THE EFFECTS OF SELENIUM SUPPLEMENTATION IN PATIENTS ON HEMODIALYSIS: A SYSTEMATIC REVIEW

JOANA DANIELA TINOCO TEIXEIRA

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Joana Daniela Tinoco Teixeira

Supervisors: Vítor Martins, Invited Assistant Professor at NOVA Medical School, Faculdade de Ciências Médicas, Universidade NOVA de Lisboa;

André Rosário, Invited Assistant Professor at NOVA Medical School, Faculdade de Ciências Médicas, Universidade NOVA de Lisboa.

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Abbreviations

CKD	Chronic Kidney Disease
GFR	Glomerular Filtration Rate
CKD-5D	Chronic Kidney Disease - Stage 5
RRT	Renal Replacement Therapy
HD	Hemodialysis
PD	Peritoneal Dialysis
PSN	Portuguese Society of Nephrology
CVD	Cardiovascular Disease
GSH	Glutathione
Se	Selenium
Zn	Zinc
GPx	Glutathione Peroxidase
ROS	Reactive Oxygen Species
DM	Diabetes Mellitus
IL	Interleukin
IL-1β	Interleukin- 1 beta
TNFα	Tumor Necrosis Factor-alpha
CRP	C-reactive protein
ESRD	End Stage Renal Disease
PI3K	Phosphatidylinositol 3-Kinase
UPP	Ubiquitin-Proteasome Proteolytic System
PMNs	Polymorphonuclear Leukocytes
HTA	Hypertension
HDL-C	High-Density Lipoprotein-Cholesterol
NRS 2002	Nutritional Risk Screen 2002
EBPG	European Best Practice Guidelines
IOM	Institute of Medicine
UL	Upper intake Level
SD	Standard Deviation
RDA	Recommended Daily Allowance
µg	Microgram
KDOQI	Kidney Disease Outcomes Quality Initiative

COX-2	Cyclooxygenase-2
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PICO	Population, Intervention, Comparator and Outcomes
PROSPERO	Prospective Register of Systematic Reviews
hs-CRP	High-sensitivity C-Reactive Protein
ERS	Erythrocyte Sedimentation Rate
MDA	Malondialdehyde
CENTRAL	Cochrane Central Register of Controlled Trials
MeSH	Medical Subject Headings
RCT	Randomized Controlled Trials
TIBC	Total Iron-Binding Capacity
Hb	Hemoglobin
SGA	Subjective Global Assessment
MIS	Malnutrition–Inflammation Score
IQR	Interquartile Range
TFTs	Thyroid Function Tests
TSH	Thyroid Stimulating Hormone
T3RU	T3 Resin Uptake
UA	Uric Acid
LDL-C	Low-Density Lipoprotein-Cholesterol
CIMT	Carotid Intima Mean Thickness
FPG	Fasting Plasma Glucose
HOMA-IR	Homeostatic Model Assessment for Insulin Resistance
QUICKI	Insulin Sensitivity Check Index
TAC	Total Antioxidant Capacity
GAPDH	Glyceraldehyde-3-Phosphate dehydrogenase
PPAR-γ	Peroxisome Proliferator-Activated Receptor-gamma
TGF-β	Transforming Growth Factor-beta
LDLR	Low-Density Lipoprotein Receptor
VLDL	Very Low-Density Lipoprotein
NS	Not Significantly
PTH	Parathyroid Hormone
BUN	Blood Urea Nitrogen
DNA	Deoxyribonucleic Acid
NF-κB	Nuclear Factor-Kappa B

Abstract

Background: The progression of chronic kidney disease (CKD) is associated with chronic systemic inflammation and an increased risk of mortality from cardiovascular disease. Selenium (Se) levels are lower in hemodialysis (HD) patients and only these low levels have been directly and inversely related to mortality and appear to increase susceptibility to oxidative stress. Se supplementation may be useful in increasing plasma Se levels, but it is unknown if Se supplementation can improve any clinical or health-related outcomes.

Aim: Investigate the effect of selenium supplementation on the inflammatory profile and oxidative stress markers in adult patients with chronic kidney disease undergoing hemodialysis.

Methodology: A literature search was carried out on PubMed, Web of Science, Scopus, and the Cochrane Central Register of Controlled Trials databases in October 2023, following a pre-specified protocol (PROSPERO). Data extraction was performed by two independent investigators.

Results: From 2481 articles identified, five randomized controlled trials were eligible and included in the systematic review. The impact of selenium supplementation on inflammatory and oxidative stress markers was found to be inconsistent. Although CRP concentrations remained stable in HD patients, a decrease was observed in individuals with diabetes. Conversely, hs-CRP concentrations showed no notable changes across the studies. Regarding interleukins, there was a decrease in IL-1 gene expression and no changes in IL-8 gene expression, but in one study selenium supplementation prevented an increase in IL-6 levels. Additionally, TNF-α gene expression decreased. Notably, serum concentrations of ferritin, iron, and transferrin remained unaffected. Similarly, ESR concentrations showed no statistically significant alterations. Regarding oxidative stress markers, MDA concentrations decreased in one study while remaining stable in another. Furthermore, homocysteine concentrations did not display substantial fluctuations in HD patients.

Conclusion: Based on the evidence gathered in this systematic review, it remains uncertain whether selenium supplementation affects inflammatory markers and oxidative stress in hemodialysis patients. Additional research is imperative to provide definitive guidance to healthcare professionals given the significant cardiovascular implications in this population.

Keywords: Selenium supplementation, Inflammatory markers, Inflammation, Oxidative stress, Chronic Kidney Disease, Hemodialysis, Systematic review

Resumo

Introdução: A progressão da doença renal crónica (DRC) está associada à inflamação sistémica crónica e ao aumento do risco de mortalidade por doenças cardiovasculares. Os níveis de selénio (Se) são mais baixos em pacientes em hemodiálise (HD) e apenas esses níveis baixos têm sido direta e inversamente relacionados à mortalidade, parecendo aumentar a suscetibilidade ao *stress* oxidativo. A suplementação de Se pode ser útil no aumento dos níveis plasmáticos de Se, mas não se sabe se a suplementação de Se pode melhorar quaisquer resultados clínicos ou relacionados à saúde.

Objetivo: Investigar o efeito da suplementação de selénio no perfil inflamatório e nos marcadores de *stress* oxidativo em pacientes adultos em hemodiálise.

Metodologia: A pesquisa bibliográfica foi realizada nas bases de *dados PubMed, Web of Science, Scopus* e *Cochrane Central Register of Controlled Trials*, em Outubro de 2023, seguindo um protocolo pré-especificado (PROSPERO). A extração de dados foi realizada por dois investigadores independentes.

Resultados: Dos 2481 artigos identificados, cinco ensaios clínicos randomizados foram elegíveis e incluídos na revisão sistemática. O impacto da suplementação de selénio nos marcadores de *stress* inflamatório e oxidativo foi inconsistente. Embora as concentrações de CRP tenham permanecido estáveis em pacientes em HD, foi observada uma diminuição em indivíduos com diabetes. Por outro lado, as concentrações de hs-PCR não apresentaram alterações notáveis entre os estudos. Em relação às interleucinas, houve diminuição da expressão do gene da IL-1 e nenhuma alteração na expressão do gene da IL-8, mas num estudo a suplementação de Se preveniu o aumento dos níveis de IL-6. Além disso, a expressão do gene TNF-α diminuiu. Notavelmente, as concentrações séricas de ferritina, ferro e transferrina permaneceram inalteradas. Da mesma forma, as concentrações de ESR não apresentaram alterações estatisticamente significativas. Relativamente a marcadores de *stress* oxidativo, as concentrações de MDA diminuíram num estudo e permaneceram estáveis em outro. Além disso, as concentrações de homocisteína não apresentaram flutuações substanciais em pacientes em HD.

Conclusão: Com base nas evidências reunidas nesta revisão sistemática, permanece incerto se a suplementação de selénio impacta os marcadores inflamatórios e o *stress* oxidativo em pacientes em hemodiálise. Mais estudos serão imperativos para fornecer orientações definitivas aos profissionais de saúde, dadas as implicações cardiovasculares significativas para esta população.

Palavras-chave: Suplementação em selénio, Marcadores inflamatórios, Inflamação, *Stress* oxidativo, Doença renal crónica, Hemodiálise, Revisão sistemática

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1. Introduction

Chronic Kidney Disease (CKD) is a prevalent health disorder that affects approximately 1 in 10 adults worldwide and if left untreated, it can have fatal consequences. Although early detection can prevent morbidity and mortality, its prevalence continues to increase annually and recent estimates predict that CKD will become the 5th leading cause of death by 2040 (1). CKD is defined as a condition in which the kidneys lose more than 50% of normal function and is characterized by the presence of kidney damage or an estimated Glomerular Filtration Rate (GFR) below 60 ml/min/1.73m^2 persisting for at least three months, being more prevalent in individuals over 65 years of age (1, 2). CKD Stage 5 (CKD-5D) is defined as an irreversible decrease in kidney function, which requires a renal replacement therapy (RRT), namely: hemodialysis (HD), peritoneal dialysis (PD), or kidney transplantation to sustain life (3).

Recent data from the Portuguese Society of Nephrology (PSN) highlights a steady increase in the prevalence of HD and PD patients since 2010. Portugal ranks among the European countries with the highest number of annual cases of patients undergoing HD, with a higher prevalence in the population between 65-80 years old (1). The most recent figures from SPN show a 2% increase in the prevalence of patients on dialysis in 2022 compared to 2021. This increase is attributed to the growing aging population in Portugal, with a notable HD mortality rate of 12.4%. Portugal is also one of the European countries with the highest prevalence of patients undergoing RRT, and cardiovascular diseases (CVD) remain a significant contributor to the mortality rate at 25.7% among these patients. Notably, 81.3% of the 1,574 patients who died in 2022 were over 65 years old, and 42.2% were over 80 years old (1).

According to the International Society of Nephrology, in the year 2023, the prevalence of chronic kidney disease in Iran was 10.37% (9.70%-11.02%), with 211.4 million on a regular hemodialysis program (4).

Despite the recognized effectiveness of HD in increasing patient survival, it is important to acknowledge that the initiation of chronic HD therapy causes a series of changes that have significant implications for an individual's physiological, nutritional, and social well-being. Hemodialysis changes patients' lifestyles and negatively impacts individual physical and mental health (5).

CKD is also related to severe deficiencies in innate and adaptive immunity, resulting in a complex state of immune dysfunction in which signs of immune

depression and activation paradoxically coexist (6, 7). Although functional imbalances of immune system cells lead patients with CKD to a higher susceptibility to infectious diseases and other complications, such as malnutrition, depression, and osteoporosis, the constant activation of immune cells promotes a chronic inflammatory state that is related to an elevated risk of CVD (8-10). The increased inflammation observed in these patients is also due to several other factors, including uremic status, elevated serum inflammatory markers, and oxidative stress, among others (11, 12).

