Review Article

Homocysteine-Lowering Interventions in Chronic Kidney Disease

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Abstract

The incidence of cardiovascular events and mortality is higher in patients with chronic kidney disease (CKD) compared to the general population. Homocysteine (Hcy) appears to be an independent risk factor for cardiovascular diseases in general populations and patients with CKD. Further, hyperhomocysteinemia can cause endothelial damage and increase the activity and production of coagulation factors, and its prevalence among patients with end-stage renal disease is approximately 85%–100%. Most treatments, which lower Hcy levels and have been considered in previous studies, include folic acid, B vitamins, omega-3 fatty acids, and N-acetylcysteine. However, the effect of therapies that can decrease Hcy levels and thus cardiovascular events in these patients is still unclear. The results are conflicting and require further investigation. To guide treatment decisions and improve patient outcomes, multiple databases were searched, including Web of Science, PubMed, and Medline to summarize the available evidence (i.e., clinical trial and meta-analyses) on Hcy-lowering interventions and cardiovascular events.

Keywords: *Chronic kidney disease, homocysteine, hyperhomocysteinemia*

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Introduction

The prevalence of cardiovascular disorders is higher in patients suffering from chronic kidney diseases (CKD) in comparison with the general population, and such disorders are considered as the leading cause of death.[1] For example, deaths from cardiovascular problems are 10–100 times higher in dialysis patients compared to the population that is matched in terms of age and gender.[2] Therefore, the prevention and treatment of cardiovascular diseases (CVDs) and an understanding of its factors in individuals with CKD are essential.[3,4] According to previous evidence,[5,6] the high prevalence of CVD among CKD patients is due to known traditional risk factors (e.g., hypertension, dyslipidemia, and diabetes mellitus) and other related factors (e.g., malnutrition or systemic inflammation increases cardiovascular morbidity and mortality in this group of patients).

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Homocysteine (Hcy) is a nonessential sulfur-containing amino acid that is produced in the metabolic cycle of Hcy-methionine and plays a crucial role in this metabolic pathway by interfering with folic acid and B12.[7] Hcy appears to cause endothelial damage and increase the activity and production of coagulation factors.[8] There is ample evidence that hyperhomocysteinemia impairs endothelial function, increases the oxidation of low-density lipids, and stimulates the inflammation and proliferation of smooth muscle cells.[9]

Epidemiological studies have shown that elevated Hcy levels increase the risk of cardiovascular events in the general population and people with CKD.[10-12] A decrease of 25% in Hcy levels in the general population reduces

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the risk of coronary artery disease (CAD) and stroke risk by 11% and 19%, respectively.[13] Decreased glomerular filtration in CKD increases Hcy levels in most patients depending on the severity of renal impairments. Given that studies have demonstrated that Hcy levels decrease after kidney transplantation, it is suggested that renal mechanisms are relatively responsible for the increase in Hcy levels in CKD patients.[14-18]

Therefore, due to the direct relationship between Hcy and cardiovascular events, therapies reducing Hcy levels may decrease the CVD burden. According to previous evidence, most treatments lowering Hcy levels are folic acid, B vitamins, omega-3 fatty acids, and N-acetylcysteine. Although patients with CKD have hyperhomocysteinemia, the impact of Hcy reductions on cardiovascular mortality in these patients is still unknown. Thus, conflicting results exist in this regard, requiring further evaluations.[8,19-22]

The effectiveness of any intervention should be thoroughly evaluated and clarified due to the high burden of CVD in CKD patients. Accordingly, this review aimed to discuss the clinical studies conducted to reduce the Hcy level in CKD patients and their benefits and harms to guide decisions and improve patient outcomes.

Methods

Materials for this review were obtained by searching ISI Web of Science, PubMed/Medline, Scopus, Cochrane central register of controlled trials, and Cochrane database of systematic reviews. Key words used as search terms were “chronic kidney disease", "homocysteine", and "hyperhomocysteinemia'. This search was performed without time limitation. Major well-designed studies which used Hcy-lowering effect as a main surrogate end point were included.

Results

The Relationship between Homocysteine Levels and Renal Function

Patients with CKD have higher levels of Hcy compared to the general population,[19,23] and the prevalence of hyperhomocysteinemia among patients with end-stage renal disease (ESRD) is about 85%–100%.[24] The important role of the kidney in the excretion and metabolism of Hcy is well known.[25] There is an inverse relationship between the estimated glomerular filtration rate (eGFR) and the plasma concentrations of Hcy.[26] Nevertheless, according to a previous study,[25] Hcy has a high plasma protein binding that allows it to remain mainly in the circulation during filtration (although its free form has a low molecular weight and can easily cross ultrafiltration barriers). On the other hand, it seems that the impaired Hcy metabolism in the kidneys has a more critical effect on increasing Hcy levels instead of reducing its excretion. Elevated uremic toxins, acidosis, and systemic inflammation may all lead to metabolic disorders.[27] The metabolic pathways of transsulfuration and remethylation, causing the effective removal of Hcy in the body, are particular affected by kidney diseases.[28,29]

Homocysteine and Cardiovascular Diseases

The association between Hcy and atherosclerotic vascular diseases and states of increased coagulation has been suggested as a risk factor for CVD since the early 1990s.[30] Elevated Hcy levels appear to be an independent risk factor for atherosclerosis.[31] Furthermore, Hcy can damage endothelial cells and increase CVD by creating several different mechanisms. Some of the hypothetical mechanisms of these effects include decreased bioavailability of nitric oxide, a potent vasodilator,[32] oxidative damage and cytotoxicity, increased proliferation of vascular smooth muscle cells, increased collagen synthesis,[33] and thrombosis.[34] It also increases cholesterol synthesis by increasing HMG Co-A 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase activity.[35]

Research[34] has reported a clear link between serum Hcy and the risk of CVD (CAD, heart disease, cerebrovascular diseases, and peripheral vascular diseases). The relationship between serum Hcy levels and the severity of CAD was investigated in a study of 70 patients who were scheduled for coronary angiography. The results showed that fasting serum Hcy levels were significantly higher in patients with CAD in comparison with patients without CAD ($P < 0.001$). Moreover, the Hcy level was significantly associated with increased CAD severity ($P < 0.001$). The findings also revealed that endothelial dysfunction due to increased Hcy is the most common and acceptable mechanism for increasing the risk of CAD.[36] Other observational studies represented that the elevated blood Hcy level is a risk factor for cardiovascular disorders.[32] The results of another *post hoc* analysis study demonstrated that high Hcy levels in patients with CKD were associated with increased CAD risk.[37] Based on the long-term cardiovascular risk assessment (for 29 months) in 175 dialysis patients, a 10 μmol/L increase in the Hcy level was associated with a 20% increase in cardiovascular problems.[38]

Therefore, it seems that lowering Hcy levels may limit or prevent cardiovascular events.[39] For example, in a meta-analysis of 30 different studies, a 25% reduction in Hcy levels was related to 11% and 19% reductions in ischemic heart disease and stroke, respectively.[13] However, in a systematic review of

15 randomized controlled trials (RCT) in 71,422 individuals, no difference was reported regarding the effects of Hcy-lowering interventions on reducing deaths or complications from myocardial infarction. In terms of stroke, this study showed a slight difference in the effect of Hcy-lowering interventions alone or compared with the placebo.[40] Nevertheless, it is yet unclear whether and how Hcy-reducing treatments may reduce CVD risk, and many researchers doubt such a link between Hcy and CVD.[39-41] Accordingly, further studies are needed to determine the exact association between decreased Hcy levels and CVD.

