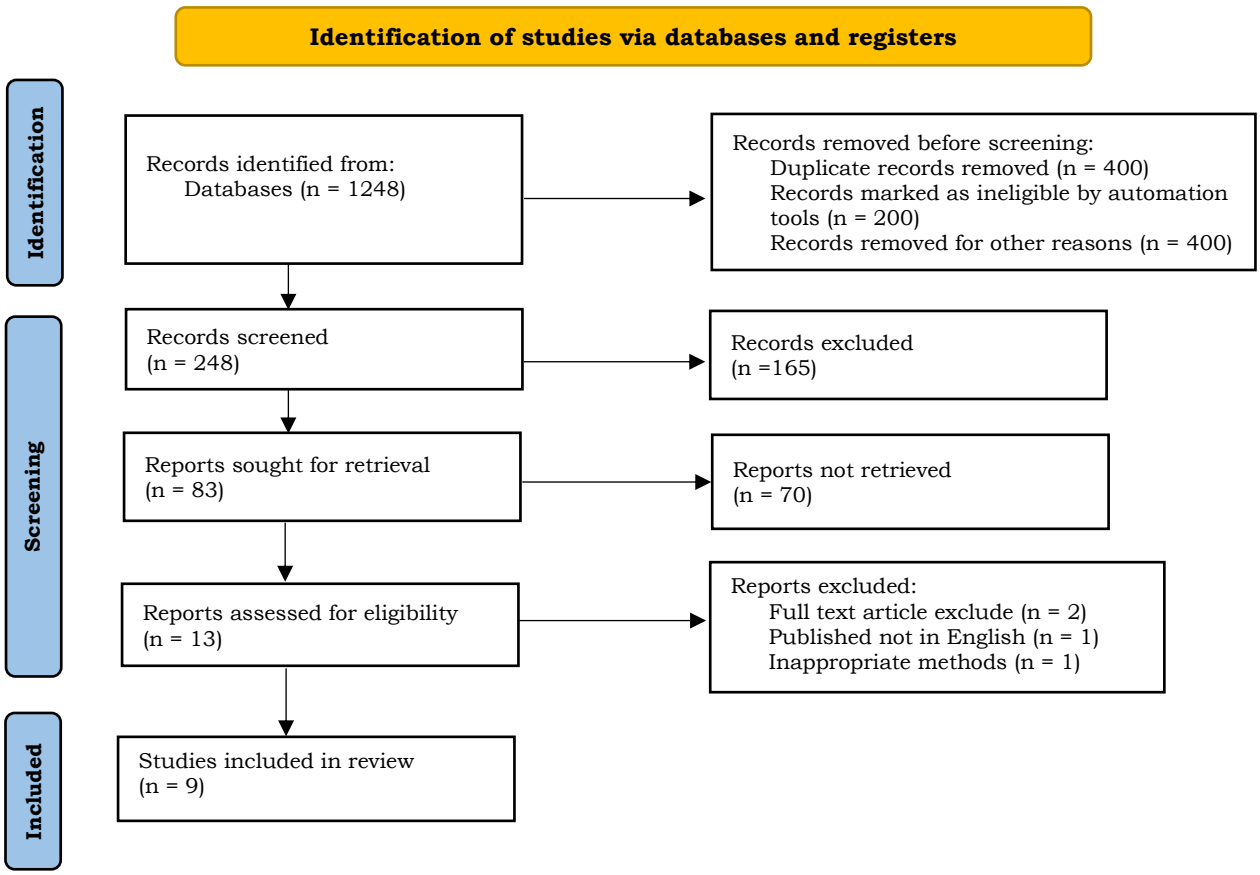

Figure 1. PRISMA flow diagram.