The progression of CKD, in addition to the increased state of oxidative stress, is associated with chronic systemic inflammation, that is, oxidative stress appears to stimulate and exacerbate an inflammatory response, and on the other hand, chronic inflammation also stimulates an oxidative response (13). Other factors also contribute to the chronic inflammatory state in CKD, including increased production of pro-inflammatory cytokines, oxidative stress itself, as well as acidosis (14), recurrent infections, intestinal dysbiosis (15), and alteration of adipose tissue metabolism (16, 17).

Oxidative stress in CKD results from increased production of pro-oxidant molecules, insufficient clearance of oxidative products, and deficient antioxidant defense mechanisms (18). Antioxidants can be endogenous (such as albumin, catalase, glutathione (GSH) and glutathione peroxidase (GPx)), produced by the body, or exogenous, found in foods and supplements (such as vitamins E, C, and D, trace elements such as zinc (Zn), copper, selenium (Se), and omega-3 polyunsaturated fatty acids) (19, 20). The markers of oxidative stress present in circulation in the blood and/or tissues have an inverse relationship with the estimated glomerular filtration rate, that is, oxidative stress is already present in the early stages of CKD, progresses with the deterioration of renal function, and it becomes more severe with the terminal phase (dialysis) (21, 22). The low amounts of pro-oxidants, normally produced by cells, have important roles in defense against invading microorganisms and malignant cells, as well as in tissue repair, and are inactivated by antioxidant systems that can neutralize free radicals, or make them less reactive (23, 24). The excessive production of reactive oxygen species (ROS) cannot be neutralized by uptake systems, creating oxidative stress, which culminates in oxidative damage to macromolecules, in addition to affecting cellular and enzymatic activity (23).

Both are interrelated factors in the final stage of CKD, with common underlying mechanisms, which include endothelial dysfunction, and common complications such as CVD, dyslipidemia, hypertension, metabolic syndrome, diabetes mellitus (DM), advanced age, atherosclerosis and increased morbidity and mortality, especially

cardiovascular, which activate pro-oxidant activity (25-27). Inflammation is characterized by an increase in inflammatory markers such as cytokines and acute phase proteins (23).

In patients undergoing HD, the responsiveness of the immune system is disrupted, which leads to pro-inflammatory cytokine dysregulation and a state of persistent inflammation (8, 9, 28). In addition to the common inflammatory cytokines, such as interleukin (IL)-6, IL-1β, IL-18, tumor necrosis factor (TNFα), IL-8, and C-reactive protein (CRP), hypoalbuminemia and elevated ferritin levels are also considered as inflammatory markers in patients with end stage renal disease (ESRD) (29-32).

Some studies have suggested that HD itself increases the production of free radicals (33, 34) and appears to activate pro-oxidant mechanisms (35), being associated with the development of atherosclerosis, chronic inflammation, mortality in general, and CVD (19). Free radicals are formed during the body's natural process of oxygen metabolism and have widespread destructive effects on the body (36).

During HD, exposure of the blood to less hemocompatible dialyzer membranes, the presence of trace amounts of endotoxins in the dialysate, the use of heparin as an anticoagulant, the intravenous administration of iron, the type of dialysis access, and the removal of antioxidant substances via dialysis (19, 37), lead to the activation of complement factors, platelets and Polymorphonuclear Leukocytes (PMNs), which release molecules with subsequent production of ROS, minutes after starting HD sessions (19, 38, 39). The advanced state of oxidative stress that characterizes these patients is mainly due to the accumulation of oxidizing products and impaired antioxidant defense mechanisms, exacerbated by restrictions on the consumption of fruits and vegetables (due to the risk of hyperkalemia), as well as the high prevalence of malnutrition, which result in a reduced intake of nutritional factors (e.g. vitamins C, D, E) (18, 26, 35).

Inflammation-induced malnutrition is caused by the increased proteolytic metabolism and/or decreased protein intake (40, 41). Inflammatory cytokines can promote protein catabolism by inhibiting phosphatidylinositol 3-kinase (PI3K) activity, which in turn activates two proteolytic pathways, the ubiquitin-proteasome proteolytic system (UPP) and caspase-3, causing a negative nitrogen balance in patients, which in turn leads to malnutrition in dialysis patients (42). As for reduced protein intake, the inflammatory factor IL-1 can cause anorexia by directly affecting the satiety center, suppressing the patient’s appetite, resulting in reduced protein intake, and malnutrition (41, 43). It is also known that inflammatory markers are involved in the pathogenesis of malnutrition and insulin resistance in these patients (44, 45).

Furthermore, it is very common for HD patients to be physically inactive in their daily lives, exacerbating chronic inflammation and the loss of muscle mass and strength, which, combined with high cardiovascular morbidity, can create a vicious cycle of health decline in these patients (9, 46, 47).

In addition to CVD, complications such as inflammation and increased CRP, hypertension (HTA), mineral-bone disorders, hyperuricemia, metabolic acidosis, hyperphosphatemia, hypoalbuminemia, anemia, and peripheral vascular disease can be targeted as other side effects of CKD (48, 49). Anemia is common among patients with CKD and increases morbidity and mortality, regardless of the stage of the disease. The majority of patients starting dialysis have a hemoglobin concentration below reference values (50). Given that CVD and infectious diseases are the main causes of morbidity and mortality, the immunological dysfunction that accompanies CKD constitutes one of the main targets for improving the results of therapeutic interventions (47, 51, 52).

Trace elements are compounds with low concentrations in the human body (<50mg/kg/body weight) but with important functions and a wide spectrum of activities (19). They serve as essential components of numerous enzymes, exert regulatory functions, and influence immune responses and free radical production. Altered blood levels of different trace elements have been described in CKD patients, especially in those treated with different types of RRT (53-56). In HD patients, deficiencies in trace elements and other nutrients are notorious due to cachexia, anorexia, and their loss through the dialysis process, which causes a state of increased catabolism and leads to a situation of oxidative stress and loss of essential amino acids, exacerbating morbidity and mortality among HD patients. Due to oxidative stress, there is a 10 to 30 times higher risk of CVD compared to the disease-free population (57).

Available data suggests that levels of cadmium, chromium, copper, lead and vanadium are higher and that levels of Se, Zn, and manganese are lower in HD patients compared to controls (58). Although there is robust evidence that there may be a deficiency or excess of certain trace elements in HD patients (58), only low plasma Se levels were directly and inversely related to mortality in these patients (14, 59, 60). Selenium deficiency may contribute to increased oxidative stress, hospitalization, and inflammation (60-64) and there is also some preliminary evidence suggesting that low Se levels may be associated with an increased risk of death in HD patients, especially due to infections (61, 65). Lower Se levels and lower plasma GPx activity have been reported in patients with CKD and while Se levels appear to be similar at different stages of the disease, decreased plasma GPx activity is associated with stage progression (66). Severe

Se deficiency leads to sudden death and cardiomyopathy in the general population (67-69).

In 2011, a study showed that serum selenium concentrations were significantly lower in the HD group than in the control group (30 healthy volunteers) ($p < 0.01$), and that serum Se levels in patients in the hemodialysis group were significantly and positively correlated with their nutrition-related indicators such as albumin and high-density lipoprotein-cholesterol (HDL-C) (70). The trial concluded that the low blood Se status in hemodialysis patients may be associated with malnutrition in patients. In 2012, Yang et al. recruited 111 patients on maintenance hemodialysis, measured serum levels of Se, Copper, and Zn, and followed them for two years; the authors found that patients with lower serum Se ($p = 0.026$) and Zn ($p = 0.001$) levels were more likely to be hospitalized for infectious diseases (71). Thereafter, in a prospective longitudinal study including 1278 HD patients, blood concentrations of 25 trace elements were assessed and followed over time, showing that low blood Se levels in patients were significantly associated with their all-cause hospitalization and mortality rates (65). In 2021, a cross-sectional study by Liu et al. including 118 patients on HD treatment used the 2002 Nutritional Risk Screen (NRS 2002) to assess the nutritional status of patients and showed that lower blood Se levels were independently associated with high nutritional risk in maintenance HD patients (72). Therefore, the use of appropriate supplements may be important for these patients.

In a 2014 study, the dietary intake of trace elements, minerals, and vitamins in HD patients from three centers in one metropolitan and two urban areas of Italy was estimated. The study revealed that around 90% of HD patients had a daily dietary intake of trace elements and vitamins below the recommended value. The mean standard deviation (± SD) daily selenium intake was 28.3 ± 18.2 µg (73). According to the European Best Practice Guidelines (EBPG) (74), Institute of Medicine (IOM) (75), and the Food and Nutrition Board from National Academies (76), the recommended daily intake of Se for HD patients is 55 µg, identical to the adult general population. Additionally, the tolerable upper intake level (UL), according to the Food and Nutrition Board from National Academies, is 400 µg to the adult population (77).

Selenium is an essential trace element with several important functions in the human body: synthesis of thyroid hormones, an important role in antioxidant mechanisms, production of prostaglandins, and promotion of growth and fertility. Is an essential constituent of the antioxidant enzyme GPx, such as selenocysteine, making it

a natural antioxidant in addition to capturing free radicals (66) and protecting against heavy metals such as mercury (78).

Dietary Se is highly bioavailable, with over 50% being absorbed in the small intestine regardless of the level. It is primarily excreted via urine (60). In terms of supplementation, it is important to know that selenium has a narrow therapeutic range where toxicity can occur with excessive dietary intake and has also been witnessed with accidental high-dose supplementation. Symptoms typically include nausea, vomiting, peripheral neuropathy, and hair or nail loss. However, like any clinical benefits, they appear more pronounced in those with lower baseline selenium levels (such as the HD population) and selenium supplementation should probably be reserved for those who are clearly selenium deficient (79).

According to data from the Portuguese Food Composition Table, dietary sources of selenium are mainly oilseed fruits (Brazil nuts), seafood, eggs, and fish. A study developed by the Department of Food and Nutrition of the Ricardo Jorge Institute that analyzed 1764 representative samples of the Portuguese diet, aimed to determine the selenium content in foods consumed by the Portuguese and calculate its contribution to the Recommended Daily Allowance (RDA) of this micronutrient. According to the authors, fish is the group richest in Se and iodine, followed by dairy products and eggs. A meal of 160g (taking into account the Portuguese per capita consumption per day) of fish constitutes a reasonable contribution to the daily intake of each of these micronutrients. Eating 300g of dairy products (milk, yogurt, or cheese) and an egg is enough to meet the Se and iodine RDA for healthy adults (80).

The 2020 update to the Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guideline for Nutrition in CKD recommends for patients in chronic dialysis treatment a higher protein intake (1.0 to 1.2g/kg/day) to maintain a stable nutritional status, controlling at the same time the intake of phosphorus (800-1.000 mg/day), and sodium (2.000 to 2.300 mg/day) restriction, to maintain serum levels in the normal range (81). Therefore, it is clear that patients with CKD, especially those on HD, are susceptible to a series of dietary restrictions that, together, lead to changes in food intake and possibly worsen diet quality (82). A systematic review of 20 studies that evaluated the dietary intake of HD patients found that energy intake ranged from 19 to 37kcal/kg/day and protein intake from 0.57 to 1.32g/kg/day, concluding that both are below what is recommended in most studies for HD patients (83). The same was observed in two other studies: Lee et al. (2020) observed that the HD patients had a mean energy and protein intake of 23.4 kcal/kg/day and 0.92 g/kg/day, respectively (84), while

Ryu et al. (2017) observed an energy intake of 1,411 ± 411 kcal/day and a protein intake of 55.5 ± 21.8 g/day) (85).

