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(REVIEW ARTICLE)

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The role of folic acid supplementation on lowering homocysteine level in chronic kidney disease

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Abstract

Cardiovascular disease (CVD) is the leading cause of death in chronic kidney disease (CKD) patients. Elevated homocysteine levels in CKD patients were thought to be one of the causes. Folic acid supplementation, which was known to improve anemia in CKD patients, can also reduce homocysteine levels, which would reduce cardiovascular events. In this review we will discuss the pathophysiology of hyperhomocysteinemia in CKD patients and studies that explain the role of folic acid to lower homocysteine levels that can also lower the risk of CVD in CKD patients. There are some conflicting results among available studies, but folic acid still seems reasonable to be considered as a suitable supplementary therapy in individuals with CKD after a thorough evaluation of the patient's folate status.

Keywords: Cardiovascular disease; Chronic kidney disease; Folate; Folic acid; Homocysteine

1. Introduction

A decrease in kidney function according to a Glomerular Filtration Rate (GFR) value of less than 60 ml/minute/1.73 m2 can be defined as chronic kidney disease (CKD). Cardiovascular abnormality is the most concerning risk factor that leads to CKD. Generally, CKD can be divided into five stages, where End-Stage Renal Disease (ESRD) is a condition where GFR value is less than 15 ml/minute [1]. Initially, in patients with early stage CKD (stage 1-2), patients are mostly asymptomatic without any finding suggesting metabolic disturbances. Among various causes of death, cardiovascular disease (CVD) is the leading cause. Compared to the general population, those who underwent haemodialysis have a 10 to 50-fold higher risk of premature mortality [2].

Non-traditional risk factors for CVD, including oxidative stress, endothelial abnormality, chronic inflammation, calcification of blood vessels, mineral and bone disorder, in addition to hyperhomocysteinemia, are gaining more attention. A homocysteine hypothesis is created based on the findings that individuals with congenitally impaired metabolism of homocysteine and therefore have a very high level of homocysteine in their blood are more prone to severe atherosclerosis. Folic acid (vitamin B9) and vitamin B12 are crucial cofactors in the metabolism of homocysteine, and disruption of their homeostasis has been associated with CKD development and higher risk of CVD. Folic acid is one of the pharmacological therapies that can be used for CKD patients. Folic acid possesses an important role during DNA synthesis, moreover to maintain erythropoiesis process. A disturbance during DNA synthesis may lead to clinical features of macrocytic anemia. Important to note that folic acid is water-soluble in nature, therefore it is easily removed during hemodialysis [3].

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2. Folate metabolism

A healthy person needs 50–100 mg of dietary folate per day to maintain normal folic acid stores. It contributes to the synthesis of nucleoproteins, purine and pyrimidine metabolism, and erythropoiesis maintenance, among other typical cellular processes. In the bowel, polyglutamates are transformed into monoglutamates, which are then carried by a specific carrier across mucosal epithelia to produce folic acid. 5-methyltetrahydrofolate (5-MTHF) is the circulating form of folic acid. Its demethylation warrants vitamin B12 and homocysteine as a cofactor and methyl acceptor, respectively. Tetrahydrofolate is created during this process, and the enzyme methionine synthase converts homocysteine to methionine. If this reaction is compromised, there won't be enough tetrahydrofolate for the one-carbon transfer reactions required for DNA synthesis. Megaloblastic erythropoiesis and macrocytic anemia would be the results of decreased DNA synthesis. Humans primarily excrete folic acid through their kidneys as 5 formyltetrahydrofolate [4].

3. Homocysteine metabolism

Homocysteine is a thiol-containing amino acid from methionine metabolism. However, it is not involved in protein synthesis. In the circulation, only 2% of total homocysteine is present as a free reduced form in the plasma. Homocysteine plasmatic level in normal condition is under 10 mmol/L. Mild hyperhomocysteinemia is when the level was above normal but still under 16 mmol/L, while severe hyperhomocysteinemia is when homocysteine level is higher than 100 mmol/L. Only non-protein bound homocysteine is subject to glomerular filtration in physiological conditions, and this results in minimal homocysteine elimination by the kidney. Most of homocysteine is reabsorbed by kidney tubules and then oxidized into carbon dioxide and sulphate [5].