Effect of Homocysteine-Lowering Interventions in Chronic Kidney Diseases Patients

Folic acid

Folic acid is a water-soluble vitamin that is naturally found in plants with dark green leaves. Humans do not synthesize folate, thus daily needs are met through folic acid supplements or foods that are rich in this vitamin.[42] The role of folic acid is well known. More precisely, it is not only a significant factor in Hcy metabolism but its disturbance in homeostasis may be directly related to cardiovascular risk and CKD progression.[43,44] The maximum reduction in plasma Hcy concentrations can be achieved with a minimum dose (0.8 mg/day) of folic acid.[45] Numerous studies have evaluated the effects of lowering the concentration of Hcy with folic acid and its consequences on the progression of CKD or CVD events. In a 1-year randomized study, 81 hemodialysis patients were divided into three groups of control, folic acid 5, and 15 mg. The results revealed that although folic acid could significantly reduce Hcy concentrations, 88% of patients still had higher-than-normal Hcy concentrations, and higher doses of folic acid were not superior to lower doses. According to the results of this study, although lowering Hcy levels can reduce cardiovascular events, conclusions about this issue cannot be cited due to the limited number of participants and the short duration of the study.[46] In another RCT, hemodialysis patients treated with 10 mg of folic acid were categorized into dose reduction (5 mg folic acid) and dose increase (15 mg folic acid) groups. The findings of this study indicated that increasing the dose of folic acid causes a significant decrease in Hcy concentrations. However, it still could not make the concentration of Hcy normal.[47] Similarly, Tamadon *et al*. found that although folic acid significantly reduced Hcy concentrations, there was no difference between low-and high-dose treatment.[48] One reason for the nonnormalization of Hcy concentrations with folic acid can be related to the short duration of studies because the maximum clinical effects of folic acid can be obtained after six months.[49,50] Another trial examined the difference between folic acid and folinic acid in hemodialysis patients. Folinic acid is a shortened form of folic acid that acts similarly to folic acid as a vitamin. The results of the above-mentioned study showed that both folic and folinic acids cause a significant reduction in Hcy concentrations and can be safely used interchangeably in these patients.[51] Likewise, Delfino *et al*. concluded that folic acid therapy lowers Hcy concentrations while improving plasma antioxidant capacity, and therefore, may effectively reduce cardiovascular death.[50] Conversely, further studies found no link between a decrease in Hcy and a reduction in cardiovascular events. In a three-arm trial in 510 chronic hemodialysis patients, Wrone *et al*. reported no difference in death and cardiovascular events with folic acid at doses of 1, 5, or 15 mg/day.[52] In an atherosclerosis and folic acid supplementation trial, 315 CKD patients (with eGFR <25 ml/min) were treated with 15 mg/day folic acid or a placebo. After an average follow-up of 3.6 years, the results were not significant in providing the beneficial effects of folic acid regarding reducing cardiovascular mortality.[53] The results of a 2-year, double-blind, randomized, placebo-controlled trial on 186 patients with ESRD demonstrated that 10 mg of folic acid (three times a week) after each dialysis session could normalize Hcy concentrations in 92.3% of patients and cause a significant reduction in intima-media thickness. However, it caused no changes in cardiovascular events compared to the control group.[54] Contrarily, Righetti *et al*. concluded that folate treatment could decrease cardiovascular events in dialysis patients by reducing Hcy.[55] A summary of all the mentioned studies in this review is provided in Table 1.

Due to the inconsistent results and differences in the protocols of studies, the number of samples, the dose of folic acid, and the measured outcomes, in a meta-analysis of seven clinical trials, Qin *et al*. studied the reducing effects of Hcy on folic acid and cardiovascular events. Based on their report, folic acid treatment could reduce CVD risk by 15% in 3886 ESRD patients, especially if treated for a long time while not receiving folate supplements before starting the treatment.[2] Nevertheless, another meta-analysis of 11 trials for a total of 10,951 CKD patients showed that doses of folic acid, which decreased serum Hcy, had no effect on reducing cardiovascular events and should not be used for this purpose.[56] The controversy in the obtained results of these two meta-analyses was due to their differences in the criteria for entering clinical studies, the study population, and their methodological differences. Accordingly, additional studies are required to reveal the exact association between Hcy reduction and cardiovascular events in CKD patients.

Table 1. Selected clinical studies of homocysteine-lowering interventions in CKD patients

Study	Design/Intervention	Participants, *n*	End point	Findings
Thambyrajah *et al*., 2000	Double blind RCT: folic acid 5 mg versus placebo	100 predialysis patients	Hcy level, endothelial function	Significant reduction in Hcy, No differences in endothelial function
Righetti *et al*., 2003	RCT: folic acid 5, 15 mg versus control	81 hemodialysis patients	Hcy level, CV events	Significant reduction in Hcy, No differences in CV events
Wrone *et al*., 2004	Three arms, double blind RCT: folic acid 1 mg or 5 mg or 15 mg	510 hemodialysis patients	Hcy level, CV events	Significant reduction in Hcy, No differences in CV events
Zoungas *et al*., 2006	Double blind RCT (ASFAST): folic acid 15 mg versus placebo	315 CKD (eGFR <25 mL/min) patients	Hcy level, CV events	Significant reduction in Hcy, No differences in CV events
Righetti *et al*., 2006	Open prospective trial: folic acid 5 mg versus control	114 hemodialysis patients	Hcy level, CV events	Folic acid decreases CV events
Delfino *et al*., 2007	Double blinded RCT: folic acid 10 mg versus placebo	46 hemodialysis patients	Hcy level, plasma antioxidant capacity	Significant reduction in Hcy, improved the total plasma antioxidant capacity
Vianna *et al*., 2007	Double blind RCT: folic acid 5 mg versus placebo	97 hemodialysis patients	Hcy level, CV events	Significant reduction in Hcy, significant decrease in intima-media thickness, No differences in CV events
Ossareh *et al*., 2010	RCT: folic acid 5 mg versus 15 mg	80 hemodialysis patients	Hcy level	Significant reduction in Hcy with 15 mg folic acid
Soleimani *et al*., 2011	RCT: 15 mg of folic acid versus 15 mg of oral folinic acid	60 hemodialysis patients	Hcy level	Folic and folinic acid decreased the blood homocysteine level with no meaningful difference
Tamadon *et al*., 2011	RCT: 2, 5, 10, and 15 mg of folic acid	31 hemodialysis patients	Hcy level	Different doses of folic acid were not significantly different
Dierkes *et al*., 2000	RCT: folic acid 800 µg+ vitamin B12 6 µg+ vitamin B6 10 mg versus folic acid 160 µg+ vitamin B6 10 mg versus placebo	61 hemodialysis patients	Hcy level	Significant reduction in Hcy with preparation including 800 µg folic acid
Manns *et al*., 2001	Double blind RCT: folic acid 1 mg+ vitamin B12 1 mg versus control	81 hemodialysis patients	Hcy level	Significant reduction in Hcy
Álvarez *et al*., 2005	Double blind RCT: folic acid 5 mg+ vitamin B6 10 mg + vitamin B12 0.4 mg versus folic acid 15 mg+ vitamin B6 100 mg+ vitamin B12 1 mg	60 hemodialysis patients	Hcy level	No differences in two vitamin regimen
Tungkasereerak *et al*., 2006	Double blind RCT: folic acid 15 mg + vitamin B6 50 mg + vitamin B12 1 mg versus control (folic acid 5 mg)	54 hemodialysis patients	Hcy level, Intima-media thickness	Significant reduction in Hcy, No differences in Intima-media thickness
Jamison *et al*., 2007	Double blind RCT: folic acid 40 mg+ vitamin B6 100 mg+ vitamin B12 2 mg versus control	2056 CKD (eGFR ≤30 mL/min) patients	Hcy level, CV events	Significant reduction in Hcy, No differences in CV events
Mann *et al*., 2008	Double blind RCT: folic acid 2.5 mg + vitamin B6 50 mg + Vitamin B12 1 mg versus control	619 CKD (eGFR <60 mL/min) patients	Hcy level, CV events	Significant reduction in Hcy, No differences in CV events
Azadibakhsh *et al*., 2009	Double blind RCT: folic acid 5 mg+ vitamin B12 1 mg versus folic acid 15 mg+ vitamin B12 1 mg	36 hemodialysis patients	Hcy level	Significant reduction in Hcy with versus folic acid 15 mg+ vitamin B12 1 mg
Heinz *et al*., 2010	RCT: folic acid 5 mg+ vitamin B6 20 mg + Vitamin B12 50 µg versus control	650 hemodialysis patients	Hcy level, CV events	Significant reduction in Hcy, No differences in CV events
Tayebi *et al*., 2016	Double blinded RCT: vitamin B12 100 µg versus control	140 hemodialysis patients	Hcy level, plasma	Significant reduction in Hcy