Considering that HD patients are more likely to present important clinical events (such as, coronary heart disease, cerebrovascular and other cardiovascular diseases) (86) and that most studies show a protein intake below the recommended daily intake, it is likely that HD patients also have a deficient intake of Se and Zn, which contributes to the low serum Se levels commonly observed in chronic HD patients (58). In addition to anorexia and dietary restrictions, the deficient nutrient intake in dialysis patients is aggravated by their advanced age, loss of residual renal function, gastrointestinal dysfunction, early satiety (particularly in peritoneal dialysis), depression and poor socioeconomic status (41).

Decreased mortality from CVD, prevention of hypertension, and regulation of mediators of inflammation in asthma are potential benefits of Se (36, 87). Selenium intake may improve lipid profiles through its effect on inhibiting P-selectin and cyclooxygenase-2 expression (COX-2) (88), and by inhibiting the production of inflammatory markers such as ILs and TNFα (89). Although two small, short-term randomized controlled trials (66, 90) have provided some evidence that Se supplementation may be useful in increasing plasma and erythrocyte Se levels, it is not known whether Se supplementation can improve any clinical or health-related outcomes (1, 61, 91).

Because CKD is a progressive condition, it is important to identify modifiable risk factors, including Zn and Se deficiency, to reduce CKD-related morbidity and mortality. (92).

This study aims to fill the gap in the literature by conducting a systematic review to investigate the relationships between inflammatory parameters, oxidative stress, and selenium supplementation in hemodialysis patients. The goal is to contribute to our understanding of the potential effects of selenium administration on ameliorating inflammatory profiles and oxidative stress in this population.

2. Aim

This systematic review aims to determine the impact of selenium supplementation on inflammatory profiles and oxidative stress markers in adult patients with chronic kidney disease undergoing hemodialysis.

3. Materials and Methods

3.1. Protocol and Registration

This study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (93) and followed a pre-specified protocol registered in the International Prospective Register of Systematic Reviews (PROSPERO).

3.2. The Review Question

Will selenium supplementation have an impact on inflammatory profiles and markers of oxidative stress in adult patients with chronic kidney disease on hemodialysis?

3.3. Study selection Criteria

The study selection criteria were defined following PICO (Population, Intervention, Comparator and Outcomes) strategy (94): 1) Adults (18 years and older) with chronic kidney disease, specifically patients in the end-stage of the disease undergoing hemodialysis (Population) excluding pregnancy, ineligible participants, with unrelated results or missing data; individuals who have consumed selenium-containing supplements within the two months preceding the study; individuals with active hepatitis, as indicated by previous studies showing decreased selenium levels in hepatitis B and C (95); 2) selenium supplementation: selenium should be administered orally in adult humans. Studies must specify the elemental amounts or doses of selenium supplements, the study duration and the observed effects of the supplementation (Intervention) excluding studies involving parenteral selenium supplementation, studies lacking specification of the amount of selenium dosage in the intervention, studies not assessing the effect of selenium supplementation in CKD patients on hemodialysis, end-stage CKD patients undergoing alternative renal replacement therapies, studies combining selenium supplementation with other medications that could potentially interfere with the results and studies not providing details on the intervention duration; 3) with any comparator, including a placebo, not exposed to selenium supplementation (Comparator); 4) who reported improvement on Inflammatory profile markers (CRP, IL-6, ferritin, high-sensitivity C-Reactive Protein (hs-CRP), iron, transferrin saturation, transferrin, iron-binding capacity, Erythrocyte

Sedimentation Rate (ESR)) and oxidative stress markers (malondialdehyde (MDA) and homocysteine) (Outcomes); 5) type of study: studies prospective, randomized, double-blind, placebo-controlled trials (parallel group or first arm of cross-over). Excluded from the review were articles that were duplicates, systematic reviews, meta-analyses, letters, conference abstracts, case reports, case series, position papers, and author's replies.

3.4. Search Strategy and Locate Studies

To identify eligible studies, a comprehensive search was conducted in October 2023 of the PubMed, Web of Science, Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL) databases, without any language or time restrictions. In addition, we manually searched the references of selected articles for eligible studies. Furthermore, ClinicalTrials.gov was searched to identify all relevant unpublished trials. Medical Subject Headings (MeSH) terms and free text terms referring to selenium supplementation were used combined with terms referring to inflammatory profile and oxidative stress in adult patients with chronic kidney disease undergoing hemodialysis. The PubMed search strategy was converted to search other databases (Supplementary Table S1).

3.5. Data Collection

EndNote was used to remove duplicates and select studies based on eligibility according to the screening criteria. Two independent reviewers assessed the eligibility of studies by screening titles, and abstracts based on predefined selection criteria. Studies considered potentially relevant were included in a full text for detailed analysis. Data extraction was carried out independently performed by two reviewers using a preconceived and standardized form. The collected information for each study was title, the first author, year of publication, country of origin, study design, sample characteristics, methods, and outcomes. Only studies that met the previously established criteria were considered eligible after a full-text assessment. Excluded trials and reasons for exclusion were recorded and any disagreements between reviewers were resolved through discussion (Figure 1).

4. Results

A total of 2481 records were identified, and 540 duplicates were removed. After screening the titles and abstracts, 1620 articles were excluded, leaving 321 articles for full-text evaluation. Of these, 11 studies involving children, animals, and patients in different stages of CKD or undergoing peritoneal dialysis, 222 reviews, guidelines, case reports, or letters, and 81 studies deemed not relevant were excluded. Additionally, 2 non-Randomized Controlled Trials (RCT) studies were excluded. Finally, 5 studies were eligible for inclusion, as shown in Figure 1. The methodology, content, and relevance of the results of the selected studies were fully analyzed to integrate them into this systematic literature review.

Studies included in this analysis were randomized controlled trials with two arms, and a total of 303 participants were included (Table 1a). These studies were conducted exclusively in Iran and were published between 2013 and 2022 (Table 1a).

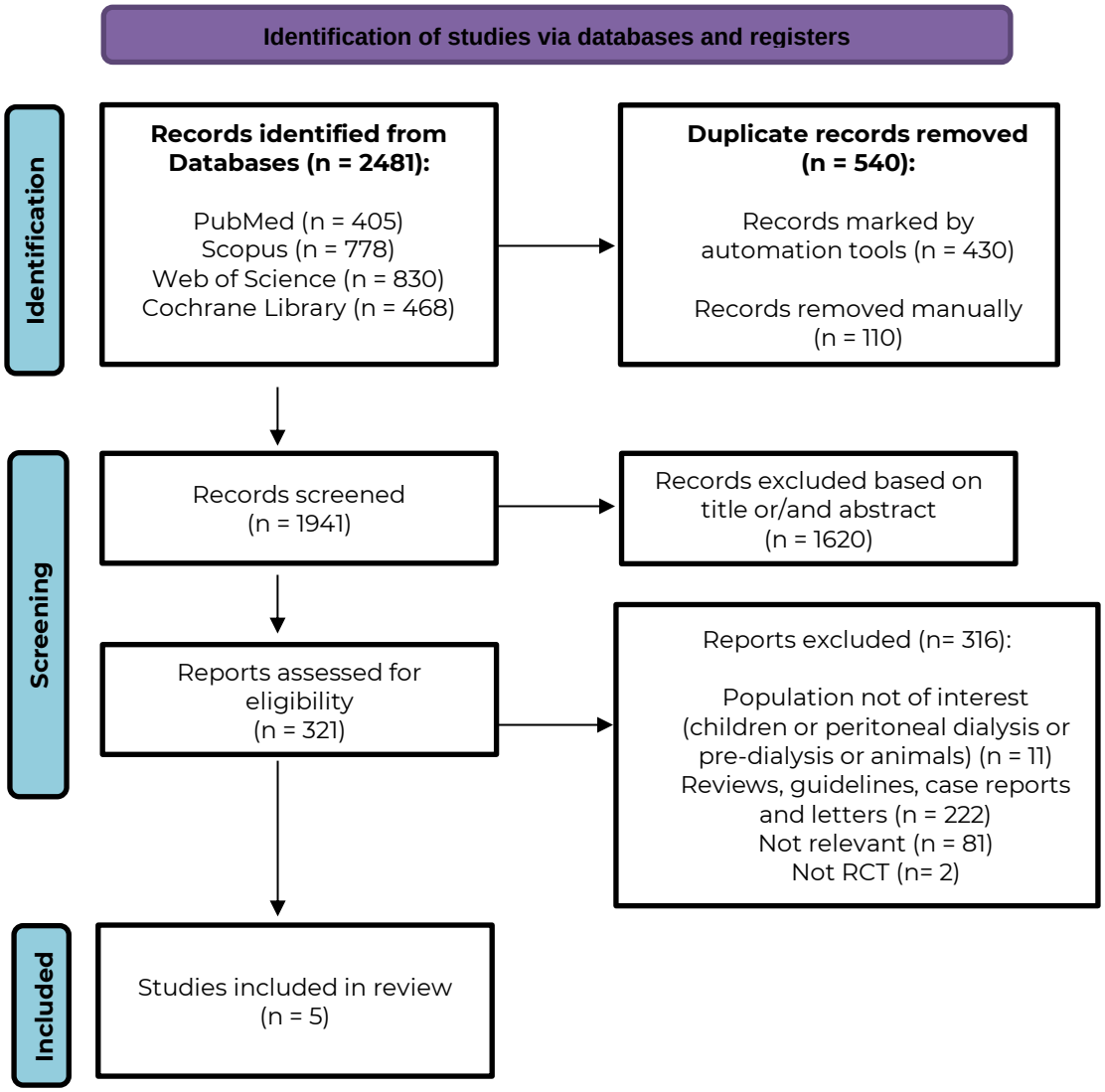

Figure 1. PRISMA study flow diagram describing the process of study selection.

