OREGANO

Nutritional Journal of Varastegan Institute for Medical Sciences

I am delighted to inform that the fourth edition of Iran's first all-English nutritional journal has been published, and I want to express my heartfelt gratitude to everyone who participated in this edition, especially Mr. Babaei who came to my assistance to start this project and persevered in the face of tribulations. Due to the unfavorable conditions of our country, we decided to stop the process of writing the new edition, but because we are nearing the end of our supervisor period, we decided to publish the last volume from our term of responsibility, and I wish all the best for the next team who are going to take this hard responsibility and I know they will continue this legacy as well as possible.

Ali Zeyqami

I'm honoured to be participant as the editor in chief of Oregano journal. But first of all, I want to express my special thanks to all of the authors, editors and designers of this edition. Certainly, working in a publication with this amount of cooperation makes everyone happy and pride.

Special thanks to Mr.Zeyqami; Director In Charge of this journal for his endeveaour to publish this volume.

The subject of this volume is the medical nutrition therapy in Kidney Diseases, which has been tried to collect all the up-to-date content of 2022 in mini_review articles, so you can read them according to your favorite topic. I hope you make the most of this volume.

Your sincerely

Arvin Babaei

MEMBERES

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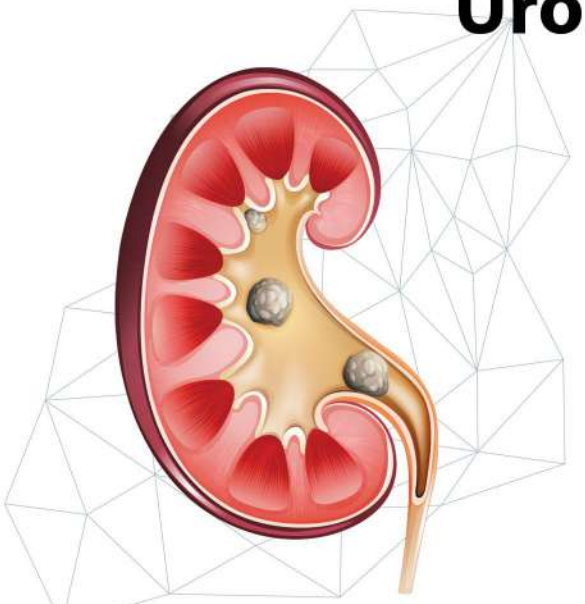
Roles of Flavonoids against Urolithiasis

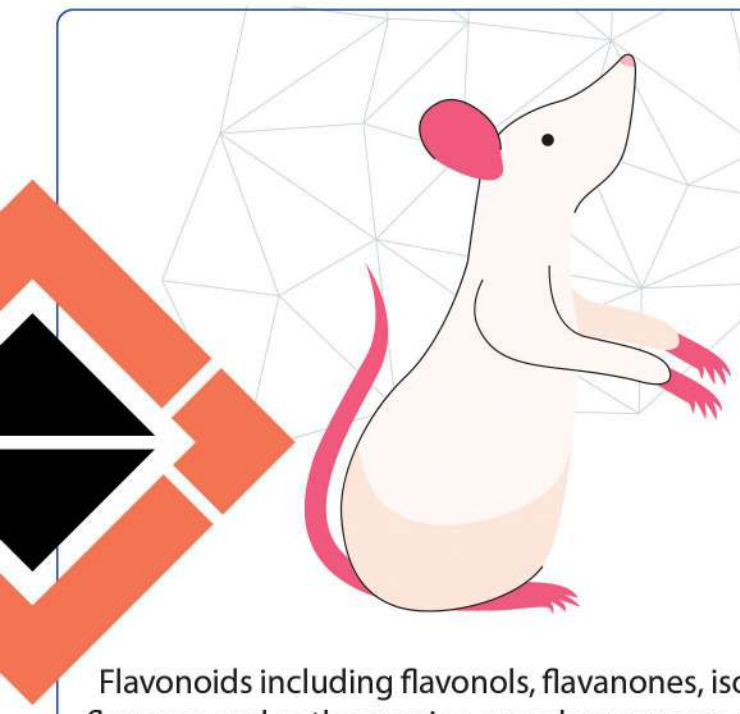


Introduction

Urolithiasis or kidney stone is the third most predominant disorder of the urogenital system caused by imbalance in the concentration of various macromolecules such as citrate, magnesium, calcium, phosphate, oxalate, uric acid, etc (1). Almost 80% of these urinary calculi are formed from calcium oxalate crystals (CaOx) or calcium phosphate, which leads to obstruction, hemorrhage and infection in urogenital system (2, 5).

Genetic factors, lifestyles, climate, sex hormone, age, industrialization, socioeconomic status, diet and environment influence urolithiasis pathogenesis and reduces the onset age (6). The worldwide prevalence is recorded as 12% and still increasing. Percentage increase in the prevalence rate has been recorded to be 40-50% in Pakistan, 14.8% in Turkey, 7.4% in Taiwan, 5% in Brazil, 4.5% in UK, 4% in India, 3.6% in USA, 2.5% in China, 2.4% in Italy. It is also 2-4 times more common in men than in women (7, 8).