Beavers *et al*., 2008	Double blind RCT: omega-3 6 g per day versus control	69 hemodialysis patients	Hcy level	No significant reduction in Hcy
Rasmussen *et al*., 2010	Double blind RCT: omega-3 1.7 g per day versus placebo	206 hemodialysis patients	Hcy level, lipid profile	No significant reduction in Hcy
Khosroshahi *et al*., 2013	RCT: omega-3 3 g per day versus placebo	100 hemodialysis patients	Hcy level	Significant reduction in Hcy
Ziaie *et al*., 2020	single group clinical trial: omega-3 1 g per day versus placebo	19 peritoneal dialysis patients	Hcy level, inflammatory markers and lipid profile	CRP, HS-CRP, and Hcy levels increased insignificantly, No significant effect on lipid profile
Scholze, *et al*., 2003	RCT: NAC 5 g IV during hemodialysis session versus placebo	20 hemodialysis patients	Hcy level	Significant reduction in Hcy after dialysis
Thaha *et al*., 2006	RCT: NAC 5 g IV during hemodialysis session versus placebo	60 hemodialysis patients	Hcy level	Significant reduction in Hcy after dialysis
Nascimento *et al*., 2010	RCT: NAC 1200 mg/day versus placebo	30 peritoneal dialysis patients	Hcy level	No significant reduction in Hcy
Renke *et al*., 2010	RCT: NAC 1200 mg/day versus placebo	20 patients with normal or slightly decreased kidney function (eGFR 61-163 ml/min)	Hcy level, Blood pressure	No significant reduction in Hcy and blood pressure
Urquhart, *et al*., 2007	RCT: 5.0 mg/kg of intravenous mesna or placebo at 2 separate dialysis sessions 1 week apart	5 hemodialysis patients	Hcy level	Significant reduction in Hcy after dialysis
Urquhart *et al*., 2008	Double blinded RCT: Mesna 5 mg/kg predialysis session versus placebo	48 hemodialysis patients	Hcy level	No significant reduction in Hcy
Cutler *et al*., 2009	RCT: Mesna 12 mg/kg predialysis session versus placebo	8 hemodialysis patients	Hcy level	No significant reduction in Hcy
Pakfetrat *et al*., 2013	RCT: zinc supplement 50 mg/day versus placebo	100 hemodialysis patients	Hcy level	Significant reduction in Hcy

CKD: chronic kidney disease, Hcy: homocysteine, CV: cardiovascular, RCT: randomized controlled trial, eGFR: estimated glomerular filtration rate, CRP: C-reactive protein, HS-CRP: high-sensitivity C-reactive protein, NAC: N-acetyl cysteine

Folic acid plus B vitamins

In addition to folate, B vitamins (including B12 and B6) are essential determinants of Hcy metabolism and act as a cofactor to convert Hcy to cysteine and methionine.[57-59] Some studies have shown the potential of supplements containing these vitamins to reduce circulating Hcy. The treatment of B vitamins to reduce Hcy and cardiovascular events, the risks attributed to Hcy, has been investigated. The results of these mixed experiments and their collective interpretation are still controversial due to design heterogeneity, study limitations, and other considerations.[60-62]

Although several studies on healthy populations and patients have evaluated the effect of different doses of folic acid supplementations in reducing Hcy, a few of them have considered the independent effects of Vitamin B12.[57] A recent clinical trial has represented that Vitamin B12 alone can significantly reduce Hcy in hemodialysis patients.[63] However, most clinical studies have examined the effects of combined treatment with folic acid and B vitamins. In a parallel clinical study involving three treatment groups, Dierkes *et al*. found that a multivitamin supplement containing at least 800 μg of folic acid could significantly decrease Hcy in ESRD patients by nearly 50%. It should be noted that two groups of patients received two different multivitamin formulations, and the third group received no multivitamins (the placebo group). In contrast, supplements containing only 160 μg of folic acid failed to reduce Hcy compared to the placebo.[32] In a randomized, double-blind trial on 81 hemodialysis patients, the addition of 1 mg of oral Vitamin B12 to patients, who did not meet Vitamin B12 deficiency by laboratory standards and received 1 mg of folic acid, reduced total Hcy. However, only 13.6% of patients had normal Hcy levels at the end.[35] Similar results were reported in another study.[64] The difference between the efficacy of multivitamins containing folic acid, Vitamin B12, and Vitamin B6 in the daily dose and multivitamin

supplementations in the super physiological daily dose in hemodialysis patients was compared in 43 patients. The results showed that a water-soluble multivitamin combination with two different doses effectively lowered Hcy levels although Hcy reached normal levels only in a small percentage of patients. Accordingly, the decrease rate in the Hcy level is directly related to the basal level of Hcy and folic acid.[65]

In another randomized, double-blind trial of 54 chronic hemodialysis patients, 6 months of treatment consisting of 15 mg of folic acid daily, 50 mg of Vitamin B6, and 1 mg of vitamin B12 compared with 5 mg of folic acid significantly decreased the serum level of Hcy. Intima-media thickness was also measured before and after the intervention. Although there was no significant difference in intima-media thickness between the two groups, the treatment group showed a tendency to have less thickness in the sixth month.[66]

In a large-scale double-blind, RCT, Jamison *et al*. treated 2056 CKD patients (with eGFR ≤30 ml/min) with high doses of supplements (including 40 mg folic acid, 100 mg Vitamin B6, and 2 mg Vitamin B12) and followed up patients for all causes of mortality for 3.2 years. Their results indicated that treatment with high doses of folic acid and B vitamins did not improve survival or reduce the incidence of vascular diseases. These negative outcomes may be due to the higher burden of CVD and less than optimal compliance with treatment.[67]