In 2013, Salehi and colleagues conducted a randomized double-blind placebo-controlled trial. The study recruited 80 patients, 40 in each group, between the ages of 18 and 80 who had been on HD for at least 3 months and did not have any acute illness or active infections. The study excluded patients who were pregnant or had used antioxidant supplements (including vitamin E, vitamin C, lipoic acid, omega-3 fatty acids, soy extracts and green tea preparations), or immunosuppressive medications within 2 months before enrollment. Participants were recruited and randomly allocated to two equal groups. The supplementation group received a daily selenium capsule (200µg), while the control group received a placebo for 12 weeks. The mean ±SD age of the supplementation and control groups was 50 (± 15.4) and 55 (± 13) years, respectively. The study aimed to evaluate the effects of selenium supplementation on oxidative and inflammatory markers and the nutritional status of patients. The study analyzed serum levels of lipoproteins, MDA, IL-6, hs-CRP, homocysteine, total iron-binding capacity (TIBC), ferritin, transferrin, and hemoglobin (Hb). Additionally, subjective global assessment (SGA) score and malnutrition–inflammation score (MIS) were assessed at both baseline and the end of the study. The study's primary outcome was the change in nutritional status, as measured by the SGA score, from baseline to the end of the treatment phase. Blood samples were taken from the patient's arm, which was used for the HD cannula, just before the HD session began (Table 1a). The study found that the group receiving the supplement experienced a decrease in serum MDA levels (median (Interquartile Range (IQR)) change = -1.2 (-3.17, -0.45) µmol/L), while the placebo group experienced an increase (median (IQR) change = 0.6 (0.01, 2.22) µmol/L; $P < 0.001$). Selenium treatment also led to a smaller increase in IL-6 levels ($P = 0.016$) when compared with placebo (supplementation group median (IQR) change = 6.05 (-20.4, 50.8) pg/mL vs. placebo group median (IQR) change = 22.95 (0.92, 1978.2) pg/mL). No significant differences ($P > 0.05$) were found between the groups that received supplementation and those that received a placebo in terms of changes in serum levels of lipoproteins, hs-CRP, homocysteine, ferritin, and transferrin or Hb levels (Table 1b).

In the 3-month clinical trial conducted by Omrani et al. (2015), 64 hemodialysis patients with selenium deficiency were divided into two groups: supplementation (32 cases receiving 200 µg selenium, mean ±SD age of 57.34 ± 13.23 years) and control (32 cases receiving placebo, mean ±SD age of 59.53 ± 14.68 years). The study included consecutive patients who had undergone at least six months of hemodialysis at a tertiary center. Exclusion criteria encompassed individuals with acute viral infections in the last three months, previous or current thyroid diseases, use of steroidal and non-steroidal

anti-inflammatory drugs and use of vitamins E and C and zinc in the last two months preceding the study. The study aimed to evaluate the effect of selenium supplementation on inflammatory markers and thyroid function tests (TFTs) in hemodialysis patients (Table 1a). The ESR, ferritin, quantitative CRP, and TFT including thyroid stimulating hormone (TSH), T3 resin uptake (T3RU), and free thyroxine T4 were measured before and after the intervention and compared between supplementation and control groups. Venous blood was obtained for laboratory markers before hemodialysis at two-time points: first at the beginning of the study and again after three months. The study found no significant difference (P>0.05) between the supplementation and control groups for CRP (14.77 ± 17.93 vs. 18.29 ± 21.56 mg/L, respectively), ESR (32.90 ± 32.62 vs. 33.91 ± 31.15 mm/h, respectively), and ferritin (528.6 ± 423.07 vs. 519.52 ± 345.59 ng/mL, respectively) (Table 1b).

Assarzadeh et al. (2022) investigated the effects of selenium administration on lipid profile and indicators related to anemia and inflammation, building upon Salehi and Omrani's previous work. The study expanded the scope of understanding in this domain. Assarzadeh et al. (2022) conducted a study on 59 hemodialysis patients who were randomly assigned to either a supplementation group (29 cases, mean ±SD age of 54.37 ± 15.1 years) receiving 200 µg of selenium once a day or a control group (30 cases, mean ±SD age of 54.06 ± 11.7 years) receiving a placebo for 3 months. The patients were selected from the population referred to the dialysis clinics of Al-Zahra and Noor hospitals. Table 1a shows the measurements of uric acid (UA), hs-CRP, ferritin, iron, TIBC, transferrin, transferrin saturation and lipid profiles including total cholesterol, triglycerides, Low-Density Lipoprotein-Cholesterol (LDL-C), and HDL-C at the beginning and end of the study. Following the intervention there was a significant decrease in serum ferritin concentration in both the supplementation and control groups (mean ± SD = 627.03 ± 569.6 ng/mL before vs. 401.24 ± 401.8 ng/mL after intervention; P = 0.009 and mean ± SD = 621.23 ± 542.8 ng/mL before vs. 403.70 ± 396.1 ng/mL after intervention; P= 0.005, respectively). However, there were no statistically significant differences between the two groups after treatment (P = 0.98). There were no statistically significant differences in the serum concentration of iron, transferrin, hs-CRP, TIBC, and transferrin saturation before and after the intervention or between both groups (P>0.05). Additionally, the study found no significant changes in lipid profile between the two groups (P>0.05). Hemoglobin levels increased slightly in the supplement group (mean ± SD = 11.10 ± 1.5 g/dL before vs. 11.28 ± 1.6 g/dL after intervention), but these changes were not statistically significant (P = 0.55). However, hemoglobin concentration decreased

significantly in the control group (mean ± SD = 11.17 ± 1.4 g/dL before vs. 10.77 ± 1.5 g/dL after intervention; P = 0.031). No statistically significant differences were found between the supplement and control groups after the intervention (P = 0.205) (Table 1b).

In the 2022 study by Salimian and colleagues, 60 diabetic patients with HD aged between 18 and 80 years old were included. Patients who had taken antioxidant and/or anti-inflammatory supplements in the 3 months before intervention, patients with infectious diseases, and patients with malignant diseases as determined by clinical examination by a specialist, were excluded from the study. Participants were randomly assigned to receive either selenium supplements or a placebo (starch). The selenium group (n = 30, mean ±SD age of 57.6 ± 11.5 years) received a daily dose of 200µg of selenium for 24 weeks, while the control group (n = 30, mean ±SD age of 61.5 ±9.8 years) received a placebo. The objective of this study was to evaluate the effects of selenium supplementation on carotid intima mean thickness (CIMT) and metabolic profiles (Table 1a). Fasting blood samples were collected at the beginning of the study and after 24 weeks of intervention. At the beginning and end of the study, the serum concentration of CRP and MDA were analyzed, along with other parameters such as glucose (fasting plasma glucose (FPG), insulin, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI)), lipids (triglycerides, total cholesterol, very low-density lipoprotein (VLDL), LDL, and HDL) and antioxidant metabolism GSH and total antioxidant capacity (TAC)). Additionally, CIMT was assessed before and after the intervention. The study found that the supplement group had a reduction in serum concentration of CRP (mean ± SD = 4.5 ± 1.7 mg/L at baseline vs. 3.9 ± 1.4 mg/L at the end of the trial), while the control group did not show any significant changes (mean ± SD = 3.8 ± 0.9 mg/L at baseline vs. 3.9 ± 0.8 mg/L at the end of the trial). After adjusting for baseline values there was a significant difference in the serum concentrations of CRP were significantly different between the two groups (P < 0.001). However, there was no significant difference in the serum concentration of MDA between the groups (P = 0.24). In the supplement group, the mean ± SD of MDA serum concentration was 2.8 ± 0.3 µmol/L at baseline and 2.6 ± 0.2 µmol/L at the end of the trial, while in the control group, the concentration was 2.7 ± 0.3 µmol/L at baseline and 2.6 ± 0.3 µmol/L at the end of the trial. Furthermore, the authors noted a significant reduction in serum insulin levels (P = 0.003), HOMA-IR (P = 0.003), total cholesterol (P = 0.008), and LDL cholesterol (P < 0.001). In addition, they observed a significant increase in QUICKI (P < 0.001), HDL cholesterol (P < 0.001), and total glutathione (GSH) (P < 0.001) compared to the placebo group. (Table 1b)

Extending the exploration into the genetic aspects, Jamal et al. (2022) conducted a study that included 40 diabetic patients aged 45 to 75 years who were undergoing. Exclusion criteria were individuals with infections, inflammatory conditions, malignant diseases, administration of selenium or other supplements at least 12 weeks before the start of the study, as well as taking medications such as immunosuppressants and antibiotics. The study randomly assigned participants into two groups: a supplementation group (n=20, mean ±SD age of 57.6 ± 11.5 years) and a control group (n=20, mean ±SD age of 61.5 ± 9.8 years). The supplementation group received 200 µg/day of selenium for 24 weeks, while the control group received a placebo. The objective of this study was to investigate the effects of selenium supplementation on the expression levels of genes associated with insulin, lipids, and inflammatory markers in diabetic patients undergoing hemodialysis (Table 1a). The study analyzed the gene expression of IL-8, IL-1, glyceraldehyde-3-Phosphate dehydrogenase (GAPDH), peroxisome proliferator-activated receptor-gamma (PPAR-γ), transforming growth factor-beta (TGF-β), TNF-α, and low-density lipoprotein receptor (LDLR) at the beginning of the study and after 24 weeks of intervention. The primary outcome was the expression of PPAR-γ and genes associated with lipid metabolism, while inflammatory biomarkers were considered secondary outcomes. Compared to the placebo, the authors observed a reduction in the expression of TNF-α (0.90 ± 0.19 vs 1.08 ± 0.19-fold change, P=0.014) and IL-1 (1.00 ± 0.11 vs 1.12 ± 0.15-fold change, P=0.020) genes. However, selenium supplementation did not affect the gene expression of IL-8 (0.98 ± 0.20 vs 1.03 ± 0.17-fold change, P=0.458) (Table 1b).

4.1. Outcome measures - Inflammatory profile markers

4.1.1. C-reactive protein (CRP)

Two studies analyzed the effect of selenium supplementation on serum CRP levels (Table 2). Omrani et al. (2015) conducted a study with 64 HD patients and found no significant difference between the supplementation (200 µg of selenium per day) and control (placebo) groups after 3 months of intervention. In contrast, Salimian et al. (2022) studied of 60 diabetic patients who received the same dosage of selenium supplementation dosage for approximately 6 months. They observed a reduction in serum CRP concentration in the supplement group, but not in the control group (placebo). After adjusting for baseline values, serum CRP concentrations differed significantly between the two groups (P < 0.001). The average age of participants in the

experimental group in both studies was identical, approximately 57 years old, and both blood samples were collected at the beginning and end of the study.

4.1.2. High-sensitivity C-reactive protein (hs- CRP)

Two studies analyzed the serum concentration of hs-CRP (Table 2). Salehi et al. (2013) found no significant difference between the supplementation (median (IQR) change = -0.85 (-2.47, 5.25) µg/mL) and control groups (median (IQR) change = 1.3 (-17.7, 4.52) µg/mL). The same results was found by Assarzadeh et al. (2022), found similar results, with no statistically significant difference in hs-CRP serum concentration between the supplementation group (mean ± SD = 0.45 ± 0.9 mg/L before vs. 0.24 ± 0.5 mg/L after intervention; P = 0.16) and control group (mean ± SD = 0.40 ± 0.8 mg/L before vs. 0.6 ± 0.8 mg/L after intervention; P = 0.32). Both studies supplemented participants with either 200 µg of selenium per day or a placebo for approximately 3 months. The sample sizes were slightly different, with 80 participants in Salehi's study and 59 participants in Assarzadeh's study. However, both studies were carried out with participants of identical ages and characteristics, specifically Iranians aged between 50-54 years.

4.1.3. Interleukins (IL-1; IL-6; IL-8)

Two studies analyzed the serum concentration of three interleukins: IL-1, IL-6, and IL-8 (Table 2). Jamal et al. (2022) investigated the effect of selenium supplementation on the expression of IL-1 and IL-8 genes, while Salehi et al. (2013) analyzed the effect of selenium supplementation on the serum concentration of IL-6.