There are two metabolic routes for homocysteine; namely remethylation and transsulfuration. During remethylation, a process catalyzed by methionine synthase (MTS) uses folate and vitamin B12 as cofactors to regenerate methionine. Since folate is not a physiologically active molecule, it must be converted to tetrahydrofolate, which is then turned to methylenetetrahydrofolate (MTHF) by methylenetetrahydrofolate reductase (MTHFR). The latter route, transsulfuration, starts with the formation of cystathionine from homocysteine and serine by cystathionine beta synthase (CBS). Afterward, cystathionine gets hydrolyzed by cystathionine ɣ-lyase into cysteine and α-ketobutyrate (CTH). CBS and cystathionine gamma-lyase (CSE) convert homocysteine to cysteine; sulfur is a byproduct of this process. Hyperhomocysteinemia-mediated downregulation of CBS and CSE may be substantially responsible for the reduced plasma levels of H2S in CKD and ESRD patients (Figure 1) [4,6].

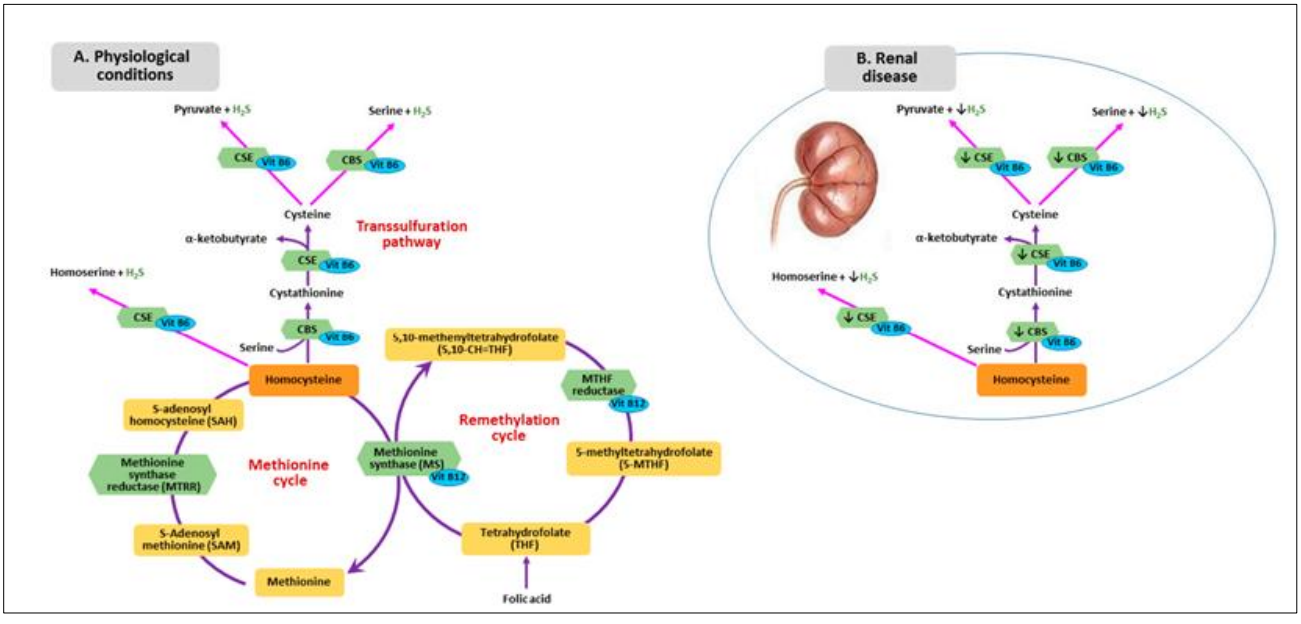

Figure 1 Metabolism of homocysteine in physiological condition (A) and in renal disease (B) [4].

4. Pathophysiology of folate deficiency and hyperhomocysteinemia in CKD

Renal failure can cause altered folate intracellular transport. Furthermore, it has been noted that in dialysis patients, serum folate levels are disproportionately higher than tissue folate stores. Thus, it would be important how folate stores are measured. Serum folate is an unsatisfactory indicator of tissue folate stores because it primarily reflects recent dietary vitamin intake. It has been proven that using cut-off values of serum folate, when compared to erythrocyte folate level, significantly overestimates the incidence of folate deficiency in patients undergoing continuous ambulatory peritoneal dialysis and haemodialysis [4].