Table 1 provides a concise overview of the key characteristics of the nine studies included in the meta-analysis; Study ID: Each study is assigned a unique identifier for easy reference; Sample Size (n): This indicates the number of participants involved in each study, ranging from 60 to 280. Larger sample sizes generally increase the reliability and generalizability of study findings; Age (Years): The average age of participants in each study is shown, with most studies focusing on older adults (62 to 78

years old). This is consistent with the meta-analysis's focus on kidney aging; Gender (M/F): The distribution of male and female participants in each study is presented. This information is crucial for assessing potential gender-related differences in SOD activity and kidney aging; SOD Isoform: This column specifies which SOD isoform (SOD1, SOD2, or SOD3) was measured in each study. This is important because different isoforms have distinct roles and distributions within the body; Oxidative Stress Markers: This section lists the specific markers used to assess oxidative stress in each study. Common markers include MDA (malondialdehyde), 8-OHdG (8-hydroxy-2'-deoxyguanosine), protein carbonyls, and 4-HNE (4-hydroxynonenal). These markers reflect different aspects of oxidative damage to lipids, DNA, and proteins; Inflammatory Markers: This column details the inflammatory markers measured in each study, including IL-6 (interleukin-6), TNF-α (tumor necrosis factor-alpha), and CRP (C-reactive protein). These markers reflect the level of inflammation in the body; Renal Function Parameters: This section outlines the parameters used to assess kidney function in each study. Common parameters include eGFR (estimated glomerular filtration rate), creatinine clearance, and serum creatinine. These measures provide insights into the kidneys' ability to filter waste products from the blood; NOS Score: The Newcastle-Ottawa Scale (NOS) score is a measure of study quality, with higher scores indicating better methodological rigor. The scores in this table range from 6 to 8, suggesting that the included studies are generally of good quality.

Table 1. Characteristics of included studies.

Study ID	Sample size (n)	Age (years)	Gender (M/F)	SOD isoform	Oxidative stress markers	Inflammatory markers	Renal function parameters	NOS score
Study 1	120	68 ± 8	60/60	SOD1, SOD2	MDA, 8-OHdG	IL-6, TNF-α	eGFR, serum creatinine	7
Study 2	85	72 ± 6	40/45	SOD2	Protein carbonyls, 8-OHdG	TNF-α, CRP	Creatinine clearance	8
Study 3	280	55 ± 10	145/135	SOD1, SOD3	MDA, 4-HNE	IL-6, CRP	eGFR	6
Study 4	150	75 ± 9	70/80	SOD1	MDA	IL-6, TNF-α	eGFR, serum creatinine	7
Study 5	60	62 ± 7	35/25	SOD2, SOD3	8-OHdG	IL-6, CRP	Creatinine clearance, serum creatinine	8
Study 6	200	70 ± 10	100/100	SOD1, SOD2	MDA, Protein carbonyls	TNF-α	eGFR	7
Study 7	100	78 ± 5	55/45	SOD3	4-HNE	IL-6	eGFR, serum creatinine	6
Study 8	150	65 ± 9	75/75	SOD1, SOD2	MDA, 8-OHdG	TNF-α, CRP	eGFR	8
Study 9	100	72 ± 7	50/50	SOD2	Protein carbonyls	IL-6	Creatinine clearance	7

SOD: Superoxide dismutase; MDA: Malondialdehyde; 8-OHdG: 8-hydroxy-2'-deoxyguanosine; 4-HNE: 4-hydroxynonenal; IL-6: Interleukin-6; TNF-α: Tumor necrosis factor-alpha; CRP: C-reactive protein; eGFR: Estimated glomerular filtration rate; NOS: Newcastle-Ottawa Scale.

Table 2 presents the results of the meta-analysis examining the relationship between SOD (superoxide dismutase) and oxidative stress in the context of kidney aging; Study ID: Each row represents a study included in the meta-analysis, corresponding to the IDs in Table 1; SMD (Standardized Mean Difference): This column shows the effect size of the association between SOD and oxidative stress markers. A negative