If urolithiasis remains untreated, the recurrence rate during 1st year increases from 10% to 50% in 10th year (9). The non-pharmacological and pharmacological therapies are available in drug therapy, analgesia, infection control and regulation of urine pH are significantly necessary. But some medications such as alkali citrate (K citrate) and thiazide diuretics are not consistently effective and may have side effects due to long-term use (10, 11). Also, surgical technologies, including laser lithotripsy, extracorporeal shock wave lithotripsy (ESWL), endoscopic stone removal and percutaneous nephrolithotomy are widely used. One of the disadvantages of these treatments is the traumatic effects of shock waves, persistent residual stone fragments and the possibility of infection. In addition, due to the significant economic burden, high recurrence and risk of chronic kidney disease, these options are not desirable (10, 12, 13).



Flavonoids including flavonols, flavanones, isoflavones and anthocyanins, are a large group of natural polyphenols. These secondary metabolites of plants, have a wide range of pharmacological properties such as anti-oxidation which may prevent renal stones formation like CaOx stones in vitro and in vivo. However, effects of flavonoid such as Diosmin, Quercetin and Apigenin on renal diseases have not been conclusived (14, 15).

Thus, the current study was aimed to investigate the protective effects of flavonoids with anti-urolithiasis activities and probable mechanisms.

Literature review

In 2018, a review study by Xiangquan Zeng et al. in china aimed to evaluate the effects of plant flavonoids on preventing the formation of CaOx stones in vitro and in vivo, which is related to their diuretic and antioxidant properties. Therefore, flavonoids or flavonoid-rich plant extracts with anti-kidney stone activities and possible mechanisms of action were investigated (15).

A study by Kezhang was conducted in 2020 in India. The purpose of this study was to examine the effect of apigenin on kidney stones. The result was that apigenin is a plant flavonoid with nephroprotective and blood pressure lowering properties. Experiments were conducted on non-fructonized rats, which ultimately led to a decrease in the relative weight of urine and its pH, as well as an increase in dry urine volume. Apgenin significantly reduced ethylene glycol (EG)-induced changes in hemodynamic and electrocardiographic parameters (16).

A study was conducted by Uzma Saleem et al. in 2020. The aim of this study was to scientifically investigate the anti-stone effect of methanolic extract of sage seeds using kidney stone models in vitro and in vivo. For the laboratory study of the nucleus, growth and aggregation assays were performed. The in vivo study was conducted on mice, and they were divided into six groups. First group was only given a vehicle. The second group was the control patient who was treated with 0.75% EG in drinking water, which caused the formation of urinary stones. The third group received Cystone (750 mg/kg, orally). IV-VI groups with extracts with doses of 100, 300 and 700 mg/kg orally, once daily. Groups III-VI additionally received 0.75% EG in their drinking water. The in vitro study revealed a concentration-dependent increase in the percentage inhibition of crystal nucleation, growth and aggregation. In vivo study revealed anti-urolithiatic activity by lowering oxalate, calcium, phosphate, sodium and potassium levels in the urine as well as serum uric acid, blood urea nitrogen, total proteins and total albumin. Salvia hispanica seeds are a good alternative to allopathic anti-urolithiatic drugs to treat urolithiasis (17).

Bawari et al. has been studied on the anti-mass potential of the hydroethanolic extract of D. carota root against calcium oxalate urinary stones in 2018. The model of hyperoxaluria caused by urinary stones was used in male Wistar rats. Urine and serum parameters and kidney histopathology were used to determine the anti-stone effect of D. carota root extract. As a result, D. carota extract significantly improved the abnormal levels of calcium, oxalate, phosphate, magnesium, citrate, protein and uric acid in rats (13).

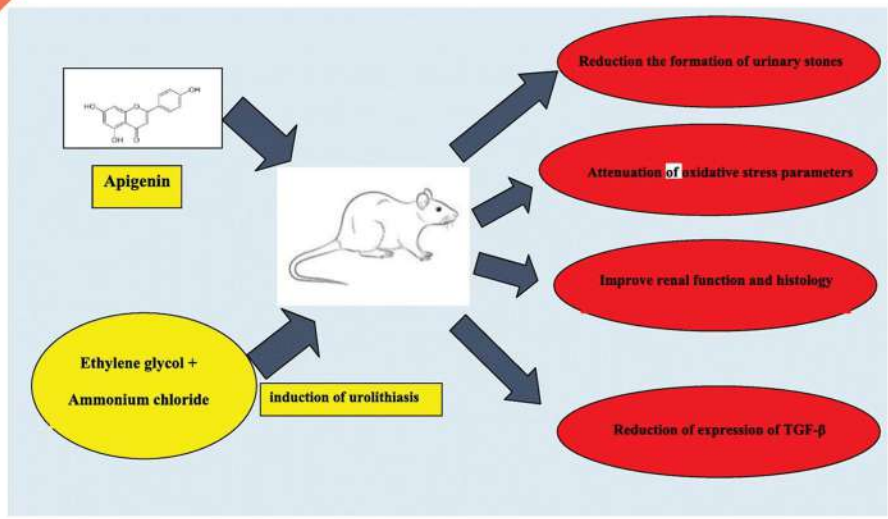


Figure 1: Graphical abstract of apigenin against urolithiasis (20)