In addition, Mann *et al*. designed an RCT of 619 chronic hemodialysis patients for 5 years with 2.5 mg of folic acid, 1 mg of vitamin B12, and 50 mg of Vitamin B6 versus a placebo. Although treatment with B vitamins decreased Hcy levels in participants with CKD, there was no difference in the risk of cardiovascular events between the two groups.[68] The results of a multicenter analysis of 650 hemodialysis patients also demonstrated that active treatment with folic acid, Vitamin B12, and Vitamin B6 did not significantly reduce overall mortality and cardiovascular risk in patients with ESRD.[69]

Due to the high importance of interventions that can decrease mortality or cardiovascular events in CKD patients and the conflicting results of clinical studies, several meta-analyses have examined the cardiovascular benefits of Hcy-lowering therapies. Likewise, Heinz *et al*. conducted a meta-analysis on a total of 23 retrospective and observational studies regarding the effect of Hcy on overall mortality and CVD risk and analyses of five RCTs to evaluate the reduction of cardiovascular events and mortality with B vitamin treatment. Based on their findings, Hcy levels are generally a risk factor for cardiovascular events and overall mortality, and taking Vitamin B supplements significantly reduces CVD while not decreasing the overall risk of mortality.[21] It should be noted that one of the limitations of this study was the small number of analyzed RCTs. In addition, some of these RCTs involved a small number of patients, or the study protocol was not of randomized or placebo-controlled type. Another meta-analysis of 4836 patients with CKD assessed the relationship between Hcy-lowering therapy and CVD. According to the results of this review, Hcy-lowering treatment was not associated with a significant reduction in the risk of CVD, stroke, and all-cause mortality.[70] A meta-analysis of 14 studies represented that Hcy-lowering therapy based on Vitamin B supplements was related to a significant decline in stroke risk in patients with CKD.[71] A recent meta-analysis examined the benefits and harms of folic acid treatment, Vitamin B6, and Vitamin B12, on all-cause mortality, and cardiovascular events in chronic hemodialysis patients. The results of the analysis of six studies on 2452 hemodialysis patients showed no significant difference in mortality and cardiovascular events in patients treated with Hcy-lowering supplements.[8]

In general, although the available evidence strongly supports the reduction of Hcy levels with medical treatments (i.e., folic acid, Vitamin B12, and Vitamin B6), the benefits of these vitamins in reducing mortality and cardiovascular events in patients with CKD and ESRD are not yet known in most cases.

Omega-3 fatty acids

In addition to Hcy-reducing treatment with folic acid and B vitamins, omega-3 unsaturated fatty acids have been considered as a group of nutrients with a potential protective effect on the cardiovascular system.[72] Data from various epidemiological studies suggest that omega-3 fatty acid supplementation effectively reduces the risk of CVD.[73-76] Based on some reports, omega-3 fatty acids can also lower cholesterol, triglycerides, and inflammation.[77,78] Although several RCTs have suggested that omega-3 supplementations may decrease CVD risk factors,[79-82] other studies have shown no beneficial effect regarding reducing cardiovascular events.[83-86]

Some clinical trials investigated the association between Hcy and omega-3 fatty acid intake.[87] Plasma Hcy levels were reported to be inversely related to omega-3 supplementation.[84] The mechanism of action of omega-3 in lowering Hcy levels is not fully understood yet. However, it has been indicated that omega-3 fatty acids may regulate the gene expression of enzymes or the activity of enzymes involved in

plasma Hcy metabolism.[88] Therefore, a limited number of studies have evaluated the impact of omega-3 fatty acids on serum Hcy levels in patients with ESRD at different doses and durations. Khosroshahi *et al*. treated 100 hemodialysis patients with 3 grams of omega-3 daily or a placebo for two months and assessed Hcy levels before and after the intervention. They showed a significant reduction in Hcy levels with short-term administration of omega-3 fatty acids in hemodialysis patients.[83] Conversely, other clinical trials failed to represent Hcy-lowering effects with omega-3 fatty acids. In a study by Rasmussen *et al*. on 206 patients with documented CVD undergoing hemodialysis in Denmark, it was found that omega-3 (1.7 grams per day for 6 months) had no significant effect on patients' Hcy levels. Nonetheless, there was an inverse relationship between plasma Hcy and docosahexaenoic acid contents in serum phospholipids.[84] A similar study was performed on 69 hemodialysis patients, and it was reported that omega-3 (6 grams/day for up to 6 months) did not reduce Hcy levels in ESRD patients.[89] In an open-label, single-group clinical trial on peritoneal dialysis patients, 21 cases were treated with 1 g/day of omega-3, followed by assessing inflammatory markers including Hcy and lipid profiles. After three months of follow-up, the results revealed that omega-3 supplementation had no significant effect on Hcy levels.[90]

Moreover, Xu *et al*. studied the effects of omega-3 on serum lipids and vascular inflammation in ESRD patients. The results of data analysis from a total of 20 RCTs including 1461 patients demonstrated that omega-3 supplementation significantly decreased triglycerides, low-density lipoprotein cholesterol, and C-reactive protein while having no significant impact on other inflammatory markers including Hcy.[88]

There are currently a limited number of studies regarding the impact of omega-3 on lowering Hcy levels in ESRD patients. Due to the conflicting findings of the dose or duration of the required treatment and the underlying mechanism, the reported results are inconclusive. Therefore, further studies are necessary for evaluating its effects on Hcy and other inflammatory markers and cardiovascular outcomes in this group of patients.

N-acetyl cysteine

NAC, a sulfur-containing and thiol-containing amino acid, is the primary precursor to the antioxidant glutathione[91,92] and may reduce Hcy-induced oxidative stress through its antioxidant properties. In addition to these properties, NAC, when orally or intravenously administered to healthy individuals, can displace circulating thiols from its protein binding site by modifying the binding of thiol components, increasing Hcy urination[93,94] and decreasing total plasma Hcy levels.[94,95]

In a placebo-controlled crossover study on 20 ESRD patients, Scholze *et al*. found that intravenous administration of NAC during dialysis could significantly increase Hcy clearance through dialysis and thus reduce serum Hcy levels. They also showed that NAC could improve pulse pressure and endothelial function by reducing Hcy and its antioxidant effects.[96] Similar results were reported in another study.[97] However, in a placebo-controlled study of 30 peritoneal dialysis patients, the oral administration of NAC over 8 weeks failed to significantly decrease plasma Hcy concentrations. However, this short-term oral NAC treatment significantly reduced circulating interleukin 6 levels and suppressed the inflammatory response.[98] The effect of oral NAC (1200 mg) with the renin-angiotensin system blockade treatment on blood pressure and cardiovascular markers (including Hcy) was compared in nondiabetic patients with normal or slightly decreased renal function (eGFR 61–163 ml/min). Based on the results, NAC did not affect blood pressure and Hcy in nondiabetic patients with CKD.[99]

Overall, although NAC appears to have beneficial effects on reducing the risk of cardiovascular events in hemodialysis patients with its antioxidant effects (13 of 2010 trials), its effects on Hcy levels and cardiovascular outcomes are still unclear and thus are not currently recommended for this purpose in CKD patients.