Jamal et al. (2022) found a significant decrease in IL-1 gene expression in the supplementation group compared to the placebo group (P=0.020) at the end of the intervention, but no significant differences were observed between the IL-8 gene expression of the supplementation and control groups (P = 0.458) at the end of the intervention (Table 2). On the other hand, Salehi et al. (2013) observed a smaller increase in IL-6 serum concentration after selenium supplementation compared to the placebo group (P = 0.016) at the end of the study.

4.1.4. Ferritin

All three studies supplemented the participants with either 200 µg of selenium or a placebo every day for approximately 3 months. The study sample size ranged from 59 (Assarzadeh et al., 2022) to 80 (Salehi et al., 2013) patients who were similar in age and

population characteristics (Iranians undergoing HD aged between 50-57 years old), but no statistically significant differences were observed (Table 2).

At the end of the study, Salehi et al. (2013) observed a median (IQR) serum ferritin concentration of 23 (-107, 216.45) ng/mL and -31.4 (-153.65, 124.35) ng/mL in the supplementation and control groups, respectively (P > 0.05). Similarly, Omrani et al. (2015) found no statistically significant differences in serum ferritin concentrations between the supplementation and control groups (528.6 ± 423.07 ng/mL vs. 519.52 ± 345.59 ng/mL, respectively; P = 0.025). Assarzadeh et al. (2022) reported similar results. Following the intervention there was a significant decrease in serum ferritin concentration in both the supplementation group (mean ± SD = 627.03 ± 569.6 ng/mL before vs. 401.24 ± 401.8 ng/mL after intervention; P = 0.009) and the control group (mean ± SD = 621.23 ± 542.8 ng/mL before vs. 403.70 ± 396.1 ng/mL after intervention; P= 0.005). However, there were no statistically significant differences between the two groups after treatment (P = 0.98).

4.1.5. Iron and Transferrin saturation

Only one study analyzed the serum iron concentration and transferrin saturation after supplementing with either 200 µg of selenium per day or a placebo for approximately 3 months (Table 2). The results showed no statistically significant differences between the supplementation and control groups for both outcomes (Assarzadeh et al., 2022).

The serum concentration of iron was measured before and after the intervention in both the supplementation and control groups. In the supplementation group, the mean serum concentration of iron was 116.48 ± 100.8 before the intervention and 107.38 ± 66.2 after the intervention (P = 0.66). In the control group, the mean serum concentration of iron was 105.4 ± 81.4 µg/dL before the intervention and 116.87 ± 74.3 µg/dL after the intervention (P = 0.38). There were no statistically significant differences between the two groups at the end of the intervention (P = 0.607). The mean transferrin saturation before and after the intervention was 33.34 ± 19.8% and 36.21 ± 21.0%, respectively, in the supplementation group (P = 0.56). In the control group, the mean transferrin saturation before and after the intervention was 33.10 ± 17.2% and 36.77 ± 19.9%, respectively (P = 0.41). There were no statistically significant differences between the groups at the end of the intervention (P = 0.96).

4.1.6. Erythrocyte sedimentation rate

Omrani and colleagues analyzed the ESR of HD patients after 3 months of either 200 µg of selenium or placebo per day (Table 2). The results showed no statistically significant differences (P = 0.9) between the supplementation group (mean ± SD = 32.90 ± 32.62 mm/h) and the control group (mean ± SD = 33.91 ± 31.15 mm/h) after 3 months of intervention.

4.1.7. Transferrin and Total Iron-Binding Capacity

Both Salehi et al. (2013) and Assarzadeh et al. (2022) found no significant difference between the supplementation and control groups after approximately 3 months of supplementing 200 µg of selenium or placebo every day in 80 and 59 HD patients, respectively.

Salehi et al. (2013) did not find any statistically significant differences in serum transferrin concentration between the groups (P > 0.05). Assarzadeh et al. (2022) reported mean serum transferrin concentrations of 209.71 ± 58.1 mg/dL at baseline and 195.21 ± 22.3 mg/dL at the end of the study in the supplementation group (P = 0.17) and 213.40 ± 55.5 mg/dL at baseline and 198.20 ± 24.9 mg/dL at the end of the intervention in the control group (P = 0.11). The study found no statistically significant differences between the two groups at the end of the intervention (P = 0.63).

Regarding TIBC, Salehi et al. (2013) reported a median (IQR) change of -15 (-276, 103.5) µg/dL and 6 (-177, 162) in the supplementation and control groups, respectively, at the end of the intervention. There were no statistically significant differences between the groups (P > 0.05). The mean ± SD TIBC at baseline was 266.55 ± 70.1 for the intervention group and 262.60 ± 55.9 for the control group. At the end of the intervention, the mean TIBC was 246.86 ± 30.2 for the intervention group and 251.60 ± 40.1 for the control group (P = 0.17 and P = 0.20, respectively). Assarzadeh et al. (2022) found no statistically significant differences between the intervention and control groups in terms of TIBC levels at the end of the study (P = 0.61).

4.1.8. TNF-α: tumor necrosis factor-alpha

Only one study analyzed TNF-α gene expression after 24 weeks of daily supplementation with either 200 µg of selenium or placebo in diabetic HD patients. The study by Jamal et al. (2022) found a decrease (0.90 ± 0.19-fold change) in TNF-α gene expression in the supplementation group and an increase (1.08 ± 0.19-fold change) in the

placebo group. The differences between the two groups were statistically significant (P=0.014).

4.2. Outcome measures - Oxidative stress markers

4.2.1. Malondialdehyde (MDA)

Salehi et al. (2013) observed a statistically significant reduction in the serum MDA concentration in the selenium supplementation group and an increase in the serum MDA concentration in the placebo group ($P < 0.001$), while Salimian et al. (2022), observed no significant differences between the two groups ($P = 0.24$) (Table 2). Both studies supplemented either 200 µg of selenium per day or a placebo. However, Salehi et al. (2013) studied the effect of selenium supplementation in HD patients, while Salimian et al. (2022) study included diabetic HD patients. Additionally, the former study had a duration of 12 weeks, while the latter had a duration of 24 weeks.

4.2.2. Homocysteine

Only one study analyzed the serum homocysteine concentration in 80 HD patients after 3 months of selenium (200 µg/day) supplementation (Table 2). Salehi et al. (2013) observed a mean ± SD change of -6.04 ± 9.04 µmol/L and -2.75 ± 10.02 µmol/L in the serum homocysteine concentration of the supplementation and control groups, respectively. However, the differences between both groups were not statistically significant ($P > 0.05$).

Table 1a: Description of methodology of randomized controlled trials in the systematic review.

Publication	Country	Study design	Arms (n)	Population (n)	Age (Years)[a]	Study objective	Intervention (Elementary dose of selenium and time of intervention)	Control	Outcomes
(Salehi et al., 2013)	Iran	Randomized, double-blind, placebo-controlled trial	2	80 (40 in each group)	The mean (± SD) ages of the experimental and control groups were 50 (± 15.4) and 55 (± 13) years, respectively	Evaluate the effects of selenium supplementation on oxidative and inflammatory markers and the nutritional status of HD patients	200µg, 1x/day; 12 weeks	Placebo capsules	Serum levels of MDA, IL-6, hs-CRP, ferritin, transferrin, homocysteine, calcium, phosphate, PTH, albumin, BUN, creatinine, Hb, TIBC
Omrani et al. (2015) (96)	Iran	Randomized, double-blind, placebo-controlled trial	2	64 (32 in each group) 15 males (46.9%) in the experimental group and 17 females (53.1%) in the control group	The mean (± SD) ages of experimental and control groups were 57.34 (± 13.23) and 59.53 (± 14.68) years, respectively	Evaluate the role of selenium supplementation regarding any possible changes in inflammatory markers and TFTs in patients with CKD undergoing hemodialysis	200µg, 1x/day; 3 months	Placebo capsules	ESR, ferritin, CRP, and TFTs including TSH, T3RU, free T4
(Assarzadeh et al., 2022)	Iran	Randomized, double-blind, placebo-controlled trial	2	59 (intervention=29; control=30)	The mean (± SD) ages of the experimental and control groups were 54.37 (±15.1) and 54.06 (±11.7) years, respectively	Investigating the effect of selenium administration in improving lipid profile, as well as indicators related to anemia and inflammation in patients undergoing hemodialysis	200µg, 1x/day; 3 months	Placebo capsules	Hs-CRP, lipid profiles including total cholesterol, triglyceride, LDL, HDL, Hb, Iron, Uric Acid, transferrin, transferrin saturation, ferritin, TIBC
Salimian et al. (2022) (97)	Iran	Randomized, double-blind, placebo-controlled trial	2	60 diabetic patients (30 in each group)	The mean (± SD) ages of the experimental and control groups were 57.6 (± 11.5) and 61.5 (± 9.8) years, respectively	Assess the effects of selenium supplementation on CIMT and metabolic profiles of diabetic hemodialysis patients	200µg, 1x/day; 24 weeks	Placebo capsules (starch)	CRP, MDA, GSH, TAC, total nitrite, total cholesterol, HDL, LDL, VLDL, triglycerides; CRP, HOMA-IR, FPG, insulin, QUICKI, CIMT
Jamal et al. (2022) (98)	Iran	Randomized, double-blind, placebo-controlled trial	2	40 diabetic patients (20 in each group)	The mean (± SD) ages of the experimental and control groups were 55 (± 11.92) and 58.37 (± 9.37) years, respectively	Investigate the effect of selenium administration on the expression of genes associated with lipid and insulin metabolism, as well as inflammatory markers	200µg, 1x/day; 24 weeks	Placebo capsules	IL-8, IL-1, GAPDH, PPAR-γ, TGF-β, TNF-α, LDLR

a) Average ages +/- standard.

Abbreviations: Se: Selenium; CKD: Chronic Kidney Disease; HD: hemodialysis; GSH: glutathione; GFR: Glomerular filtration rate; hs-CRP: high-sensitivity CRP; LDL: Low-density lipoprotein; HDL-C: high-density lipoprotein cholesterol; TIBC: Total iron-binding capacity; ESR: Erythrocyte sedimentation rate; TFTs: thyroid function tests; CRP: C-reactive protein; MDA: malondialdehyde; TAC: total antioxidant capacity; VLDL: lipoprotein, very low-density lipoprotein; FPG: fasting plasma glucose; HOMA-IR: homeostasis model of assessment-insulin resistance; QUICKI: quantitative insulin sensitivity check index; CIMT: carotid intima-media thickness; IL-6: Interleukin-6; PTH: parathyroid hormone; BUN: blood urea nitrogen; Hb: hemoglobin; GAPDH: glyceraldehyde-3-Phosphate dehydrogenase; PPAR-γ: peroxisome proliferator-activated receptor-gamma; LDLR: low-density lipoprotein receptor; TGF-β: transforming growth factor-beta; TNF-α: tumor necrosis factor-alpha; IL-1: interleukin-; IL-8: interleukin-8; TSH: thyroid stimulating hormone; T3RU: T3 Resin Uptake.