Discussion

For the prevention and treatment of kidney stones, particularly the CaOx type, flavonoids have received extensive research. We have discovered the potential of plant flavonoids against urolithiasis induced by EG in uninephrectomized animals (15). Recent research has demonstrated that plant flavonoids can successfully prevent the development of CaOx stones both in vitro and in vivo, which is consistent with their diuretic, antioxidant, anti-inflammatory, antibacterial and other protective effects. Thus, the anti-urolithiasis activities of flavonoids or extracts of plants rich in flavonoids as well as their potential mechanisms of action were reviewed (10). Treatment with flavonoids such as apigenin significantly reduced a crucial component of nucleation, which improved CaOx crystal growth. Further evidence for this idea came from dropping calcium levels in both urine and serum (3).

In addition, because urine has an acidic pH, it can dissolve stone-forming promoters to prevent their crystallization. Since diosmin, as a flavonoid, significantly decreased urine pH (compared to the positive control group), this indicates that diosmin has excellent anti-urolithiatic activity (18). Furthermore, CaOx crystal growth-induced toxicity causes the release of a variety of inflammatory mediators, which leads to an inflammatory response supported by elevated relative weights of the kidneys. Treatment with flavonoids significantly reduced the relative increase in kidney weight, possibly as a result of their anti-inflammatory properties (14, 19).

The antiurolithic effects of flavonoids can be applied through other mechanisms, but what were mentioned were the most basic mechanisms of this action.

Conclusion

The present study unveiled anti-urolithiatic activity of flavonoids. The extract prevented the formation of calcium oxalate stones by inhibiting early steps of stone formation, nucleation, aggregation and growth. Moreover, the extract displayed anti-urolithiatic activity by decreasing oxalate, calcium, phosphate, total proteins, albumin, blood urea nitrogen and uric acid levels.

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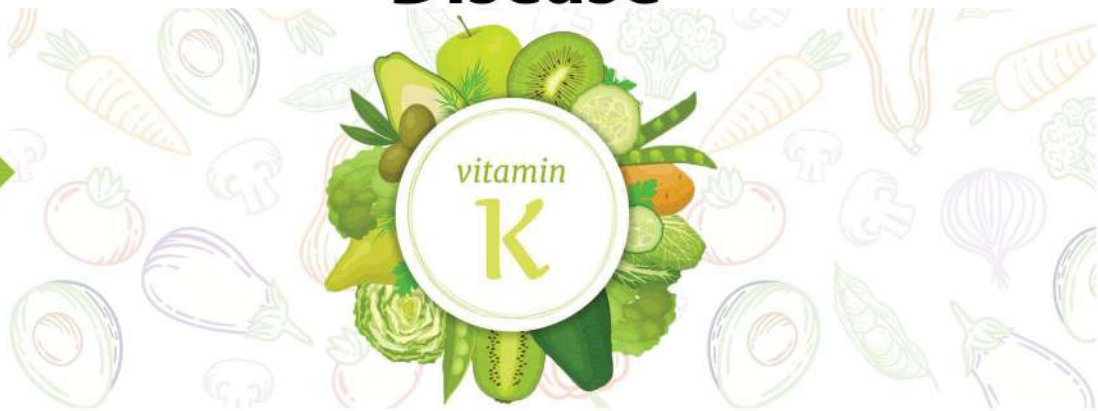
Vitamin K and Chronic Kidney Disease



Introduction

Chronic Kidney Disease (CKD) is a progressive, irreversible disease characterized by a chronic reduction in kidney function and structural kidney damage. Around 1.2 million deaths were attributable to CKD in 2016, ranking 12th in the list of leading causes of death, and this number is expected to rise to 2.8 million deaths by 2060. Recently Wei et al. reported on circulating desphospho-uncarboxylated matrix c-carboxyglutamate (Gla) protein (dp-ucMGP), a marker of poor vitamin K status, as a predictor of incident CKD. Wei et al. found that a high plasma dp-ucMGP level, representing a vitamin K deficiency, was associated with an increased risk of progression to an estimated Glomerular Filtration Rate (eGFR) development of microalbuminuria (1).

CKD is characterized by simultaneous vascular calcifications (VC) and impaired bone metabolism. Even though the mechanistic link of this crosstalk between the vascular and skeletal system is poorly understood so far, some hormones, including parathyroid hormone (PTH) and 1,25-dihydroxy vitamin D3 are acknowledged to orchestrate both skeletal and vascular mineralization as well as stem cell regeneration (2). Recently, growing evidence seems to suggest that vitamin K supplementation could be a tool to prevent the rapid progression of vascular calcifications and to preserve bone health in CKD patients (3, 4).