Mesna

Similar to NAC, mesna (sodium-2-mercaptoethanesulfonic acid) has been used as a thiol exchange agent in combination with hemodialysis to reduce Hcy levels. *In vitro*, mesna released 36.5% of the protein-bound Hcy within 30 min. *In vivo*, intravenous bolus 5 mg/kg pre-dialysis significantly decreased Hcy after dialysis.[100] However, the administration of mesna (5 mg/kg three times a week) before dialysis for 8 weeks did not significantly reduce Hcy concentrations.[101] Due to the safety and limited side effects of mesna, increasing the dose to 12 mg/kg was investigated. and the results showed that increasing its dose could not lower Hcy concentrations.[102] Although mesna could reduce Hcy levels after dialysis, its long-term treatment could not represent positive effects in this regard.

Other Supplements

Although no study has so far determined the role of zinc in reducing Hcy, a double-blind, RCT evaluated the

effect of zinc supplementation on serum Hcy levels in ESRD patients. The administration of zinc for 6 weeks in 100 hemodialysis patients could significantly decrease Hcy compared to the placebo.[103] However, as far as it is known, no further studies have been performed on ESRD patients.

Discussion and Conclusion

Cardiovascular mortality rates are high in ESRD patients, and high Hcy levels in these patients have been studied as an important therapeutic target. Routine Hcy measurement is not currently recommended in this respect. In addition, reviewing the published evidence suggests that the treatment of hyperhomocysteinemia may not currently be a reasonable therapeutic goal for reducing cardiovascular risk in CKD patients. The question of whether Hcy-lowering therapies reduce the risk of these cardiovascular complications is still of increasing concern in the general population and the ESRD population. Different responses to Hcy-reducing therapies may be influenced by differences in gender, genotype, and nutritional status of these populations. Data on the optimal dose of supplements, the exact target of Hcy, and the duration of treatment are still limited for examining their effectiveness.

Overall, it seems reasonable to consider folic acid with/without supplementation with B vitamins after the careful assessment of folate status as adjunctive therapy in patients with CKD. Agents such as NAC and mesna may displace Hcy from the protein binding site, thus facilitating its removal during dialysis. Nevertheless, their use has not been effective in the continued consumption. Although the exact dose and frequency of use have not been determined, omega-3 and other related antioxidants are also interesting agents that have the potential to lower Hcy levels. Further, high doses of omega-3 can be safely used in CKD patients.

Robust interventional studies are still necessary for determining whether plasma Hcy depletion has beneficial effects on CKD patients. Finally, the difference in effectiveness between various Hcy-lowering treatments has not been compared in the literature.

Authors' Contribution

S. Badri, S. Vahdat, S. Seirafian, and M. Pourfarzam developed the idea of research and criticized the findings. T. Gholipur, and S. Ataei searched and recruited the studies. All authors contributed in manuscript preparation and revision.

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Conflicts of interest

There are no conflicts of interest.

References

1. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. The New England journal of medicine. 2004;351(13):1296-305.
2. Qin X, Huo Y, Langman CB, Hou F, Chen Y, Matossian D, et al. Folic acid therapy and cardiovascular disease in ESRD or advanced chronic kidney disease: a meta-analysis. Clinical journal of the American Society of Nephrology: CJASN. 2011;6(3):482-8.
3. Weaver DJ, Mitsnefes M. Cardiovascular Disease in Children and Adolescents With Chronic Kidney Disease. Seminars in nephrology. 2018;38(6):559-69.
4. Gholipur-Shahraki T, Feizi A, Mortazavi M, Badri S. Effects of Carnitine on Nutritional Parameters in Patients with Chronic Kidney Disease: An Updated Systematic Review and Meta-Analysis. J Res Pharm Pract. 2018;7(2):57-68.
5. Badri S, Dashti-Khavidaki S, Lessan-Pezeshki M, Abdollahi M. A review of the potential benefits of pentoxifylline in diabetic and non-diabetic proteinuria. Journal of pharmacy & pharmaceutical sciences: a publication of the Canadian Society for Pharmaceutical Sciences, Societe canadienne des sciences pharmaceutiques. 2011;14(1):128-37.
6. Baigent C, Burbury K, Wheeler D. Premature cardiovascular disease in chronic renal failure. Lancet (London, England). 2000;356(9224):147-52.
7. Bostom AG, Carpenter MA, Kusek JW, Levey AS, Hunsicker L, Pfeffer MA, et al. Homocysteine-lowering and cardiovascular disease outcomes in kidney transplant recipients: primary results from the Folic Acid for Vascular Outcome Reduction in Transplantation trial. Circulation. 2011;123(16):1763-70.
8. Nigwekar SU, Kang A, Zoungas S, Cass A, Gallagher MP, Kulshrestha S, *et al*. Interventions for lowering plasma homocysteine levels in dialysis patients. The Cochrane database of systematic reviews. 2016(5):Cd004683.
9. Kang A, Nigwekar SU, Perkovic V, Kulshrestha S, Zoungas S, Navaneethan SD, *et al*. Interventions for lowering plasma homocysteine levels in kidney transplant recipients. The Cochrane database of systematic reviews. 2015(5):Cd007910.
10. Wald DS, Law M, Morris JK. Homocysteine and cardiovascular disease: evidence on causality from a meta-analysis. BMJ (Clinical research ed). 2002;325(7374):1202.
11. Liu M, Li XC, Lu L, Cao Y, Sun RR, Chen S, *et al*. Cardiovascular disease and its relationship with chronic kidney disease. European review for medical and pharmacological sciences. 2014;18(19):2918-26.
12. Bayés B, Pastor MC, Bonal J, Romero R. "New" cardiovascular risk factors in patients with chronic kidney disease: role of folic acid treatment. Kidney international Supplement. 2005(93):S39-43.
13. Homocysteine and risk of ischemic heart disease and stroke: a meta-analysis. Jama. 2002;288(16):2015-22.
14. Nerbass FB, Draibe SA, Feiten SF, Chiarello PG, Vannucchi H, Cuppari L. Homocysteine and its determinants in nondialyzed chronic kidney disease patients. Journal of the American Dietetic Association. 2006;106(2):267-70.
15. Menon V, Wang X, Greene T, Beck GJ, Kusek JW, Selhub J,

et al. Homocysteine in chronic kidney disease: Effect of low protein diet and repletion with B vitamins. Kidney international. 2005;67(4):1539-46.