Table 1b: Results and conclusions of the randomized controlled trials included in the systematic review.

Publication	Main results	Conclusion
(Salehi et al., 2013)	• The supplementation group's serum MDA levels decreased (median (IQR) = -1.2 (-3.17, -0.45) µmol/L), while the placebo group's levels increased (median (IQR) = 0.6 (0.01, 2.22) µmol/L; P < 0.001) • Selenium treatment also led to a smaller increase in IL-6 levels (P = 0.016) when compared with placebo (selenium group median (IQR) = 6.05 (-20.4, 50.8) pg/mL vs. placebo group median (IQR) = 22.95 (0.92, 1978.2) pg/mL) • Serum levels of lipoproteins, hs-CRP, homocysteine, ferritin, and transferrin or Hb levels: There were NS differences between the supplementation and placebo groups	This study shows that Se may be an effective complementary supplement for reducing the severity of malnutrition in HD patients by alleviating oxidative stress and inflammation
Omrani et al. (2015) (96)	• No significant difference was found between experimental and control groups for CRP (14.77 ± 17.93 vs. 18.29 ± 21.56 mg/L), ESR (32.90 ± 32.62 vs. 33.91 ± 31.15 mm/h), ferritin (528.6 ± 423.07 vs. 519.52 ± 345.59 ng/mL), TSH (3.7 ± 2.22 vs. 2.84 ± 1.88 µU/mL), free T4 (7.19 ± 1.98 vs. 7.02 ± 1.87 µg/dL) and T3RU (30.04 ± 2.28% vs. 29.2 ± 1.98%)	Oral Se supplementation did not have any significant effect on TFTs or acute phase reactants
(Assarzadeh et al., 2022)	• Serum ferritin concentration ↓ significantly in both the intervention (mean ± SD = 627.03 ± 569.6 ng/mL before vs. 401.24 ± 401.8 ng/mL after intervention; P = 0.009) and the control group (mean ± SD = 621.23 ± 542.8 ng/mL before vs. 403.70 ± 396.1 ng/mL after intervention; P= 0.005), but there were no statistically significant differences between groups after treatment (P = 0.98) • There were no statistically significant differences between the serum concentration of iron, transferrin, hs-CRP, TIBC, and transferrin saturation before and after the intervention or between both groups (P>0.05) • This study found that changes in lipid profile were not significant between both groups (P>0.05) • Hemoglobin ↑ slightly in the supplement group (mean ± SD = 11.10 ± 1.5 g/dL before vs. 11.28 ± 1.6 g/dL after intervention), but these changes were not statistically significant (P = 0.55). However, hemoglobin concentration ↓ significantly in the control group (mean ± SD = 11.17 ± 1.4 g/dL before vs. 10.77 ± 1.5 g/dL after intervention; P = 0.031). There were no statistically significant differences between the supplement and control group after the intervention (P = 0.205)	Se supplementation could reduce some risk factors related to their mortality, such as the ratio of uric acid to HDL-C. However, the changes related to lipid profile, hemoglobin level, and hs-CRP biomarker were not significant
Salimian et al. (2022) (97)	• CRP: ↓ in the supplement group (mean ± SD = 4.5 ± 1.7 mg/L at baseline vs. 3.9 ± 1.4 mg/L at the end of the trial), but not in the control group (mean ± SD = 3.8 ± 0.9 mg/L at baseline vs. 3.9 ± 0.8 mg/L at the end of the trial). After adjusting for the baseline values, the serum concentration of CRP was statistically significant between both groups (P < 0.001) • MDA: The serum concentration was not significantly different between groups (P = 0.24). In the supplement group, the mean ± SD MDA serum concentration was 2.8 ± 0.3 µmol/L at baseline and 2.6 ± 0.2 µmol/L at the end of the trial, while in the control group, the concentration was 2.7 ± 0.3 µmol/L at baseline and 2.6 ± 0.3 µmol/L at the end of the trial • The authors observed a significant ↓ in serum insulin levels (P = 0.003), HOMA-IR (P = 0.003), total cholesterol (P = 0.008), LDL cholesterol (P < 0.001), and a significant increase in QUICKI (P < 0.001), HDL cholesterol (P < 0.001), and total GSH (P < 0.001) compared to placebo	Se supplementation had beneficial effects on markers of insulin metabolism, total cholesterol, LDL-C, HDL-C, CRP, and GSH levels in diabetic hemodialysis patients
Jamal et al. (2022) (98)	• In comparison with the placebo, this intervention also ↓ of gene expression TNF-α (0.90 ± 0.19 vs 1.08 ± 0.19-fold change, P=0.014) and IL-1 (1.00 ± 0.11 vs 1.12 ± 0.15-fold change, P=0.020) were detected. Gene expression of IL-8 was not affected by selenium supplementation (0.98 ± 0.20 vs 1.03 ± 0.17-fold change, P=0.458)	Se supplementation had positive effects on gene expression associated with metabolic status inflammatory markers in diabetic hemodialysis patients

Abbreviations: ↑: Increase; ↓: Decreases; NS: Not Significant; Se: Selenium; HD: hemodialysis; GSH: glutathione; hs-CRP: high-sensitivity CRP; LDL-C: Low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TIBC: Total iron-binding capacity; ESR: Erythrocyte sedimentation rate; TFTs: thyroid function tests; CRP: C-reactive protein; MDA: malondialdehyde; TAC: total antioxidant capacity; VLDL: lipoprotein, very low-density lipoprotein; IL-6: Interleukin-6; TNF-α: tumor necrosis factor-alpha; IL-1: interleukin-; IL-8: interleukin-8; HOMA-IR: homeostasis model of assessment-insulin resistance; QUICKI: quantitative insulin sensitivity check index; ESR: Erythrocyte sedimentation rate; TSH: thyroid stimulating hormone; T3RU: T3 Resin Uptake.

Table 2: Summary of inflammation outcome study findings.

Outcome evaluated	Publications	Main results
Inflammatory profile markers		
CRP	Omrani et al. (2015) (96)	NS difference was found between supplementation and control groups for CRP (14.77 ± 17.93 vs. 18.29 ± 21.56 mg/L), (P= 0.49)
	Salimian et al. (2022) (97)	Significant reduction in CRP in the experimental group (mean ± SD = 4.5 ± 1.7 mg/L at baseline vs. 3.9 ± 1.4 mg/L at the end of the trial) but not in the control group (mean ± SD = 3.8 ± 0.9 mg/L at baseline vs. 3.9 ± 0.8 mg/L at the end of the trial). After adjusting for the baseline values, the serum concentrations of CRP were significantly different between both groups (P < 0.001)
Hs-CRP	(Salehi et al., 2013)	NS different (P>0.05) between the supplementation (median (IQR) change = -0.85 (-2.47, 5.25) µg/mL) and control groups (median (IQR) change = 1.3 (-17.7, 4.52) µg/mL)
	(Assarzadeh et al., 2022)	↓ in the supplementation group (mean ± SD = 0.45 ± 0.9 mg/L before vs. 0.24 ± 0.5 mg/L after intervention; P = 0.16) and ↑ in the control group (mean ± SD = 0.40 ± 0.8 mg/L before vs. 0.6 ± 0.8 mg/L after intervention; P = 0.32), however, none of these changes were significant (P=0.091)
IL-1	Jamal et al. (2022) (98)	↓ gene expression in the selenium group compared with the placebo group (1.00 + 0.11 vs 1.12+0.15-fold change, P=0.020)
IL-6	(Salehi et al., 2013)	Selenium supplementation hindered an ↑in IL-6 levels compared with the placebo group (median (IQR) change = 6.05 (-20.4, 50.8) pg/mL vs. median (IQR) change = 22.95 (0.92, 1978.2) pg/mL, respectively; P = 0.016). Serum levels of IL-6 ↑ in both groups; however, this increment was significantly lower in the selenium group
IL-8	Jamal et al. (2022) (98)	NS difference was found between experimental and control groups (0.98+0.20 vs 1.03+0.17-fold change, P=0.458). The gene expression of IL-8 was not affected by selenium supplementation
Ferritin	(Salehi et al., 2013)	NS is different between the two groups. Median (IQR) serum concentration of ferritin of 23 (-107, 216.45) ng/mL in the supplementation group and -31.4 (-153.65, 124.35) ng/mL in the control group (P > 0.05)
	Omrani et al. (2015 (96)	NS difference was found between experimental and control groups (528.6 ± 423.07 vs. 519.52 ± 345.59 ng/mL), (P>0.05)
	(Assarzadeh et al., 2022)	NS difference was found between experimental and control groups (401.24 ± 401.8 vs 403.70 ± 396.1 ng/mL), (P=0.98)
Iron	(Assarzadeh et al., 2022)	NS difference was found between experimental and control groups (107.38 ± 66.2 vs 116.87 ± 74.3 µg/dL), (P=0.607)
Transferrin saturation	(Assarzadeh et al., 2022)	NS difference was found between experimental and control groups (36.31 ± 21.0 vs 36.77 ± 19.9 %), (P=0.96)
ESR	Omrani et al. (2015) (96)	NS difference was found between experimental and control groups for ESR (32.90 ± 32.62 vs. 33.91 ± 31.15 mm/h) (P>0.05)
Transferrin	(Salehi et al., 2013)	NS different between two groups (P > 0.05)
	(Assarzadeh et al., 2022)	NS difference was found between experimental and control groups (195.21 ± 22.3 vs. 198.20 ± 24.9 mg/dL) (P=0.63)
TIBC	(Salehi et al., 2013)	Median (IQR) change of -15 (-276, 103.5) µg/dL and 6 (-177, 162) µg/dL in the supplementation and control groups, respectively, at the end of the intervention. There were no statistically significant differences between both groups (P > 0.05)
	(Assarzadeh et al., 2022)	NS difference was found between experimental and control groups (246.86 ± 30.2 vs. 251.60 ± 40.1 µg/dL) (P=0.61)
TNF-α	Jamal et al. (2022) (98)	Expression of gene of TNF-α ↓ in selenium group compared with placebo group (0.90+0.19 vs 1.08 + 0.19-fold change, P=0.014)

Oxidative stress markers		
MDA	(Salehi et al., 2013)	↓ significantly in the supplementation group (median (IQR) change = -1.2 (-3.17, -0.45) µmol/L) compared with ↑ levels in the placebo group (median (IQR) change = 0.6 (0.01, 2.22) µmol/L) (P < 0.001)
	Salimian et al. (2022)(97)	NS difference was found between experimental and control groups (2.6 ± 0.2 vs. 2.6 ± 0.3 µg/dL) (P=0.24)
Homocysteine	(Salehi et al., 2013)	NS difference was found between experimental and control groups (-6.04 ± 9.04 µmol/L vs. -2.75 ± 10.02 µmol/L) (P>0.05)

Abbreviations: ↑: Increase; ↓: Decreases; NS: Not Significantly.