Arteriovenous Fistula (AVFs) is a frequently used vascular access type for CKD patients requiring hemodialysis (HD) (5, 6). Vascular calcification implies a highly regulated network of calcification-inducing and -protecting factors that is regulated partly by vitamin K status of the vessel wall. Vitamin K is a fat-soluble vitamin acting as the cofactor for γ-glutamyl carboxylase enabling the carboxylation of vitamin K–dependent proteins. Coagulation factors II, VII, IX and X are the most well-known vitamin K–dependent proteins. Matrix Gla Protein (MGP), a vitamin K–dependent protein produced by vascular smooth muscle cells (VSMCs), is a powerful vascular calcification inhibitor in media and of intimal atherosclerotic plaques calcification (7). CKD patients have significantly lower circulating vitamin K concentrations compared with the general population and HD patients have a poor overall vitamin K status owing to low vitamin K intake (8). In addition, a high number of CKD patients at risk of arterial and venous thrombosis receive oral anticoagulants (Vitamin K Antagonists; VKA). VKAs not only interact with carboxylation of coagulation factors but also impair MGP carboxylation (9, 10). Our aim is to investigate the effect of vitamin K on AVFs and VC in CKD patients.

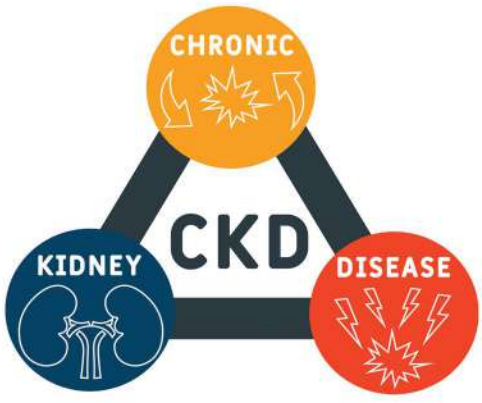
Literature review

A study was conducted by Federica Bellone et al. in 2022 in Italy. They were retrieved from the online databases pubmed, scoupus and Web of knowledge, by matching the following keywords: "chronic kidney disease", "vitamin K", "vascular calcification", "bone metabolism", "osteoporosis" and "cardiovascular disease". The aim of this study was to focus on the current knowledge of vitamin K biological functions, its involvement in the relationships among cardiovascular diseases (especially in hypertensive patients) and bone metabolism in CKD patients. Some of the serious complications of CKD are represented by Cardiovascular Disease (CVD) and skeletal. This study showed CKD is commonly associated whit vitamin K deficiency (4).

Lu Dai et al. conducted a research article about functional vitamin K insufficiency in 2021. The main focus is on data regarding the prevalence of vitamin K deficiency and its association with clinical outcome in patients with advanced CKD. To further explore the clinically equivocal association between dp-ucMGP and VC, the present observational cohort study aimed to investigate the association between functional vitamin K deficiency and all-cause and cardiovascular mortality and whether this association is modified by the presence of VC, evaluated by Coronary Artery Calcium (CAC) and Aortic Valve Calcium (AVC), in advanced CKD. The result showed, patients with CKD suffer from vitamin K deficiency and are at high risk of VC and premature death (11).

Emma Zaragatski has been studied on role of vitamin K in 2015 in Germany. The objective of this study is to investigate the effect of vitamin K status on AVF Neointimal Hyperplasia (NIH) and calcification in experimental CKD. This study showed, vitamin K antagonists have detrimental effects on AVF remodeling, whereas K2 reduced NIH and calcification indicating vasoprotective effects. Hence, K2 administration may be useful to prevent NIH (10).

A study was done by Dion Groothof et al. in 2022. Circulating dp-ucMGP, a marker of vitamin K status, is associated with renal function. The authors aimed to assess association between circulating dp-ucMGP and incident CKD. Wei et al. included 3969 participants with a mean age of 52.3 years, of whom 48.0% were male, enrolled in the general population based on prevention of renal and vascular END-stage disease study. The result showed, plasma dp-ucMGP was substantially higher in males than females. Therefore baseline characteristics of the study participants are shown according to sex-stratified quartile of dp-ucMGP (1).