16. Locatelli F, Pisoni RL, Combe C, Bommer J, Andreucci VE, Piera L, *et al*. Anaemia in haemodialysis patients of five European countries: association with morbidity and mortality in the Dialysis Outcomes and Practice Patterns Study (DOPPS). Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2004;19(1):121-32.
17. van Guldener C, Janssen MJ, Stehouwer CD, Jakobs C, Bronzwaer JG, Surachno J, *et al*. The effect of renal transplantation on hyperhomocysteinaemia in dialysis patients, and the estimation of renal homocysteine extraction in patients with normal renal function. The Netherlands journal of medicine. 1998;52(2):58-64.
18. Guttormsen AB, Ueland PM, Svarstad E, Refsum H. Kinetic basis of hyperhomocysteinemia in patients with chronic renal failure. Kidney international. 1997;52(2):495-502.
19. Robinson K. Renal disease, homocysteine, and cardiovascular complications. Circulation. 2004;109(3):294-5.
20. Suliman ME, Lindholm B, Bárány P, Qureshi AR, Stenvinkel P. Homocysteine-lowering is not a primary target for cardiovascular disease prevention in chronic kidney disease patients. Seminars in dialysis. 2007;20(6):523-9.
21. Heinz J, Kropf S, Luley C, Dierkes J. Homocysteine as a risk factor for cardiovascular disease in patients treated by dialysis: a meta-analysis. American journal of kidney diseases: the official journal of the National Kidney Foundation. 2009;54(3):478-89.
22. Cianciolo G, De Pascalis A, Di Lullo L, Ronco C, Zannini C, La Manna G. Folic Acid and Homocysteine in Chronic Kidney Disease and Cardiovascular Disease Progression: Which Comes First? Cardiorenal medicine. 2017;7(4):255-66.
23. Langan RC, Goodbred AJ. Vitamin B12 Deficiency: Recognition and Management. American family physician. 2017;96(6):384-9.
24. Bostom AG, Shemin D, Gohh RY, Beaulieu AJ, Bagley P, Massy ZA, *et al*. Treatment of hyperhomocysteinemia in hemodialysis patients and renal transplant recipients. Kidney international Supplement. 2001;78:S246-52.
25. Bostom A, Brosnan JT, Hall B, Nadeau MR, Selhub J. Net uptake of plasma homocysteine by the rat kidney in vivo. Atherosclerosis. 1995;116(1):59-62.
26. Friedman AN, Bostom AG, Laliberty P, Selhub J, Shemin D. The effect of N-acetylcysteine on plasma total homocysteine levels in hemodialysis: a randomized, controlled study. American journal of kidney diseases: the official journal of the National Kidney Foundation. 2003;41(2):442-6.
27. Righetti M. Homocysteine-lowering vitamin B treatment decreases cardiovascular events in hemodialysis patients. Clinical chemistry and laboratory medicine. 2007;45(12):1586-9.
28. Brattström L, Wilcken DE. Homocysteine and cardiovascular disease: cause or effect? The American journal of clinical nutrition. 2000;72(2):315-23.
29. van Guldener C, Stehouwer CD. Homocysteine and methionine metabolism in renal failure. Seminars in vascular medicine. 2005;5(2):201-8.
30. Arnadottir M, Hultberg B, Nilsson-Ehle P, Thysell H. The effect of reduced glomerular filtration rate on plasma total homocysteine concentration. Scandinavian journal of clinical and laboratory investigation. 1996;56(1):41-6.
31. Selhub J, Miller JW. The pathogenesis of homocysteinemia: interruption of the coordinate regulation by S-adenosylmethionine of the remethylation and transsulfuration of homocysteine. The American journal of clinical nutrition. 1992;55(1):131-8.
32. Dierkes J, Domröse U, Bosselmann KP, Neumann KH, Luley C. Homocysteine lowering effect of different multivitamin preparations in patients with end-stage renal disease. Journal of renal nutrition : the official journal of the Council on Renal Nutrition of the National Kidney Foundation. 2001;11(2):67-72.
33. Wilcken DE, Gupta VJ, Betts AK. Homocysteine in the plasma of renal transplant recipients: effects of cofactors for methionine metabolism. Clinical science (London, England : 1979). 1981;61(6):743-9.
34. Falk E, Zhou J, Møller J. Homocysteine and atherothrombosis. Lipids. 2001;36 Suppl:S3-11.
35. Manns B, Hyndman E, Burgess E, Parsons H, Schaefer J, Snyder F, *et al*. Oral vitamin B(12) and high-dose folic acid in hemodialysis patients with hyper-homocyst(e)inemia. Kidney international. 2001;59(3):1103-9.
36. Robinson K, Gupta A, Dennis V, Arheart K, Chaudhary D, Green R, *et al*. Hyperhomocysteinemia confers an independent increased risk of atherosclerosis in end-stage renal disease and is closely linked to plasma folate and pyridoxine concentrations. Circulation. 1996;94(11):2743-8.
37. Spence JD, Bang H, Chambless LE, Stampfer MJ. Vitamin Intervention For Stroke Prevention trial: an efficacy analysis. Stroke. 2005;36(11):2404-9.
38. Zoccali C, Benedetto FA, Mallamaci F, Tripepi G, Fermo I, Focà A, *et al*. Inflammation is associated with carotid atherosclerosis in dialysis patients. Creed Investigators. Cardiovascular Risk Extended Evaluation in Dialysis Patients. Journal of hypertension. 2000;18(9):1207-13.
39. Wu CC, Zheng CM, Lin YF, Lo L, Liao MT, Lu KC. Role of homocysteine in end-stage renal disease. Clinical biochemistry. 2012;45(16-17):1286-94.
40. Martí-Carvajal AJ, Solà I, Lathyris D, Dayer M. Homocysteine-lowering interventions for preventing cardiovascular events. The Cochrane database of systematic reviews. 2017;8(8):Cd006612.
41. Faeh D, Chiolero A, Paccaud F. Homocysteine as a risk factor for cardiovascular disease: should we (still) worry about? Swiss medical weekly. 2006;136(47-48):745-56.
42. Liew SC. Folic acid and diseases - supplement it or not? Revista da Associacao Medica Brasileira (1992). 2016;62(1):90-100.
43. Cianciolo G, La Manna G, Colì L, Donati G, D'Addio F, Persici E, *et al*. 5-methyltetrahydrofolate administration is associated with prolonged survival and reduced inflammation in ESRD patients. American journal of nephrology. 2008;28(6):941-8.
44. Soohoo M, Ahmadi SF, Qader H, Streja E, Obi Y, Moradi H, *et al*. Association of serum vitamin B12 and folate with mortality in incident hemodialysis patients. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2017;32(6):1024-32.
45. Dose-dependent effects of folic acid on blood concentrations of homocysteine: a meta-analysis of the randomized trials. The American journal of clinical nutrition. 2005;82(4):806-12.
46. Righetti M, Ferrario GM, Milani S, Serbelloni P, La Rosa L, Uccellini M, *et al*. Effects of folic acid treatment on homocysteine levels and vascular disease in hemodialysis patients. Medical science monitor : international medical journal of experimental and clinical research. 2003;9(4):Pi19-24.
47. Ossareh S, Shayan-Moghaddam H, Salimi A, Asgari M, Farrokhi F. Different doses of oral folic acid for homocysteine-lowering therapy in patients on hemodialysis: a randomized controlled trial. Iranian journal of kidney diseases. 2009;3(4):227-33.
48. Tamadon MR, Jamshidi L, Soliemani A, Ghorbani R, Malek

F, Malek M. Effect of different doses of folic acid on serum homocysteine level in patients on hemodialysis. Iranian journal of kidney diseases. 2011;5(2):93-6.