Patients with CKD and ESRD have greater homocysteine levels in their blood than the general population. As it is suggested, hyperhomocysteinemia in CKD is mostly due to a disturbed homocysteine metabolism in the kidney, rather than a low GFR. Even while homocysteine may cross the ultrafiltration barrier, the vast majority (90%) circulates throughout the body in its protein-bound form. In addition, renal disorder may influence the kidney's transsulfuration and remethylation mechanisms. Multiple metabolic disturbances which include acidosis, systemic inflammation, and hormone dysregulation, as well as co-existing comorbidities and polypharmacy, may contribute to malnutrition, including folic acid deficiency, in CKD and ESRD patients. Anorexia, gastroparesis, sluggish intestinal transit or diarrhea, increased gut mucosal permeability, and impaired gut flora are additional aggravating factors. Patients who are uremic have impaired folic acid metabolism. Organic and inorganic anions, in which their clearance is diminished in patients with CKD, block the membrane transport of 5-MTHF, hence preventing its incorporation into nucleic acids and proteins. Even with normal plasma folate levels, the rate of folate absorption into body tissues may be changed, since folate transport is much slower in uremia [7].

5. Hyperhomocysteinemia and CVD

The harmful role of hyperhomocysteinemia on the cardiovascular system in CKD and ESRD is associated with the advancement of atherosclerosis in the setting of an already elevated risk of vascular damage resulting from the uremic syndrome. The mechanisms by which endothelial damage occurs are: [8]

- Oxidative stress. Hyperhomocysteinemia promotes generation of reactive oxygen species (ROS), thus lowering the nitrogen monoxide (NO) bioavailability. These mechanisms stimulate latent matrix-metalloproteinase and inactivate the tissue inhibitor of metalloproteinase. That eventually is leading to cardiovascular remodeling as well as collagen deposition. Hyperhomocysteinaemia greatly lowers the expression of the endothelial synthase nitric oxide protein (eNOS) in a dose-dependent manner, which eventually leads to reduced basal NO generation, the creation of free radicals, and consequent endothelial damage.
- Inflammation. Nuclear factor kappa B (NF-B) refers to transcription factor renowned for its capacity to produce cytokines, chemokines, and leukocyte adhesion molecules. This transcription factor is activated in hyperhomocysteinemia. That also promotes the production of proinflammatory chemokines in endothelial cells, notably MCP-1 and IL-8, by boosting transendothelial migration of monocytes, vascular inflammation, and atherogenesis. The formation of LDL owing to N-homocysteination leads in the accumulating process of cholesterol. Moreover, it increases the growth of foam cells in atherosclerosis by facilitating the absorption of oxidized LDL by macrophage scavenger receptors.
- Smooth muscle cells proliferation. By increasing the expression of adhesion molecules, proinflammatory cytokines, and the VSMC mitogen, hyperhomocysteinemia may vastly increase the propagation of vascular smooth muscle cells (VSMC). In addition, it may harm the kidneys by decreasing plasma and tissue adenosine levels and by directly inducing sclerosis in glomerular cells. Due to the enhanced VSMC proliferation produced by the decrease in plasma adenosine, process of sclerotic in the arteries and glomeruli is sped up. The process of atherosclerotic and inflammatory state prevalent in CKD are enhanced by these pathways [8].