5. Discussion

CKD progression is associated with chronic systemic inflammation and increased oxidative stress (13). The available data suggests that selenium serum concentrations are lower in HD patients compared to controls (58). Moreover, some studies have shown that the serum concentration of selenium was directly and inversely related to mortality in these patients (14, 59, 60). Currently, there is no systematic review on the role of selenium supplementation in inflammatory parameters in HD patients. This study aimed to investigate the effect of selenium supplementation administration on improving the inflammatory profile and oxidative stress in patients undergoing HD. Previous reports have suggested a beneficial role of selenium supplementation in HD patients due to its potential positive effects on oxidative stress and inflammation (99, 100).

This systematic literature review analyzed five studies conducted in Iran that investigated the effect of selenium supplementation on the inflammatory profile and oxidative stress markers of HD patients. The biomarkers analyzed included CRP, hs-CRP, IL-1, IL-6, IL-8, ferritin, iron, transferrin saturation, ESR, transferrin, TIBC, TNF-α, MDA and homocysteine. The results showed improvement in only three biomarkers after selenium supplementation, with significant differences between the supplemented and control groups. These studies reported a decrease in the concentrations of MDA (101) and CRP (97), and in one study selenium supplementation hindered an increase in IL-6 levels (101). Additionally, Jamal's study found a significant decrease in the expression of TNF-α and IL-1 genes in the supplementation group compared to the control group (98).

Despite providing similar dosages of selenium supplementation to HD patients of similar age, Omrani et al. (2015) found no statistically significant difference in serum CRP levels among HD patients after 3 months of intervention, while Salimian et al. (2022) observed a significant reduction in serum CRP levels after 6 months. However, the latter study included exclusively diabetic hemodialysis patients, suggesting that the response to selenium supplementation may vary based on other underlying conditions.

Cumulative evidence over time has suggested that the state of inflammation and duration of HD are determinants of oxidative stress (102), and the increase in these inflammatory biomarkers occurs due to the overproduction of ROS (which can cause reactions oxidative damage, damage to lipids, proteins and deoxyribonucleic acid (DNA) (103, 104)) and decreased antioxidant defenses (including selenium-dependent reactions). Markers of oxidative stress have been independently associated with CRP

values, suggesting a strong link between oxidative stress and inflammation in these patients (105, 106). Within acute phase proteins, CRP is one of the most important inflammatory markers in CKD, which has been associated with malnutrition (107), and is an independent predictor of risk for atherosclerosis, CVD and mortality in individuals in HD (108, 109).

The beneficial effects of selenium supplementation on CRP concentrations in some studies can be explained by the inhibition of nuclear factor kappa B (NF-κB) activation (110) and the increase in selenoprotein biosynthesis (111). There is evidence that the availability of Se, and therefore the activity of selenium-dependent GPx, is inversely correlated with the activation of nuclear factor kappa B (a protein complex that performs functions as a transcription factor - NF-κB) in response to exposure to cytokines (112, 113). Furthermore, selenium intake in chronic inflammatory status restores the depleted hepatic and serum selenium levels by increasing selenoprotein biosynthesis, which suppresses CRP production and attenuates the inflammatory process (111). This evidence may explain the results found in the study by Salimian et al. (2022) which observed a reduction in serum CRP concentration in the supplement group, but not in the control group (placebo), in diabetic patients on HD. However, it is important to note that the CRP values of the two groups (supplementation vs. control) at the beginning of the study appear different (4.5 ± 1.7 mg/L vs 3.8 ± 0.9 mg/L, respectively), and this decrease was observed in the supplementation group can only be justified by this difference, the CRP value in the supplementation group was higher. The authors do not statistically compare CRP values between groups at baseline (97).

DM is a multifactorial disease, and chronic inflammation is a common feature in the natural course of diabetes. The levels of inflammatory and oxidative stress biomarkers, many of which are secreted by adipocytes, play an important role in the etiology, pathogenesis, and complications of diabetes (114). The beneficial effects of selenium supplementation on CRP levels observed in the study by Salimian et al. (2022) might be explained by the fact that diabetes mellitus can affect several functions of the immune system, predisposing them to exacerbated chronic inflammation. On the other hand, Omrani et al. (2015) observed no significant effects of selenium intake for 12 weeks in acute phase reactants, such as CRP levels, in people on HD (96).

Future studies should address the controversies in the literature by using larger samples and longer study periods with more patients. In both studies ((Salimian et al. (2022) and Omrani et al. (2015)), confounding variables such as infection that could affect acute phase reactants were not monitored. To obtain a better assessment of the effect

of selenium on this inflammatory marker and others, it is recommended to control these variables in future studies, as CRP is a sensitive biomarker.

In the present review, two studies analyzed the serum concentration of hs-CRP. Both studies found no significant differences between the group that received selenium supplementation and the control group. The participants in both studies were supplemented with 200 µg of selenium per day or placebo for approximately 3 months. Both Salehi et al. (2013) and Assarzadeh et al. (2022) recruited participants aged 50-54, maintaining consistency in demographic characteristics despite the minor difference in sample sizes.

In end-stage CKD patients, hs-CRP is a strong predictor of both cardiovascular and all-cause mortality, and is associated with oxidative stress, vascular calcification, and endothelial dysfunction (115). Additionally, elevated hs-CRP seems to be independently associated with CVD among dialysis patients (116), and higher serum hs-CRP levels, as well as an increased trend over time, were predictive of worse prognosis among peritoneal dialysis patients (117). In a study by Assarzadeh et al. (2022), however, hs-CRP was not outside the range (<2.0 mg/L for lower risk of heart disease (118)) in both groups (0.24±0.5 for the intervention group vs 0.6±0.8 for control group), but after the end of the intervention, it decreased in the supplementation group and increased in the control group. None of these changes were statistically significant, but they may pave the way for further studies to investigate the effect of Se supplementation on hs-CRP levels. Perhaps these differences could reach significance levels in studies with larger samples and longer durations.

Other interventions involving selenium supplementation have shown varying results on different pathologies characterized by a chronic inflammatory status. For instance, in their 2016 study, Farrokhian et al. revealed that selenium supplementation (200 µg/day) in patients with DM and coronary disease for 12 weeks resulted in significantly reduced insulin levels, insulin resistance, hs-CRP, and increased insulin sensitivity scores, but did not affect other metabolic profiles (119). In line with these findings, supplementation with a daily capsule containing 50 µg selenium, 8 mg zinc, 400 µg vitamin A, 125 mg vitamin C, and 40 mg vitamin E among patients with rheumatoid arthritis resulted in a significant decrease in hs-CRP concentrations over 12 weeks (120). In another study, the intake of selenium-containing dietary supplements was associated with decreased CRP levels (121). However, other researchers have not found such favorable effects of selenium supplementation on hs-CRP concentrations. For example, administration of cereal selenized onion biscuits with bioactive complexes

such as selenium in organic form, quercetin (onion), curcumin (Curcuma), and catechins (green tea) among healthy adults for 2 months did not influence hs-CRP concentrations (122).

Furthermore, the findings of Salehi et al. (2013) provide valuable insights into the potential mechanisms underlying the observed effects of selenium supplementation. Salehi et al. (2013) study revealed a smaller increase in serum IL-6 concentration following selenium supplementation, suggesting a possible role of selenium in modulating inflammatory pathways. This observation aligns with previous research indicating that selenium regulates the expression of selenoprotein genes, thereby inhibiting the activation of the NF-κB signaling pathway and therefore decreasing the production of inflammatory cytokines such as IL-6 (111, 123). Based on the results of studies included in this review, the observed beneficial effect of selenium supplementation in improving the inflammatory profile of HD patients, such as IL-6, may be partially mediated by the inhibition of oxidative damage and inflammation.

In contrast, the studies by Salehi et al. (2013) and Salimian et al. (2022) present conflicting evidence on serum MDA levels after selenium supplementation. Salehi's study, which focused on HD patients, demonstrated a significant reduction in MDA levels. However, Salimian's study, which involved diabetic HD patients, found no significant changes. MDA, which is a biomarker of lipid peroxidation (120, 124), plays a crucial role in various diseases, including atherosclerosis. It also seems to be a good predictor of mortality in HD patients (120), especially due to CVD (125). However, MDA has a low molecular weight and is water-soluble and can be removed by HD, therefore its value as a biomarker of oxidative stress in these individuals is limited (126, 127).

Corroborating the results found in Salehi's study, in an interventional study by Ardalan, selenium and vitamin E administration to HD patients prevented the iron infusion-induced increase in serum levels of MDA (100). In another interventional study selenium supplementation decreased plasma levels of MDA and increased levels of antioxidant enzymes like glutathione peroxidase in HD patients (99).

Regarding iron metabolism, the effect of selenium supplementation on ferritin, iron, transferrin saturation, transferrin, TIBC and ESR was not significant in any of the outcomes in relation to the placebo group. The studies had the same dosage, intervention time, and similar characteristics (Iranians on HD aged 50-57 years). The sample size of just the studies ranged from 59 (Assarzadeh et al., 2022) to 80 (Salehi et al., 2013).

In patients undergoing HD, serum ferritin appears to be a good predictor of hospitalization, and its levels, when high, are associated with an increased risk of early death, according to what was reported in the Kalantar-Zadeh (128). In addition to common inflammatory cytokines, such as interleukin IL-6, IL-1, TNFα, IL-8, and CRP, elevated ferritin levels are also considered inflammatory markers in patients with ESRD (29-32).

In Assarzadeh's study, among all biomarkers measured, serum ferritin levels decreased in both groups, but were still above the normal range at the end of the study in the intervention group (401.24±401.8 ng/mL). Kalantar-Zadeh et al. reported the interrelationship between serum ferritin, inflammation, and mortality risk in HD patients (128). The authors showed that, in HD patients, the risk of mortality was higher only in the serum ferritin ranges >1200 ng/mL compared to the reference range (100-199 ng/mL), but the hazard ratios were close to 1 (no association) in models after adjusting for other variables related to malnutrition and inflammation. The authors argue that the increased risk of mortality in HD patients with high serum ferritin was mainly due to the confounding effects of systemic inflammation and/or malnutrition.

Ferritin levels appear to be affected by some systemic conditions, in addition to inflammation, that may result in increased mortality and other adverse outcomes. These results reinforce, once again, the importance of carefully monitoring serum ferritin concentrations, mortality rate, and their relationship in patients with and without signs of inflammation.

Jamal et al. (2022) found a significant decrease in IL-1 and TNF-α gene expression in the supplementation group, but no significant differences were observed in IL-8 gene expression after 24 weeks of daily supplementation with 200 µg of selenium or placebo in diabetic patients on HD. Moreover, Jamilian et al. reported that selenium supplementation (200 µg/ day) reduced TNF-α and TGF-β gene expression in six weeks (129). However, no changes were observed in the expression of the IL-8 gene in women with gestational diabetes. Another study indicated that a daily intake of 200 µg of selenium downregulated TNF-α and IL-1; however, it did not change IL-8 and TGF-β expressions (130). An animal study demonstrated that selenium supplementation decreased the gene expression of TNF-α and IL-1 in hepatic cells (131). Furthermore, previous studies have suggested that selenium inhibits the NF-κB pathway, resulting in decreased expression of TNF-α and IL-1 (89, 132). Among the major limitations of Jamal's study are the inability to determine the effects of selenium administration on other biomarkers of oxidative stress and inflammation. Additionally, a biomarker was not used

to verify adherence to selenium intake, and variables in protein levels were not measured. Furthermore, serum selenium levels were not assessed before the intervention. The results of different studies may vary due to several factors, including the type of study and duration of the intervention.