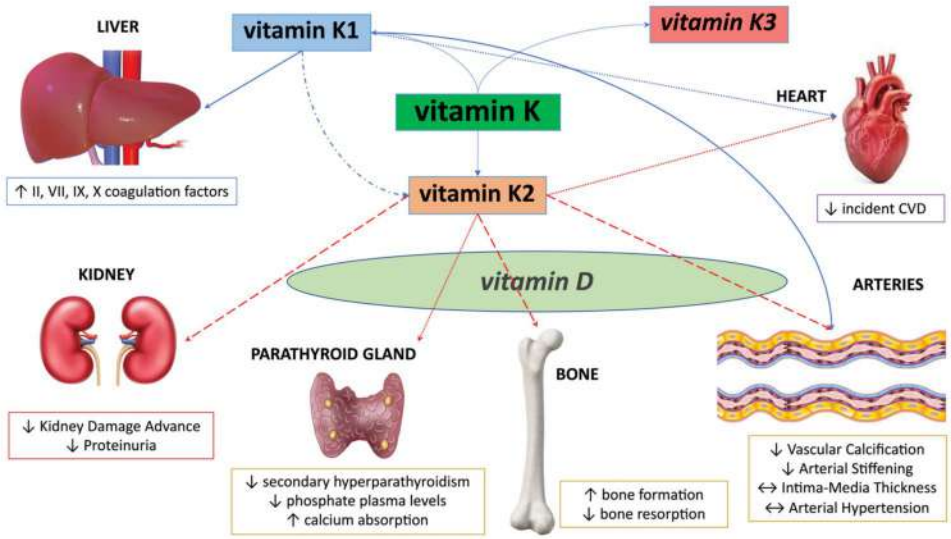


Figure 1: Vitamin K vitamers potential role on liver, kidney, parathyroid gland, bone, arteries and heart. Potential synergism with vitamin D (on parathyroid, bone and arteries) is also depicted (4).

Discussion

In people with CKD, there is a possibility of disturbances in bone metabolism and CVD and due to disturbances in the regulation of mineral substances, phosphate retention occurs (12, 13).

This disease causes the transformation of vascular smooth cells into osteoblast-like cells. It is important to evaluate vitamin K in this disease and it should be taken as a supplement. There are two types of this vitamin; K1 and K2, and the half-life of the second type is longer, so its supplement is cheaper, but it is better to take K1 because of its conversion ability (14). The toxicity of this vitamin has not been confirmed, but there may be doubts due to excessive coagulation. Supplemental vitamins potassium and vitamin D can have a protective role (15). Vitamin D and K are effective in bone protection and slowing down the process of CKD and improving cardiovascular function (16). In Huntington's patients, VKA is used to prevent thrombotic events. However, there are not enough indications for this information. Functional vitamin K is a known risk factor in mortality in chronic diseases. Vitamin K plays an important role in preventing aging and health of the body and can be directly and indirectly involved in this factor (17).

Conclusion

In our reviewed studies, it has been shown some positive effects of vitamin K on CKD patients. As vitamin K deficiency has increased the risk of death in CKD patients, this effect is especially evident on the cardiovascular system, however, the specific therapeutic dose of vitamin K for this disease is unclear and requires more studies.

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Plant-based Diets: Can They Work for Kidney Patients?

Introduction

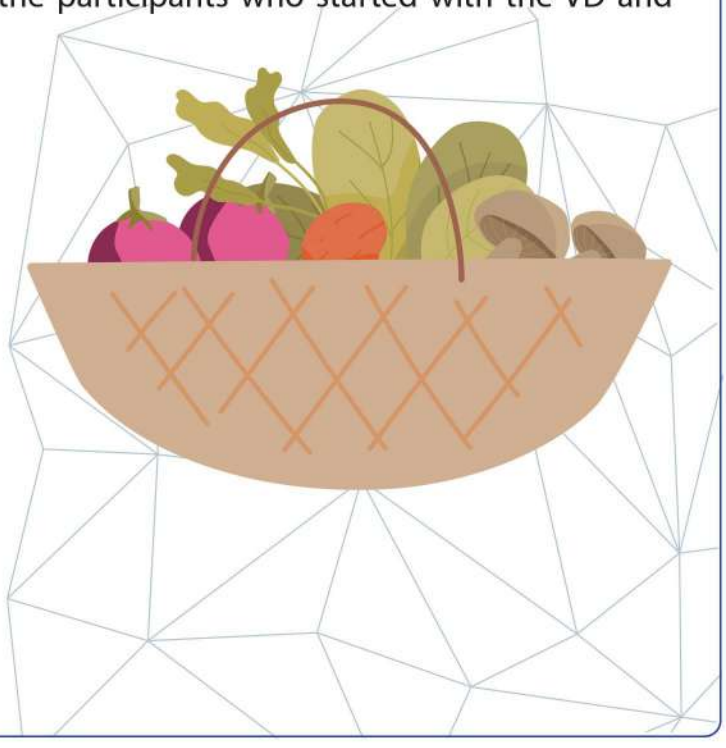
The existence of kidney disease is defined by the presence of lesions in the parenchyma of one or both kidneys. The most common sign that in kidney disease discovery exists, is by detecting evidence of changes in kidney function that arise as a consequence of lesions. The other common signs are; swelling, sudden pain, changes in the appearance of urine, fatigue and feeling weak. Kidney disease often gets worse over time and may lead to kidney failure and other health problems, such as stroke or heart attack (1).