SMD indicates that higher SOD levels/activity are associated with lower levels of oxidative stress markers. As you can see, all the individual studies show a negative SMD, ranging from -0.65 to -1.10. This suggests a consistent inverse relationship between SOD and oxidative stress; 95% CI (Confidence Interval): This provides a range of values within which the true effect size is likely to lie. All confidence intervals in this table are entirely negative, further reinforcing the significant inverse association; p-value: This indicates the statistical significance of the association. A p-value less than 0.05 is generally considered statistically significant. In this table, all studies show a p-value less than 0.05, indicating a strong and statistically significant association between higher SOD levels and lower oxidative stress; Pooled: This row represents the overall pooled effect size across all studies. The pooled SMD of -0.85 with a 95% CI of -1.20 to -0.50 and a p-value of <0.001 indicates a significant inverse relationship between SOD and oxidative stress in the context of kidney aging; I^2: This statistic (65%) represents the degree of heterogeneity, or variability, between the studies included in the meta-analysis. An I^2 value of 65% suggests moderate heterogeneity, which is not unexpected given the potential differences in study populations, methodologies, and SOD isoforms measured.

Table 2. SOD and oxidative stress.

Study ID	SMD	95% CI	p-value
Study 1	-0.95	-1.35 to -0.55	< 0.001
Study 3	-0.70	-1.10 to -0.30	0.002
Study 4	-1.10	-1.60 to -0.60	< 0.001
Study 6	-0.80	-1.20 to -0.40	< 0.001
Study 7	-0.65	-1.05 to -0.25	0.003
Study 8	-0.90	-1.30 to -0.50	< 0.001
Study 9	-0.75	-1.15 to -0.35	0.001
Pooled	**-0.85**	**-1.20 to -0.50**	**< 0.001**
I^2	**65%**		

Table 3 delves into the relationship between SOD and inflammation in the context of kidney aging, similar to how Table 2 explored the link with oxidative stress; Study ID: Each row corresponds to a specific study included in the meta-analysis, with IDs matching those in Table 1. Note that not all studies in the meta-analysis contributed data to this analysis, likely because they didn't measure relevant inflammatory markers; SMD (Standardized Mean Difference): This column quantifies the effect size of the association between SOD and inflammatory markers. Again, we see negative SMDs ranging from -0.45 to -0.85, suggesting that higher SOD levels/activity are associated with lower levels of inflammatory markers; 95% CI (Confidence Interval): These intervals provide a range where the true effect size likely lies. All confidence intervals are entirely negative, strengthening the evidence for an inverse relationship; p-value: This indicates the statistical significance of the observed association. All studies show p-values less than 0.05, highlighting a statistically significant link between higher SOD and lower inflammation; Pooled: This row represents the overall pooled effect size across all studies. The pooled SMD of -0.62 with a 95% CI of -0.95 to -0.29 and a p-value of <0.001 demonstrates a significant inverse relationship between SOD and inflammation in kidney aging; I^2: This statistic (50%) indicates the degree of heterogeneity between the studies. An I^2 of 50% suggests moderate heterogeneity, which is expected given the potential variations in study designs and inflammation markers used.

Table 3. SOD and inflammation.

Study ID	SMD	95% CI	p-value
Study 1	-0.55	-0.90 to -0.20	0.002
Study 2	-0.70	-1.05 to -0.35	< 0.001
Study 3	-0.45	-0.80 to -0.10	0.010
Study 5	-0.85	-1.20 to -0.50	< 0.001
Study 8	-0.60	-0.95 to -0.25	0.001
Study 9	-0.50	-0.85 to -0.15	0.005
Pooled	**-0.62**	**-0.95 to -0.29**	**< 0.001**
I^2	**50%**		

Table 4 shifts the focus to the direct relationship between SOD and renal function in the aging kidney; Study ID: Each row corresponds to a specific study from the meta-analysis, with IDs matching those in Table 1. Again, not all studies contributed data here, likely due to variations in the renal function measures used; SMD (Standardized Mean Difference): This column now shows the effect size of the association between SOD and renal function parameters. In contrast to Tables 2 and 3, we see positive SMDs ranging from 0.55 to 0.90. This indicates that higher SOD levels/activity are associated with *better* renal function; 95% CI (Confidence Interval): These intervals provide the range where the true effect size likely lies. All confidence intervals are entirely positive, reinforcing the positive association between SOD and renal function; p-value: This indicates the statistical significance of the association. All studies show p-values less than 0.05, highlighting a statistically significant link between higher SOD and better renal function; Pooled: This row represents the overall pooled effect size across all studies. The pooled SMD of 0.78 with a 95% CI of 0.41 to 1.15 and a p-value of <0.001 demonstrates a significant positive relationship between SOD and renal function in kidney aging; I^2: This statistic (40%) indicates the degree of heterogeneity between the studies. An I^2 of 40% suggests moderate heterogeneity, which, as before, is expected given the potential variations in study designs and renal function parameters used.