49. Pöge U, Look M, Gerhardt T, Klehr HU, Sauerbruch T, Woitas RP. Intravenous treatment of hyperhomocysteinemia in patients on chronic hemodialysis--a pilot study. Renal failure. 2004;26(6):703-8.
50. Alvares Delfino VD, de Andrade Vianna AC, Mocelin AJ, Barbosa DS, Mise RA, Matsuo T. Folic acid therapy reduces plasma homocysteine levels and improves plasma antioxidant capacity in hemodialysis patients. Nutrition (Burbank, Los Angeles County, Calif). 2007;23(3):242-7.
51. Soleimani A, Usefzadeh M, Mianehsaz E, Foroozanfard F, Nikoueinejad H, Moraveji SA, *et al*. Comparison of oral folic acid and folinic acid on blood homocysteine level of patients on hemodialysis. Iranian journal of kidney diseases. 2011;5(1):45-9.
52. Wrone EM, Hornberger JM, Zehnder JL, McCann LM, Coplon NS, Fortmann SP. Randomized trial of folic acid for prevention of cardiovascular events in end-stage renal disease. Journal of the American Society of Nephrology : JASN. 2004;15(2):420-6.
53. Zoungas S, McGrath BP, Branley P, Kerr PG, Muske C, Wolfe R, *et al*. Cardiovascular morbidity and mortality in the Atherosclerosis and Folic Acid Supplementation Trial (ASFAST) in chronic renal failure: a multicenter, randomized, controlled trial. Journal of the American College of Cardiology. 2006;47(6):1108-16.
54. Vianna AC, Mocelin AJ, Matsuo T, Morais-Filho D, Largura A, Delfino VA, *et al*. Uremic hyperhomocysteinemia: a randomized trial of folate treatment for the prevention of cardiovascular events. Hemodialysis international International Symposium on Home Hemodialysis. 2007;11(2):210-6.
55. Righetti M, Serbelloni P, Milani S, Ferrario G. Homocysteine-lowering vitamin B treatment decreases cardiovascular events in hemodialysis patients. Blood purification. 2006;24(4):379-86.
56. Jardine MJ, Kang A, Zoungas S, Navaneethan SD, Ninomiya T, Nigwekar SU, *et al*. The effect of folic acid based homocysteine lowering on cardiovascular events in people with kidney disease: systematic review and meta-analysis. BMJ (Clinical research ed). 2012;344:e3533.
57. McNulty H, Pentieva K, Hoey L, Ward M. Homocysteine, B-vitamins and CVD. The Proceedings of the Nutrition Society. 2008;67(2):232-7.
58. Finkelstein JD. The metabolism of homocysteine: pathways and regulation. European journal of pediatrics. 1998;157 Suppl 2:S40-4.
59. Toborek M, Hennig B. Dietary methionine imbalance, endothelial cell dysfunction and atherosclerosis. Nutrition Research. 1996;16(7):1251-66.
60. Clarke R, Bennett D, Parish S, Lewington S, Skeaff M, Eussen SJ, *et al*. Effects of homocysteine lowering with B vitamins on cognitive aging: meta-analysis of 11 trials with cognitive data on 22,000 individuals. The American journal of clinical nutrition. 2014;100(2):657-66.
61. McCaddon A, Miller JW. Assessing the association between homocysteine and cognition: reflections on Bradford Hill, meta-analyses, and causality. Nutrition reviews. 2015;73(10):723-35.
62. Smith AD, de Jager CA, Refsum H, Rosenberg IH. Homocysteine lowering, B vitamins, and cognitive aging. The American journal of clinical nutrition. 2015;101(2):415-6.
63. Tayebi A, Biniaz V, Savari S, Ebadi A, Shermeh MS, Einollahi B, et al. Effect of Vitamin B12 supplementation on serum homocysteine in patients undergoing hemodialysis: A randomized controlled trial. Saudi journal of kidney diseases and transplantation : an official publication of the Saudi Center for Organ Transplantation, Saudi Arabia. 2016;27(2):256-62.
64. Azadibakhsh N, Hosseini RS, Atabak S, Nateghiyan N, Golestan B, Rad AH. Efficacy of folate and vitamin B12 in lowering homocysteine concentrations in hemodialysis patients. Saudi journal of kidney diseases and transplantation : an official publication of the Saudi Center for Organ Transplantation, Saudi Arabia. 2009;20(5):779-88.
65. Sánchez Alvarez JE, Pérez Tamajón L, Hernández D, Alvarez González A, Delgado P, Lorenzo V. [Efficacy and safety of two vitamin supplement regimens on homocysteine levels in hemodialysis patients. Prospective, randomized clinical trial]. Nefrologia : publicacion oficial de la Sociedad Espanola Nefrologia. 2005;25(3):288-96.
66. Tungkasereerak P, Ong-ajyooth L, Chaiyasoot W, Ong-ajyooth S, Leowattana W, Vasuvattakul S, *et al*. Effect of short-term folate and vitamin B supplementation on blood homocysteine level and carotid artery wall thickness in chronic hemodialysis patients. Journal of the Medical Association of Thailand = Chotmaihet thangphaet. 2006;89(8):1187-93.
67. Jamison RL, Hartigan P, Kaufman JS, Goldfarb DS, Warren SR, Guarino PD, *et al*. Effect of homocysteine lowering on mortality and vascular disease in advanced chronic kidney disease and end-stage renal disease: a randomized controlled trial. Jama. 2007;298(10):1163-70.
68. Mann JF, Sheridan P, McQueen MJ, Held C, Arnold JM, Fodor G, *et al*. Homocysteine lowering with folic acid and B vitamins in people with chronic kidney disease--results of the renal Hope-2 study. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2008;23(2):645-53.
69. Heinz J, Kropf S, Domröse U, Westphal S, Borucki K, Luley C, *et al*. B vitamins and the risk of total mortality and cardiovascular disease in end-stage renal disease: results of a randomized controlled trial. Circulation. 2010;121(12):1432-8.
70. Pan Y, Guo LL, Cai LL, Zhu XJ, Shu JL, Liu XL, *et al*. Homocysteine-lowering therapy does not lead to reduction in cardiovascular outcomes in chronic kidney disease patients: a meta-analysis of randomised, controlled trials. The British journal of nutrition. 2012;108(3):400-7.
71. Ji Y, Tan S, Xu Y, Chandra A, Shi C, Song B, *et al*. Vitamin B supplementation, homocysteine levels, and the risk of cerebrovascular disease: a meta-analysis. Neurology. 2013;81(15):1298-307.
72. Delgado-Lista J, Perez-Martinez P, Lopez-Miranda J, Perez-Jimenez F. Long chain omega-3 fatty acids and cardiovascular disease: a systematic review. The British journal of nutrition. 2012;107 Suppl 2:S201-13.
73. McKenney JM, Sica D. Prescription omega-3 fatty acids for the treatment of hypertriglyceridemia. American journal of health-system pharmacy: AJHP: official journal of the American Society of Health-System Pharmacists. 2007;64(6):595-605.
74. Mita T, Watada H, Ogihara T, Nomiyama T, Ogawa O, Kinoshita J, *et al*. Eicosapentaenoic acid reduces the progression of carotid intima-media thickness in patients with type 2 diabetes. Atherosclerosis. 2007;191(1):162-7.
75. Garrido-Sánchez L, García-Fuentes E, Rojo-Martínez G, Cardona F, Soriguer F, Tinahones FJ. Inverse relation between levels of anti-oxidized-LDL antibodies and eicosapentanoic acid (EPA). The British journal of nutrition. 2008;100(3):585-9.
76. Ubeda N, Achón M, Varela-Moreiras G. Omega 3 fatty acids in the elderly. The British journal of nutrition. 2012;107 Suppl 2:S137-51.
77. Schunck WH, Konkel A, Fischer R, Weylandt KH. Therapeutic potential of omega-3 fatty acid-derived epoxyeicosanoids in