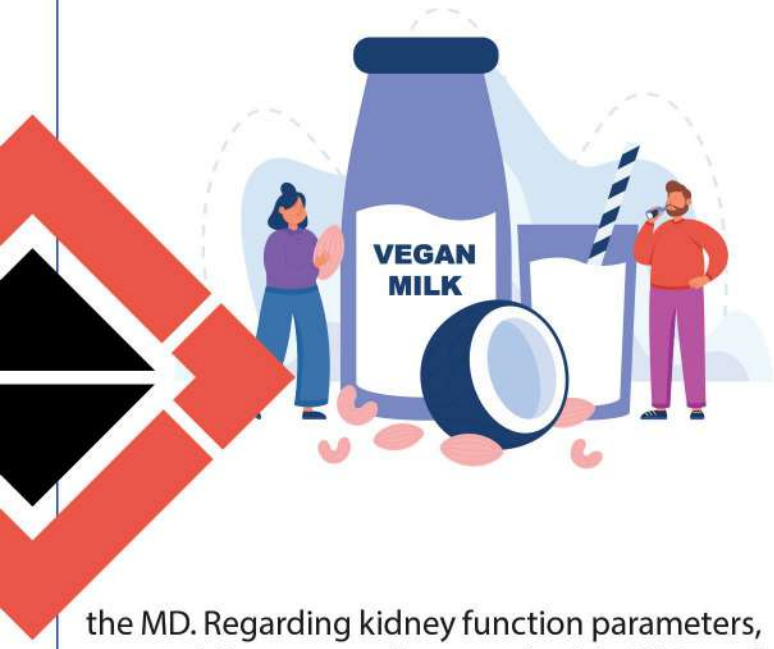
Today this problem is growing fast so approximately 2 in 1000 Americans are living with End-Stage Kidney Disease (ESKD). Kidney problems include kidney failure, acute kidney injury, kidney cysts, kidney stones and kidney infections. Diabetes, heart disease and a family history of kidney failure are some risk factors for kidney disease (2).

Plant-based diets have been identified as a fundamental dietary component for health among a wide variety of eating patterns. Plant-based diets are an umbrella term used to describe eating patterns that included a large proportion of plant-dominant diets including flexitarian, vegetarian, Mediterranean and vegan diets. Unrefined, whole, plant-based diets are recommended over their highly processed forms. The consumption of whole, plant-based diets is useful in the preventing/treating many lifestyle-related diseases in Western societies, including type 2 diabetes mellitus (T2DM), obesity, hypertension and hyperlipidemia. In recent years, their utility for chronic kidney disease (CKD) and its resultant complications have become increasingly apparent. Plant-based diets should be viewed as complementary to existing medical therapies and can help reduce the burden and cost of existing therapies to patients. In contrast to medications, however, dietary changes have the potential to address the root cause of lifestyle diseases for many patients and, as a result, may improve multiple disease processes simultaneously (3). This study aims to investigate the relationship between plant-based diets and kidney diseases.

Literature review

A randomized and crossover trial study was conducted by Monica Dinu, et al. in 2021 in Italy aimed to compare the effects of a vegetarian diet (VD) and a Mediterranean diet (MD) on kidney function in a group of subjects with the medium-to-low cardiovascular risk profile. The result showed that no significant differences in demographic characteristics and cardiovascular traditional risk factors were found between the participants who started with the VD and





the MD. Regarding kidney function parameters, no participant was diagnosed with CKD, and the proportion of mild estimated Glomerular Filtration Rate (eGFR) impairment was not significantly different between the VD and MD groups (4).

A randomized matched interventional study in 2019 by Nimrit Goraya, et al. in America was conducted to compare the effect of 60 months of dietary acid reduction with added daily oral NaHCO3 (HCO3) or added fruits and vegetables (F+V) on the primary analysis of Cystatin C-calculated eGFR and the secondary analyses of effect on urine kidney injury parameters and indicators of Cardiovascular Disease (CVD) risk. This study has shown that F+V had lower low-density lipoprotein, Lp (a), and higher serum vitamin K1 than HCO3 and usual care at 5 years (5).

A study in 2022 by Claudia D'Alessandro, et al. in Italy was done which analyzed the composition in terms of nutrients, ingredients and additives of 560 products available on the market and online shopping sites to understand the characteristics of these products. This study showed that processed plant-based meat substitutes have a higher content of salt, lipids, mostly unsaturated, and fiber than animal-based ones. In addition, protein content is lower in plant-based products than in corresponding animal ones (6).

Claudia Mesquita de Carvalho, et al. conducted a systematic review study in 2019 in Brazil. This study aimed to evaluate the effect of dietary fiber (supplemental or dietary pattern rich in fiber) on Diabetic Kidney Disease (DKD). Seven trials were included and the studies were organized into three categories (vegetarian, Dietary Approaches to Stop Hypertension (DASH) diet and fiber supplement), two evaluated supplements and five dietary patterns. According to the study, a vegetarian diet reduced albuminuria in three trials, two in participants with T1DM and one in patients with T2DM; and one study demonstrated a change in eGFR in T1DM (7).

Discussion

Processed plant-based meat substitutes have a higher content of salt (+467%), lipids (+26%), mostly unsaturated and fiber than regular animal-based ones. The protein content is lower (-40%) in plant-based products concerning corresponding animal ones. Of the 49 additives on the label (on average 2 per product), 20 contain phosphorus, sodium, potassium or nitrogen. Several plant-based processed products may contain elevated amounts of salt and additives, which make them not optimal for CKD patients. Although a plant-based diet remains a very important tool for CKD nutritional management, patients should be aware of the extra content of sodium and additives in processed plant-based products compared to animal-based processed foods (6).