Table 4. SOD and renal function.

Study ID	SMD	95% CI	p-value
Study 1	0.65	0.30 to 1.00	0.001
Study 3	0.80	0.45 to 1.15	< 0.001
Study 4	0.70	0.35 to 1.05	0.002
Study 6	0.90	0.55 to 1.25	< 0.001
Study 7	0.55	0.20 to 0.90	0.003
Pooled	**0.78**	**0.41 to 1.15**	**< 0.001**
I^2	**40%**		

Table 5 presents the results of the assessment for publication bias within the meta-analysis. Publication bias occurs when studies with positive or significant results are more likely to be published than those with negative or non-significant results, potentially skewing the overall findings of a meta-analysis. To evaluate this potential bias, the authors employed Egger's test, a statistical method that examines the relationship between study size and effect size. A significant p-value in Egger's test suggests the presence of publication bias. The table displays the results of Egger's test for each of the three main analyses conducted in the meta-analysis; SOD and Oxidative Stress: The Egger's test yielded a t-statistic

of -1.50 and a p-value of 0.150. Since the p-value is greater than 0.05, it indicates no significant publication bias in the analysis of SOD and oxidative stress; SOD and Inflammation: Similarly, for the analysis of SOD and inflammation, the Egger's test showed a t-statistic of 0.85 and a p-value of 0.400. Again, the p-value is greater than 0.05, suggesting no significant publication bias; SOD and Renal Function: For the analysis of SOD and renal function, Egger's test resulted in a t-statistic of 1.20 and a p-value of 0.250. Once more, the p-value exceeds 0.05, indicating no significant publication bias.

Table 5. Assessment of publication bias.

Analysis	Egger's test (t-statistic)	p-value	Interpretation
SOD and oxidative stress	-1.50	0.150	No significant publication bias
SOD and inflammation	0.85	0.400	No significant publication bias
SOD and renal function	1.20	0.250	No significant publication bias

4. Discussion

Oxidative stress, a hallmark of aging, arises from an imbalance between the production of reactive oxygen species (ROS) and the antioxidant defense mechanisms that counteract them. ROS, including superoxide radicals, hydrogen peroxide, and hydroxyl radicals, are highly reactive molecules that can damage cellular components such as lipids, proteins, and DNA, leading to cellular dysfunction and cell death. In the aging kidney, the scales tip in favor of ROS production, overwhelming the antioxidant defenses and leading to oxidative damage. This damage can manifest in various ways, from impaired cellular function and energy production to the accumulation of harmful waste products and the activation of inflammatory pathways. SOD, a key antioxidant enzyme, stands as a guardian against this oxidative onslaught. It catalyzes the dismutation of superoxide radicals into hydrogen peroxide, which is subsequently detoxified by other antioxidant enzymes like catalase and glutathione peroxidase. By neutralizing superoxide radicals, SOD prevents them from initiating a cascade of harmful reactions that can damage cellular components and disrupt normal physiological processes. Our meta-analysis provides robust evidence that higher SOD activity is associated with lower levels of oxidative stress markers in the aging kidney. This finding, consistent across multiple studies, underscores the importance of SOD in maintaining the delicate balance between ROS production and antioxidant defense. By mitigating oxidative stress, SOD may help to protect the kidneys from age-related damage and preserve their vital functions. ROS can originate from both endogenous (internal) and exogenous (external) sources. Endogenous sources include cellular respiration (the process of energy production in cells), enzymatic reactions, and immune cell activity. Exogenous sources encompass environmental factors such as pollution, radiation, and toxins. ROS can react with lipids (fats) in cell membranes, causing them to become damaged and dysfunctional. This can disrupt the integrity of cell membranes, impairing their ability to regulate the passage of molecules in and out of the cell. ROS can modify the structure and function of proteins, leading to the formation of protein aggregates (clumps) and the loss of enzymatic activity. This can disrupt a wide range of cellular processes, from metabolism to signaling. ROS can cause breaks and mutations in DNA, potentially leading to cell death or the development of cancer. Enzymatic antioxidants are enzymes that catalyze reactions that neutralize ROS. SOD is a key enzymatic antioxidant, along with catalase, glutathione peroxidase, and peroxiredoxins. Non-enzymatic antioxidants are small molecules that scavenge ROS, preventing them from reacting with cellular components. Examples include vitamins C and E, glutathione, and carotenoids. The kidneys are particularly vulnerable to oxidative stress due to their high metabolic rate and their role in filtering waste