The study discusses both strengths and limitations that require attention. A notable limitation is the absence of quality assessment of the included studies and meta-analysis due to time constraints imposed by the master's program. Additionally, the systematic review was carried out with a total sample of only 303 participants. Furthermore, it should be noted that studies had a limited duration, and all were conducted solely in Iran, a country with distinct demographic characteristics and lifestyle habits compared to those of European population. Additionally, although all studies used the same method for collecting samples, Jamal's study used lymphocytes from blood instead of serum. Moreover, samples were collected at the beginning and end of each study. Initial group differences were not significant in all studies, except for Omrani's study which lacked demographic data. Furthermore, several studies did not measure the initial serum selenium levels of participants, unlike Omrani's study. This makes it difficult to accurately assess the impact of selenium supplementation on the studied biomarkers. The absence of baseline measurements raises uncertainty about the effectiveness of selenium supplementation in hemodialysis patients. Additionally, most studies have limited reporting of dietary trace element intake, including no data on selenium consumption. This restricts our understanding of potential dietary influences on trace element levels in hemodialysis patients. Only two studies (Salimian et al., 2022 and Jamal et al., 2022) provided dietary intake data, which showed no significant differences between control and intervention groups. However, detailed information on daily intake was lacking. There are no discrepancies in appearance between selenium and placebo capsules in included studies. It should be noted that the studies also do not mention the dialysis method used in Iran.

The strengths of this systematic review are mainly attributed to the rigorous methodology employed, which includes: 1) adherence to the PRISMA guidelines and registration in the PROSPERO database; 2) clearly defined objectives; 3) provide a clear definition of inclusion and exclusion criteria, based on the PICO strategy; 4) comprehensive database searches and examination of reference lists; 5) described the study selection process using a flowchart; 6) listed the excluded studies and reasons; 7) provided the characteristics of individual studies; 8) two independent authors performed study selection and data extraction. Additionally, this review is the first to explore the

relationship between inflammatory parameters, oxidative stress, and selenium supplementation in hemodialysis patients.

The main contribution of our systematic review is to provide a clear overview of the available evidence on the topic and its potential usefulness in contributing to future guidelines. Additionally, it also identifies important flaws that should be avoided when designing new studies to address this issue in the future. This review is a significant contribution to the medical community, as it aims to understand the impact of selenium on inflammatory parameters and markers of oxidative stress from a functional nutrition perspective. The review takes a dynamic approach to correcting nutritional imbalances in patients.

Future studies should include longer treatment periods to provide conclusive evidence on the clinical benefits of Se supplementation. Additionally, it is essential to control for factors such as infections and other confounding variables to accurately assess the effect of selenium on inflammatory markers. The inconsistencies observed across studies may be due to differences in biomarkers, treatment durations, and participant demographics. To investigate the effects of Se supplementation on clinical outcomes, such as cardiovascular events and mortality, it is necessary to conduct larger sample size, prospective, randomized, and placebo-controlled trials with comprehensive control for potential biases. Furthermore, managing inflammation and oxidative stress in hemodialysis patients requires a multifaceted approach that includes lifestyle interventions and optimization of dialysis procedures. Conducting randomized controlled trials in this population is challenging due to associated comorbidities, chronic inflammation, and complex hemodynamic management. Furthermore, ethical considerations in European countries add further complexity to conducting such trials.

6. Final Considerations

The results of the present systematic review yielded inconsistent results regarding the effects of Se supplementation. While Se supplementation significantly decreased CRP and MDA levels, and prevented the increase of IL-6 levels, there was no significant improvement in hs-CRP, IL-1, IL-8, ferritin, iron, transferrin saturation, ESR, transferrin, TIBC, TNF-α, or homocysteine.

There is currently insufficient evidence to recommend vitamin and trace element supplementation in patients with end-stage renal disease. The EBPG guidelines reports that there is no recommendation for selenium supplementation for patients with CKD, but if prescribed, serum levels should be closely monitored (133). The KDOQI Clinical Practice Guideline for Nutrition in CKD: 2020 UPDATE, recommends against routine selenium supplementation in adults with CKD 1-5D. The evidence suggests that it does not improve nutritional, inflammatory or micronutrient status (2C) (81). However, this review is relevant because here has been no systematic review to date. Additionally, there are three recent 2022 studies included in this review on the effect of selenium supplementation on inflammatory parameters that were not included in the 2020 guidelines. These studies could provide new data on the topic and add information for future guidance.

Malnutrition and CVD are very common in CKD patients, especially those on dialysis. Paying attention to the nutritional problems of CKD patients and integrating nutritional therapy throughout CKD treatment is of great importance to improve the diagnosis and overall treatment of CKD, delay disease progression, improve patient prognosis and reduce disease and inflammation. Many of the available studies have demonstrated that blood Se concentrations in dialysis patients are significantly lower than those in the healthy population. Additionally, these studies have found that blood Se concentrations are positively correlated with mortality. Some small sample trials have also demonstrated that Se supplementation can improve patient's malnutrition status and inflammatory states. However, there is still a lack of prospective, large-sample, multicenter, randomized, placebo-controlled, double-blind, long-term clinical studies to unequivocally clarify these effects and their impact on patient outcomes, as current data are inconsistent. Further studies are needed to provide a more comprehensive description of potential mechanisms and metabolic pathways comprehensively through which Se may ameliorate inflammation and oxidative stress in dialysis patients.

Most studies on the relationship between the inflammatory profile and blood Se have been conducted in patients on maintenance hemodialysis. However, data on this relationship in patients on peritoneal dialysis are currently limited. Therefore, further research is needed to compare and investigate the evidence of correlation between plasma Se and inflammatory profile in patients with different dialysis techniques, to provide new diagnostic insights to predict and reduce the occurrence of malnutrition and cardiovascular events in patients with end-stage renal disease treated with dialysis.

In conclusion, antioxidant therapy has not yet been widely adopted in recommendations or in daily clinical practice to reduce oxidative stress and its complications. This systematic review is an important contribution as it seeks to complement the available information and understand the impact of selenium on inflammatory parameters and markers of oxidative stress from a functional nutrition perspective.

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Supplementary Table S1. Query: (#1 AND #2 AND #3).

#	PUBMED	SCOPUS	WEB OF SCIENCE	COCHRANE
1	"inflammation"[MeSH Terms] OR "inflamm*"[MeSH Terms] OR "inflammatory factors"[Title/Abstract] OR "inflammatory profile"[Title/Abstract] OR "c reactive protein"[Title/Abstract] OR "CRP"[Title/Abstract] OR "NO"[Title/Abstract] OR "nitric oxide"[Title/Abstract] OR "high sensitivity c reactive protein"[Title/Abstract] OR "hs-CRP"[Title/Abstract] OR "oxidative stress"[Title/Abstract] OR "interleukins"[Title/Abstract] OR "IL"[Title/Abstract]	TITLE-ABS-KEY(inflammation) OR TITLE-ABS-KEY(inflamm*) OR TITLE-ABS-KEY(inflammatory factors) OR TITLE-ABS-KEY(inflammatory profile) OR TITLE-ABS-KEY(c reactive protein) OR TITLE-ABS-KEY (CRP) OR TITLE-ABS-KEY(ON) OR TITLE-ABS-KEY(nitric oxide) OR TITLE-ABS-KEY(high sensitivity c reactive protein) OR TITLE-ABS-KEY(hs-CRP) OR TITLE-ABS-KEY(oxidative stress) OR TITLE-ABS-KEY(interleukins) OR TITLE-ABS-KEY(IL)	TI=(inflammation OR inflamm* OR inflammatory factors OR inflammatory profile OR c reactive protein OR CRP OR ON OR nitric oxide OR high sensitivity c reactive protein OR hs-CRP OR oxidative stress OR interleukins OR IL) OR AB=(inflammation OR inflamm* OR inflammatory factors OR inflammatory profile OR c reactive protein OR CRP OR ON OR nitric oxide OR high sensitivity c reactive protein OR hs-CRP OR oxidative stress OR interleukins OR IL)	((inflammatory factors) OR (inflammatory profile) OR (c reactive protein) OR (CRP) OR (NO) OR (nitric oxide) OR (high sensitivity c reactive protein) OR (hs-CRP) OR (oxidative stress) OR (interleukins) OR (IL)):ti,ab,kw OR MeSH descriptor: [Inflammation] explode all trees
2	"selenium"[MeSH Terms] OR "selenium compounds"[MeSH Terms] OR "se"[Title/Abstract] OR "Se"[Title/Abstract] OR "selenium"[Title/Abstract]	TITLE-ABS-KEY(selenium) OR TITLE-ABS-KEY(selenium AND compounds) OR TITLE-ABS-KEY(se)	TI=(selenium OR selenium compounds OR se OR Se) OR AB=(selenium OR selenium compounds OR se OR Se)	((selenium) OR (Se) Or (se)):ti,ab,kw OR MeSH descriptor: [Selenium] explode all trees OR MeSH descriptor: [Selenium Compounds] explode all trees
3	"renal insufficiency, chronic"[MeSH Terms] OR "kidney failure, chronic"[MeSH Terms] OR "renal insufficiencies chronic"[Title/Abstract] OR "chronic kidney disease"[Title/Abstract] OR "CKD-5"[Title/Abstract] OR "chronic renal disease"[Title/Abstract] OR "hemodialysis*"[Title/Abstract] OR	TITLE-ABS-KEY (renal AND insufficiency AND chronic) OR TITLE-ABS-KEY (kidney AND failure AND chronic) OR TITLE-ABS-KEY (renal AND insufficiencies AND chronic) OR TITLE-ABS-KEY (chronic AND kidney AND disease) OR TITLE-ABS-KEY (ckd-5) OR TITLE-ABS-KEY (chronic AND renal AND disease)	TI=(renal insufficiency chronic OR kidney failure chronic OR renal insufficiencies chronic OR chronic kidney disease OR CKD-5 OR chronic renal disease OR hemodialysis* OR dialysis renal) OR AB=(renal insufficiency	((renal insufficiencies chronic) OR (chronic kidney disease) OR (CKD-5) OR (chronic renal disease) OR (hemodialysis*) OR (dialysis

	"dialysis renal"[Title/Abstract] OR "renal dialysis"[MeSH Terms] OR "renal dialysis"[MeSH Terms]		chronic OR kidney failure chronic OR renal insufficiencies chronic OR chronic kidney disease OR CKD-5 OR chronic renal disease OR dialysis renal OR hemodialysis*)	renal)):ti,ab,kw OR MeSH descriptor: [Renal Insufficiency, Chronic] explode all trees OR MeSH descriptor: [Kidney Failure, Chronic] explode all trees OR MeSH descriptor: [Renal Dialysis] explode all trees
#1 AND #2 AND #3	405 Resulted	778 Resulted	830 Resulted	463 Resulted