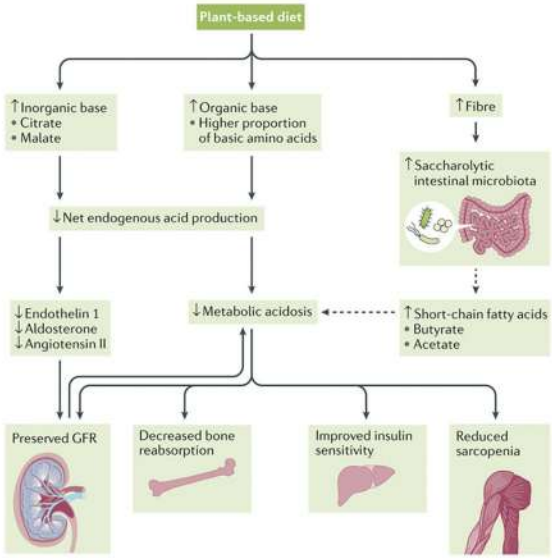


Figure 1: Effect of a plant-based diet on GFR (8)

After 3 months, VD resulted in a significant decrease in creatinine, urea nitrogen levels, BUN and BUN/creatinine ratio and an increase in eGFR, while MD did not affect kidney function markers. However, as VD generally offers protein quantities that are consistent with low-protein diets (i.e., 0.6-0.8 g/kg/day) and high amounts of fiber, recently it has been postulated that it may have additive positive effects on kidney function (4).

The current study showed that dietary acid reduction with either NaHCO3 or F+V yielded a comparable improvement of metabolic acidosis in patients with CKD, but F+V yielded better improvement in CVD risk indicators including SB, LDL, Lp (a), BMI and serum vitamin K1 as secondary outcomes of these studies in which the primary outcome was changed in eGFR (5).

Dietary fiber plays an important role in glycemic control. In the general population, consumption of fiber-rich foods can reduce serum creatinine levels and may increase eGFR in CKD patients without DM. High fiber intake, mainly from legumes and vegetables, was related to a lower incidence of CKD after six years of follow-up. For every additional 5 g/day of fiber intake, there was an 11% reduction in the risk of CKD (7).

Conclusion

In conclusion, metabolic acidosis improvement and eGFR preservation were comparable in CKD patients treated with F+V or oral NaHCO3 but F+V better-improved CVD risk indicators, such findings suggest a possible role of plant-based diets in the prevention of metabolic complications for these patients.

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Garlic and Chronic Renal Failure

Introduction

Chronic Renal Failure (CRF) is associated with oxidative stress that promotes production of reactive oxygen species and cytokine release. Aqueous Garlic Extract (AGE) treatment alleviated CRF-induced oxidative changes in the injured tissues, while CRF-induced elevations in the blood levels of the pro-inflammatory cytokines and LDH were reduced. As a result, CRF-induced oxidative tissue injury occurs via the activation of pro-inflammatory mediators and by neutrophil infiltration into tissues and the protective effects of garlic on CRF-induced injury can be attributed to its ability to inhibit neutrophil infiltration and pro-inflammatory mediators (1).

These findings suggest that garlic, as a supplement, may have a potential therapeutic use in delimitating the systemic oxidant effects of CRF on remote organs (2). The gentamicin (Gent) family of aminoglycoside antibiotics are highly effective antimicrobial agents, particularly against severe gramnegative bacterial infections. However, Gent produces nephrotoxicity as a side effect list of other serious side effects (3).

Gent-induced kidney injury may be explicated by increased production of reactive oxygen (ROS) and nitrogen species (RNS), reduction in natural antioxidant defense and activation of inflammatory processes (4). However, the exact mechanism of Gent-induced nephrotoxicity remains unclear and necessitates further investigations (5). Kidney injury molecule-1 (Kim-1) is one of the biomarkers used for early discovery of renal injury. In addition, allyl-methyl-thiosulfonate, 1-propenyl-allylthiosulfonate and y-L-glutamyl-S-alkyl-L-cysteine are important sulfur-containing compounds present in garlic homogenate (6).

These volatile sulfur-containing thiosulfinates are responsible for the pungent aroma, taste and biological effects of garlic (7). Moreover, garlic has a large number of antioxidants and flavonoids which can be utilized in detoxification systems (8). Garlic has numerous pharmacological actions and medical applications, for example: lowers serum cholesterol levels, decreases oxidative stress, stimulates the immune system, enhances detoxification of foreign compounds and has antibacterial and antifungal actions (9).

Garlic Extract (GE) and its various components were postulated to have an important cytoprotective role in the setting of ischemia/reperfusion (I/R) injury through their antioxidant and anti-inflammatory properties (10). The aim of the present study was to elucidate the possible protective effects of AGE on CRF by checking out the other articles on this topic.