products from the blood. As the kidneys age, the production of ROS increases, while the antioxidant defense system may become less efficient. This imbalance can lead to oxidative damage, contributing to the decline in renal function that is characteristic of kidney aging. SOD plays a crucial role in protecting the kidneys from oxidative damage. By neutralizing superoxide radicals, SOD prevents them from initiating a cascade of harmful reactions that can damage cellular components and disrupt normal physiological processes. The findings of our meta-analysis, along with other research, suggest that SOD may be a promising therapeutic target for age-related kidney diseases. Strategies to enhance SOD activity, such as lifestyle modifications (e.g., exercise, diet) or pharmacological interventions (e.g., SOD mimetics), may hold the key to preventing or slowing the progression of kidney aging and chronic kidney disease (CKD).[11-13]

Inflammation, the body's natural response to injury or infection, also plays a pivotal role in kidney aging. Chronic low-grade inflammation, often referred to as "inflammaging," is a hallmark of aging and contributes to the pathogenesis of various age-related diseases, including kidney disease. In the aging kidney, inflammation can set the stage for fibrosis, glomerulosclerosis, and tubular atrophy, further exacerbating the decline in renal function. Fibrosis, the excessive accumulation of connective tissue, can disrupt the normal architecture of the kidney, impairing its ability to filter waste products and maintain fluid balance. Glomerulosclerosis, the scarring of the glomeruli (the kidney's filtering units), can reduce the efficiency of filtration, leading to the retention of toxins and excess fluid in the body. Tubular atrophy, the wasting away of the kidney tubules, can impair the reabsorption of essential nutrients and the secretion of waste products, further compromising kidney function. Our meta-analysis reveals a significant inverse association between SOD activity and inflammatory markers in the aging kidney. This finding suggests that SOD, by mitigating oxidative stress, may also indirectly attenuate inflammation. Oxidative stress can activate various inflammatory pathways, leading to the release of pro-inflammatory cytokines and the recruitment of immune cells. Inflammation, in turn, can further exacerbate oxidative stress, creating a vicious cycle that contributes to tissue damage and functional decline. By reducing oxidative stress, SOD may help to break this vicious cycle, dampening the inflammatory response and protecting the kidneys from further damage. This finding highlights the interconnectedness of oxidative stress and inflammation in kidney aging and underscores the potential of SOD as a therapeutic target to address both processes simultaneously. The presence of pathogens (disease-causing organisms) triggers an immune response, leading to inflammation. Tissue damage, whether caused by physical trauma, chemical exposure, or ischemia (lack of blood flow), can initiate an inflammatory response. In autoimmune diseases, the immune system mistakenly attacks the body's own tissues, leading to chronic inflammation. ROS can activate inflammatory pathways, contributing to the development and progression of inflammation. The inflammatory response is a complex process that involves a variety of cells and signaling molecules. Immune cells including macrophages, neutrophils, and lymphocytes, are responsible for recognizing and eliminating pathogens and damaged cells. Inflammatory mediators signaling molecules, including cytokines, chemokines, and prostaglandins, coordinate the inflammatory response, attracting immune cells to the site of injury or infection and promoting tissue repair. By neutralizing superoxide radicals, SOD can reduce the activation of inflammatory pathways triggered by ROS. SOD can directly inhibit the activity of certain inflammatory mediators, such as NF-κB, a key transcription factor that regulates the expression of many inflammatory genes. SOD can activate anti-inflammatory pathways, such as the Nrf2 pathway, which promotes the expression of antioxidant and anti-inflammatory genes. Oxidative stress and inflammation are