cardiovascular and inflammatory diseases. Pharmacology & therapeutics. 2018;183:177-204.
78. Calder PC. Omega-3 fatty acids and inflammatory processes: from molecules to man. Biochemical Society transactions. 2017;45(5):1105-15.
79. Daud ZA, Tubie B, Adams J, Quainton T, Osia R, Tubie S, *et al*. Effects of protein and omega-3 supplementation, provided during regular dialysis sessions, on nutritional and inflammatory indices in hemodialysis patients. Vascular health and risk management. 2012;8:187-95.
80. Kooshki A, Taleban FA, Tabibi H, Hedayati M. Effects of omega-3 fatty acids on serum lipids, lipoprotein (a), and hematologic factors in hemodialysis patients. Renal failure. 2011;33(9):892-8.
81. Bouzidi N, Mekki K, Boukaddoum A, Dida N, Kaddous A, Bouchenak M. Effects of omega-3 polyunsaturated fatty-acid supplementation on redox status in chronic renal failure patients with dyslipidemia. Journal of renal nutrition : the official journal of the Council on Renal Nutrition of the National Kidney Foundation. 2010;20(5):321-8.
82. Khalatbari Soltani S, Jamaluddin R, Tabibi H, Mohd Yusof BN, Atabak S, Loh SP, *et al*. Effects of flaxseed consumption on systemic inflammation and serum lipid profile in hemodialysis patients with lipid abnormalities. Hemodialysis international International Symposium on Home Hemodialysis. 2013;17(2):275-81.
83. Tayebi-Khosroshahi H, Dehgan R, Habibi Asl B, Safaian A, Panahi F, Estakhri R, *et al*. Effect of omega-3 supplementation on serum level of homocysteine in hemodialysis patients. Iranian journal of kidney diseases. 2013;7(6):479-84.
84. Rasmussen LE, Svensson M, Jørgensen KA, Schmidt EB, Christensen JH. The content of docosahexaenoic acid in serum phospholipid is inversely correlated with plasma homocysteine levels in patients with end-stage renal disease. Nutrition research (New York, NY). 2010;30(8):535-40.
85. Bowden RG, Jitomir J, Wilson RL, Gentile M. Effects of omega-3 fatty acid supplementation on lipid levels in endstage renal disease patients. Journal of renal nutrition : the official journal of the Council on Renal Nutrition of the National Kidney Foundation. 2009;19(4):259-66.
86. Lok CE, Moist L, Hemmelgarn BR, Tonelli M, Vazquez MA, Dorval M, *et al*. Effect of fish oil supplementation on graft patency and cardiovascular events among patients with new synthetic arteriovenous hemodialysis grafts: a randomized controlled trial. Jama. 2012;307(17):1809-16.
87. Rizzo G, Laganà AS. The Link between Homocysteine and Omega-3 Polyunsaturated Fatty Acid: Critical Appraisal and Future Directions. Biomolecules. 2020;10(2).
88. Xu T, Sun Y, Sun W, Yao L, Sun L, Liu L, *et al*. Effect of omega-3 fatty acid supplementation on serum lipids and vascular inflammation in patients with end-stage renal disease: a meta-analysis. Scientific reports. 2016;6:39346.
89. Beavers KM, Beavers DP, Bowden RG, Wilson RL, Gentile M. Omega-3 fatty acid supplementation and total homocysteine levels in end-stage renal disease patients. Nephrology (Carlton, Vic). 2008;13(4):284-8.
90. Ziaie S, Polroudi Moghaddam M, Samadian F, Sistanizad M, Afzal G, Saffaei A, *et al*. Omega-3 in Patients Undergoing Continuous Ambulatory Peritoneal Dialysis, Effects on Inflammatory Markers and Lipid Profile. Iranian journal of kidney diseases. 2020;14(2):126-32.
91. Mokhtari V, Afsharian P, Shahhoseini M, Kalantar SM, Moini A. A Review on Various Uses of N-Acetyl Cysteine. Cell journal. 2017;19(1):11-7.
92. Badri S, Soltani R, Sayadi M, Khorvash F, Meidani M, Taheri S. Effect of N-acetylcysteine against Vancomycin-Induced Nephrotoxicity: A Randomized Controlled Clinical Trial. Archives of Iranian medicine. 2020;23(6):397-402.
93. Yenicerioglu Y, Yilmaz O, Sarioglu S, Ormen M, Akan P, Celik A, *et al*. Effects of N-acetylcysteine on radiocontrast nephropathy in rats. Scandinavian journal of urology and nephrology. 2006;40(1):63-9.
94. Ventura P, Panini R, Pasini MC, Scarpetta G, Salvioli G. N - Acetyl-cysteine reduces homocysteine plasma levels after single intravenous administration by increasing thiols urinary excretion. Pharmacological research. 1999;40(4):345-50.
95. Hultberg B, Andersson A, Masson P, Larson M, Tunek A. Plasma homocysteine and thiol compound fractions after oral administration of N-acetylcysteine. Scandinavian journal of clinical and laboratory investigation. 1994;54(6):417-22.
96. Scholze A, Rinder C, Beige J, Riezler R, Zidek W, Tepel M. Acetylcysteine reduces plasma homocysteine concentration and improves pulse pressure and endothelial function in patients with end-stage renal failure. Circulation. 2004;109(3):369-74.
97. Thaha M, Yogiantoro M, Tomino Y. Intravenous N-acetylcysteine during haemodialysis reduces the plasma concentration of homocysteine in patients with end-stage renal disease. Clinical drug investigation. 2006;26(4):195-202.
98. Nascimento MM, Suliman ME, Silva M, Chinaglia T, Marchioro J, Hayashi SY, *et al*. Effect of oral N-acetylcysteine treatment on plasma inflammatory and oxidative stress markers in peritoneal dialysis patients: a placebo-controlled study. Peritoneal dialysis international: journal of the International Society for Peritoneal Dialysis. 2010;30(3):336-42.
99. Renke M, Tylicki L, Rutkowski P, Larczynski W, Neuwelt A, Aleksandrowicz E, *et al*. The effect of N-acetylcysteine on blood pressure and markers of cardiovascular risk in non-diabetic patients with chronic kidney disease: a placebo-controlled, randomized, cross-over study. Medical science monitor : international medical journal of experimental and clinical research. 2010;16(7):Pi13-8.
100. Urquhart BL, Freeman DJ, Spence JD, House AA. The effect of mesna on plasma total homocysteine concentration in hemodialysis patients. American journal of kidney diseases: the official journal of the National Kidney Foundation. 2007;49(1):109-17.
101. Urquhart BL, Freeman DJ, Cutler MJ, Mainra R, Spence JD, House AA. Mesna for treatment of hyperhomocysteinemia in hemodialysis patients: a placebo-controlled, double-blind, randomized trial. Clinical journal of the American Society of Nephrology : CJASN. 2008;3(4):1041-7.
102. Cutler MJ, Urquhart BL, Freeman DJ, Spence JD, House AA. Mesna for the treatment of hyperhomocysteinemia in hemodialysis patients. Blood purification. 2009;27(3):306-10.
103. Pakfetrat M, Shahroodi JR, Zolgadr AA, Larie HA, Nikoo MH, Malekmakan L. Effects of zinc supplement on plasma homocysteine level in end-stage renal disease patients: a double-blind randomized clinical trial. Biological trace element research. 2013;153(1-3):11-5.