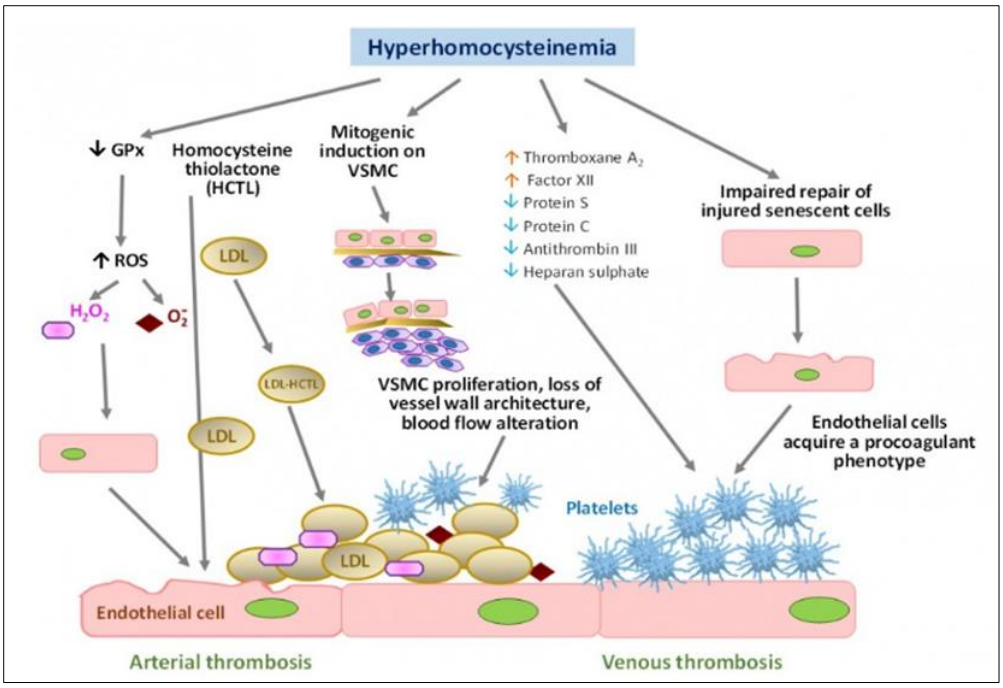

Figure 2 Pathogenesis of hyperhomocysteinemia-associated endothelial damage [8]

6. Folic acid supplementation on CKD to lower homocysteine level

As long as patients with CKD obtain enough folate through their diet, clinically significant folate deficiency is unlikely. In terms of anemia, additional folic acid supplementation apparently does not have a positive impact on erythropoiesis nor on response to recombinant human erythropoietin (EPO) treatment until there is severe folate deficiency in CKD and ESRD patients. If significant increases in mean cell volume or hypersegmented polymorphonuclear leucocytes are observed in these patients, a diagnosis of folate deficiency should be considered, particularly in those who are malnourished, have a history of alcohol abuse, or are hyporesponsive to recombinant human erythropoietin. Red blood cell folate measurements give a more precise picture than serum folate measurements, which may not always represent folate levels in tissues. Low erythrocyte folate concentrations need supplementation in these individuals [9].

The management of hyperhomocysteinaemia now includes folate supplementation, despite the fact that substantial folate deficit is uncommon in well-nourished individuals. In the last decade, this element of folate metabolism has become more significant in individuals with dialysis. Homocysteine builds up if it is not removed by the transsulphuration route or by methionine synthase in a folic acid-dependent transmethylation process. If more folate is available, homocysteine elimination may be enhanced. Thus, it was hoped that pharmaceutical folate supplementation would reduce homocysteine levels by enhancing the remethylation route from homocysteine to methionine and using methylcobalamin as a coenzyme [10].

In relatively few studies, adverse effects of folate treatment have been documented. A minor number of hypersensitivity responses and neurological and gastrointestinal adverse effects have been seen in healthy volunteers taking 15 mg/day of folate supplementation. These results have not been validated by larger research, and folic acid is still considered to be reasonably safe and well-tolerated. If anticonvulsants such as phenytoin, primidone, or phenobarbitone are also being used, attention should be exercised while using drugs that influence folate metabolism. Drugs that affect the metabolism of folate should be used with caution, especially if anticonvulsants like phenytoin, primidone, or phenobarbitone are also being taken [11].

The ideal dosage of folic acid and vitamin B supplements required to ward off cardiovascular disease in individuals with ESRD—which range from 2.5 to 5 mg of folic acid 3 times per week to more than 15 mg per day—remains unknown. Adults should consume no more than 1 mg of folic acid daily from fortified foods and supplements, according to the National Institutes of Health. In many centers, chronic haemodialysis patients receive a regular 1–5 mg/day folate nutritional supplements. The majority of studies indicate that a 25–30% drop in plasma homocysteine levels can be anticipated with folate therapy at 5 mg/day and should be noteworthy in 1–2 months. If the patient does not react to this level and their vitamin B6 reserves are in balance, the dose may be raised gradually up to 15 mg/day [4].

In a one-year, placebo-controlled, non-blinded, randomized control trial (RCT) on 81 chronic hemodialysis patients, Righetti et al. found that only twelve percent of patients who received therapy had normal homocysteine blood levels. This study found no survival benefit between folic acid and placebo [12]. Wrone et al. observed no difference in mortality or cardiovascular events among 510 patients on chronic dialysis who were randomly randomized to receive 1, 5, or 15 mg/day of folic acid. In a different RCT, groups of hemodialysis patients receiving 10 mg of folic acid were separated into those getting dosage increases of 15 mg and those receiving reductions of 5 mg dose. The findings of this study demonstrated that increasing the amount of folic acid reduces homocysteine levels significantly. It is not able, however, return homocysteine concentration to normal range. Similar findings were suggested by Tamadon et al. who discovered that folic acid treatment at low and high doses revealed no effect on homocysteine concentrations, despite folic acid significantly lowering these levels. The short study duration may have contributed to the failure of folic acid to normalize homocysteine concentrations because it takes six months for folic acid to have its full clinical impact [13].