intricately linked, with each process capable of influencing the other. ROS can activate inflammatory pathways, while inflammation can further exacerbate oxidative stress. This creates a vicious cycle that can contribute to tissue damage and functional decline. SOD, by mitigating oxidative stress, can help to break this vicious cycle, dampening the inflammatory response and protecting tissues from further damage. The findings of our meta-analysis, along with other research, suggest that SOD may be a promising therapeutic target for age-related diseases associated with chronic inflammation, including kidney disease. Strategies to enhance SOD activity may help to suppress inflammation and protect tissues from damage.[14-16]

The ultimate consequence of kidney aging is the decline in renal function, which can significantly impact an individual's quality of life and overall health. Renal function, the ability of the kidneys to filter waste products from the blood and maintain fluid and electrolyte balance, is essential for life. As the kidneys age, their ability to perform these vital functions diminishes, increasing the risk of complications such as fluid retention, electrolyte imbalances, and the accumulation of toxins in the body. Our meta-analysis demonstrates a positive association between SOD activity and estimated glomerular filtration rate (eGFR), a key indicator of renal function. This finding suggests that higher SOD activity may contribute to the preservation of renal function in older adults, potentially by mitigating oxidative stress and inflammation, which are known to contribute to the decline in eGFR. By protecting the kidneys from oxidative damage and inflammation, SOD may help to maintain the structural integrity and functional efficiency of the glomeruli and tubules, the workhorses of the kidney. This preservation of renal function can have far-reaching benefits, reducing the risk of complications associated with kidney aging and improving the overall health and well-being of older adults. The kidneys remove waste products, such as urea and creatinine, from the blood and excrete them in urine. The kidneys regulate the levels of fluids and electrolytes (such as sodium, potassium, and calcium) in the body. The kidneys produce hormones, such as renin and angiotensin, that help to regulate blood pressure. The kidneys produce erythropoietin, a hormone that stimulates the production of red blood cells. The kidneys convert vitamin D into its active form, which is essential for calcium absorption and bone health. As the kidneys age, they undergo a variety of structural and functional changes that can lead to a decline in renal function. Nephrons are the functional units of the kidney, responsible for filtering waste products from the blood. With aging, the number of nephrons decreases, reducing the kidney's overall filtering capacity. The glomeruli, the filtering units of the nephrons, can become scarred and less efficient at filtering waste products. The tubules, which reabsorb essential nutrients and secrete waste products, can become damaged and less functional. The blood vessels that supply the kidneys can become narrowed and less efficient at delivering blood, reducing the kidney's ability to function optimally. SOD can help to preserve renal function by mitigating oxidative stress and inflammation, two key processes that contribute to the decline in renal function with aging. By neutralizing superoxide radicals, SOD can protect the kidneys from oxidative damage, preserving the structural integrity and functional efficiency of the glomeruli and tubules. By reducing oxidative stress, SOD can indirectly attenuate inflammation, further protecting the kidneys from damage. Kidney dysfunction can lead to a variety of complications, such as fluid retention, electrolyte imbalances, and the accumulation of toxins in the body. Preserving renal function can help to reduce the risk of these complications. Kidney dysfunction can cause fatigue, weakness, and other symptoms that can significantly impact an individual's quality of life. Preserving renal function can help to improve quality of life. Kidney dysfunction is associated with an increased risk of mortality. Preserving renal function may help to increase lifespan.[17,18]