A double-blind RCT by Zoungas et al. randomized 315 individuals with CKD on dialysis with an estimated glomerular filtration rate (eGFR) below 25 mL/min to receive folic acid 15 mg/day or a placebo. After a median of 3.6 years of follow-up, the data indicate that folic acid supplementation provides no effect [14]. Jamison et al. on a study involving 2056 patients with advanced CKD/ESRD requiring renal replacement therapy and elevated homocysteine levels, randomized patients to either a combination therapy group with folic acid, vitamin B12, and pyridoxine or a control group (placebo). The trial failed to meet both its main and secondary goals, a reduction in all-cause mortality, cardiovascular death, amputations, and thrombosis of the vascular access, respectively. However, homocysteine levels have fallen dramatically after 3,2 years of observation [15].

Total homocysteine level is a risk factor for both CVD incidence and death in ESRD patients who do not take supplemental folic acid supplements or reside in locations where folic acid fortification is mandated, according to a meta-analysis by Heinz et al. This impact was greater in prospective research than in retrospective investigations. According to the prospective studies included in the meta-analysis, an increase in total homocysteine concentration of 5 mmol/L is related with a 7% increase in the risk of overall mortality and a 9% increase in the risk of cardiovascular events in ESRD patients not taking supplements. Another meta-analysis investigated the relationship between folic acid supplementation and CVD in 3886 individuals with ESRD or advanced CKD (creatinine clearance of 30 mL/min). Folic acid decreased cardiovascular risk by 15% in patients with ESRD; this advantage was stronger in those treated for more than 24 months and in patients from areas with minimal or inadequate grain fortification [16].

In a concurrent clinical investigation with three therapy groups, Dierkes et al. discovered that a multivitamin supplement which contains minimum 800 mcg of folic acid may substantially lower homocysteine levels in individuals with ESRD by close to 50%. In contrast, supplements containing just 160 mcg of folic acid did not lower homocysteine levels when compared to a placebo. Despite the fact that only a small percentage of patients' homocysteine levels restored to normal levels, the findings revealed that a water-soluble multivitamin combination in two distinct dosages efficiently diminished homocysteine levels despite the fact that only a small proportion of patients' homocysteine levels returned to normal. As a result, the homocysteine level decline rate is directly correlated with both the homocysteine and folic acid baseline levels [13].

According to the most recent study by Tu et al, there was no discernible difference between those receiving 5 mg of folic acid per day and those receiving 5 mg per week in terms of mortality and cardiovascular event rates. Arteriovenous shunt thrombosis was less frequent in the group receiving 5 mg of folic acid daily, though. This suggests that patients with ESRD may benefit from taking a larger folic acid supplement to avoid thrombosis events [17]. In a similar research, folic acid supplements were related to fewer negative effects in people with deep vein thrombosis [18].

Duration on anemia, dialysis, and severe immunosuppression are likely to induce a convergence of responses of immunes, dysmetabolic shifts, a prothrombotic state, and inflammatory aberrations in kidney transplant recipients, which increases their cardiovascular risk considerably than the general population. Total homocysteine levels are decreased in stable kidney transplant recipients taking multivitamins containing high doses of folic acid, vitamin B6, and vitamin B12, but neither CVD outcomes nor overall mortality are decreased. Finally, because there is conflicting evidence regarding how homocysteine-lowering treatments affect the progression of CKD, more research with progression of CKD as the primary endpoint and more homogenous population selection are necessary. Though further research is still needed, it is reasonable to treat folic acid deficiency in order to slow the progression of CKD and prevent more phenomena that might lead to toxicity [3].

7. Conclusion

The evidence that is available today does not completely support that hyperhomocysteinemia, folic acid, and vitamin B12 changes are reliable risk factors for cardiovascular disease and mortality in those with ESRD and CKD. Additionally, these variables do not provide a therapeutic target that has been proven effective in reducing cardiovascular risk and CKD progression. Folic acid seems reasonable to be considered as a suitable supplementary therapy in individuals with CKD while awaiting the outcomes of confirmatory trials. Folic acid could be provided for those having early-stage CKD who do not require to limit their potassium or phosphorus intake through diet, in a balanced diet form which is high in natural sources of folate. After a thorough evaluation of the patient's folate status, folic acid can be pharmaceutically supplemented for those with advanced CKD who are receiving dialysis.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest.

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