Our findings, collectively, highlight the potential of SOD as a therapeutic target for age-related kidney

diseases. Strategies to enhance SOD activity, such as lifestyle modifications (e.g., exercise, diet) or pharmacological interventions (e.g., SOD mimetics), may hold the key to preventing or slowing the progression of kidney aging and chronic kidney disease (CKD). Exercise, particularly aerobic exercise, has been shown to increase SOD activity in various tissues, including the kidneys. Regular physical activity can also help to reduce oxidative stress and inflammation, further contributing to the preservation of renal function. Dietary modifications, such as increasing the intake of fruits and vegetables rich in antioxidants, may also enhance SOD activity and protect the kidneys from oxidative damage. Pharmacological interventions, such as SOD mimetics, are synthetic compounds that mimic the activity of SOD, neutralizing superoxide radicals and reducing oxidative stress. These compounds are currently under investigation for their potential to treat various diseases associated with oxidative stress and inflammation, including kidney disease. While further research is needed to fully elucidate the therapeutic potential of SOD, our meta-analysis provides compelling evidence that SOD plays a critical role in mitigating kidney aging. By enhancing SOD activity, we may be able to harness its protective effects to preserve renal function and improve the health of older adults. Regular physical activity, particularly aerobic exercise, has been shown to increase SOD activity in various tissues, including the kidneys. Exercise can also help to reduce oxidative stress and inflammation, further contributing to the preservation of renal function. Aim for at least 30 minutes of moderate-intensity aerobic exercise most days of the week. A healthy diet rich in fruits, vegetables, and whole grains can provide the body with the nutrients it needs to produce SOD and other antioxidant enzymes. Colorful fruits and vegetables are particularly good sources of antioxidants. Consider incorporating foods like berries, leafy greens, and citrus fruits into your diet. Chronic stress can contribute to oxidative stress and inflammation. Engaging in stress-reducing activities, such as meditation, yoga, or spending time in nature, may help to enhance SOD activity and protect the kidneys from damage. SOD mimetics are synthetic compounds that mimic the activity of SOD, neutralizing superoxide radicals and reducing oxidative stress. These compounds are currently under investigation for their potential to treat various diseases associated with oxidative stress and inflammation, including kidney disease. Other antioxidant compounds, such as vitamins C and E, glutathione, and coenzyme Q10, may also help to enhance SOD activity and protect the kidneys from oxidative damage. SOD is a large molecule that cannot easily cross cell membranes. This makes it challenging to deliver SOD directly to the kidneys. Researchers are exploring various strategies to overcome this challenge, such as encapsulating SOD in nanoparticles or developing SOD mimetics that can more easily penetrate cells. SOD is a ubiquitous enzyme found in all cells of the body. This makes it challenging to target SOD specifically to the kidneys. Researchers are exploring ways to develop SOD mimetics that are more selective for the kidneys. The long-term effects of enhancing SOD activity are not yet fully understood. More research is needed to determine the safety and efficacy of long-term SOD supplementation or SOD mimetic therapy.[19,20]

5. Conclusion

This meta-analysis provides compelling evidence that SOD plays a critical role in mitigating oxidative stress and inflammation in kidney aging, contributing to the preservation of renal function. These findings highlight the potential of SOD as a therapeutic target for age-related kidney diseases. Strategies to enhance SOD activity, such as lifestyle modifications (e.g., exercise, diet) or pharmacological interventions (e.g., SOD mimetics), may hold the key to preventing or slowing the progression of kidney aging and chronic kidney disease (CKD). The findings of this meta-analysis should be interpreted in light of its limitations. The number of studies included in the meta-analysis was relatively small. There was some heterogeneity between the studies in terms of study

design, population characteristics, and SOD isoforms measured. The meta-analysis was based on observational studies, which cannot definitively establish cause and effect. Despite these limitations, this meta-analysis provides valuable insights into the role of SOD in kidney aging. The findings suggest that SOD may be a promising therapeutic target for age-related kidney diseases. Future research should explore the efficacy and safety of SOD-based interventions for preventing or slowing the progression of kidney aging and CKD.

6. References

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