Literature Review

H.M. Galal, N.M. Abd el-Rady conducted a research article about AGE that suppresses experimental Gent-induced renal pathophysiology mediated by oxidative stress in 2019. The main focus is on scrutinizing the expected nephroprotective effects of the AGE and scrutinizing some factors like interleukin 6 (IL-6) and interferon (INF), malondialdehyde (MDA), superoxide dismutase (SOD) and Kim-1. In this study, we understand that AGE can reduce Gent-induced renal dysfunction (11).

A study was done by M. Deniz et al. in 2011. The aim of this article was the GE ameliorates renal and cardiopulmonary injury in the rats with CRF. They randomly divided rats into either the

CRF or the sham-operated control groups. The result showed AGE treatment can reduce serum levels of blood urea nitrogen (BUN) and creatinine in AGE treated CRF group. In the sham-operated control group, serum levels of lactate dehydrogenase (LDH) and pro-inflammatory cytokines, TNF-α and IL-1β were noticeably increased, known as systemic tissue injury (12).

A. M. S. Gomaa et al. has been studied on role of GE. The objective of this study is garlic (Allium sativum) exhibits a cardioprotective effect in the experimental CRF rat model. They checked out the changes in specific cardiac parameters and protective effects of GE in a rat model of Gent-induced CRF. This study showed prescription of GE in the experimental CRF model helped protect the heart by reducing oxidative stress and controlling cardiac Na^+/K^+-ATPase activity and $Ca2^+$ levels (13).

A study was conducted by M. Ribeiro, L. Al-varenga, and L.F.M.F. Cardozo et al. in 2021. This study aims to focus on the therapeutic effects of Garlic on cardiovascular, hepatic, gut, diabetes and chronic kidney disease (CKD). The result showed, that garlic is simple but effective means of mitigating complications often observed in diseases of ageing, such as CKD and also garlic has a positive effect on the maintenance of normative gut microbiota. As patients with CKD have many disorders linked to chronic inflammation, oxidative stress and uremic dysbiosis, garlic can be used as a hopeful "Food as Medicine" strategy that may quell these complications (14).

Discussion

The members of the Allium family, including garlic, contain very high levels of biochemically active organic sulfur compounds and their extracts have been known to protect organs from various injuries (15, 17). The compounds in garlic (S-allylcysteine, S-allyl-mercapto cysteine, S-allyl-cysteine sulfoxide and allicin), through their radical scavenging abilities, have been suggested to be responsible for its preventive effects against oxidative injury (18). It was previously shown in several nephrotoxicity models that oxidative damage in the kidney tissue was prevented by AGE, which was demonstrated by reduced MDA levels and restored renal functions (19, 24).

It was previously reported that chronic garlic intake significantly decreased lipid peroxidation, while endogenous antioxidants, such as GSH (glutathione), SOD and GPx (glutathione Peroxidase) were found to be increased (25). In turn, MPO (myeloperoxidase) plays a fundamental role in oxidant production by neutrophils. Furthermore, the results also suggest that garlic has a preventive effect through the inhibition of neutrophil infiltration (22, 26). In accordance with the MPO results, increased proinflammatory cytokines TNF-α and IL-1β levels were also suppressed by garlic treatment (27). The normalization of inflammatory cytokines after oral intake of GE could be explained by its allicin (diallyl-thiosulfinate) content that exhibited anti-inflammatory effect by reducing the expression of intercellular adhesion molecule-1 and inflammatory cytokines (TNF-α, IL-1, IL-6, IL-8, T-cell, interferon-α and IL-2) while stimulating IL-10 production (28).

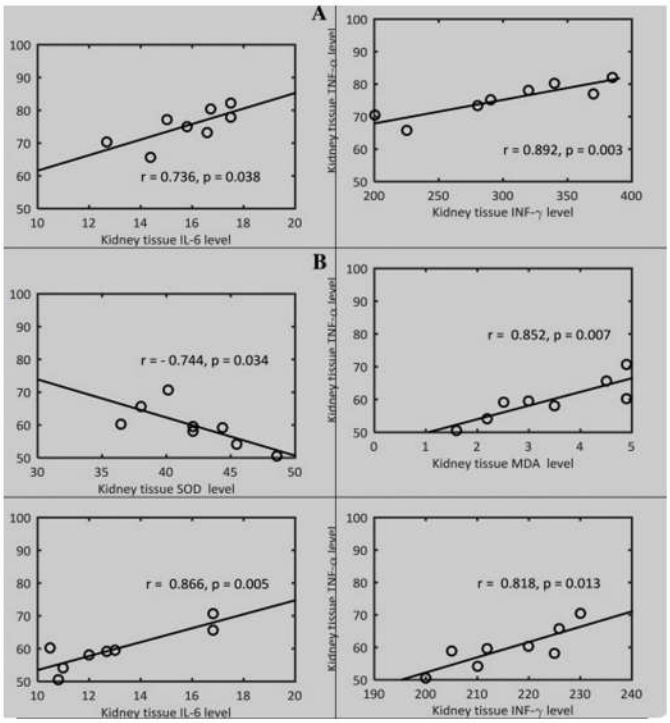

Figure 1: Correlation between levels of kidney tissue inflammatory, oxidative stress markers in: A. Gent-treated group. B. Gent-AGE-treated group (29).

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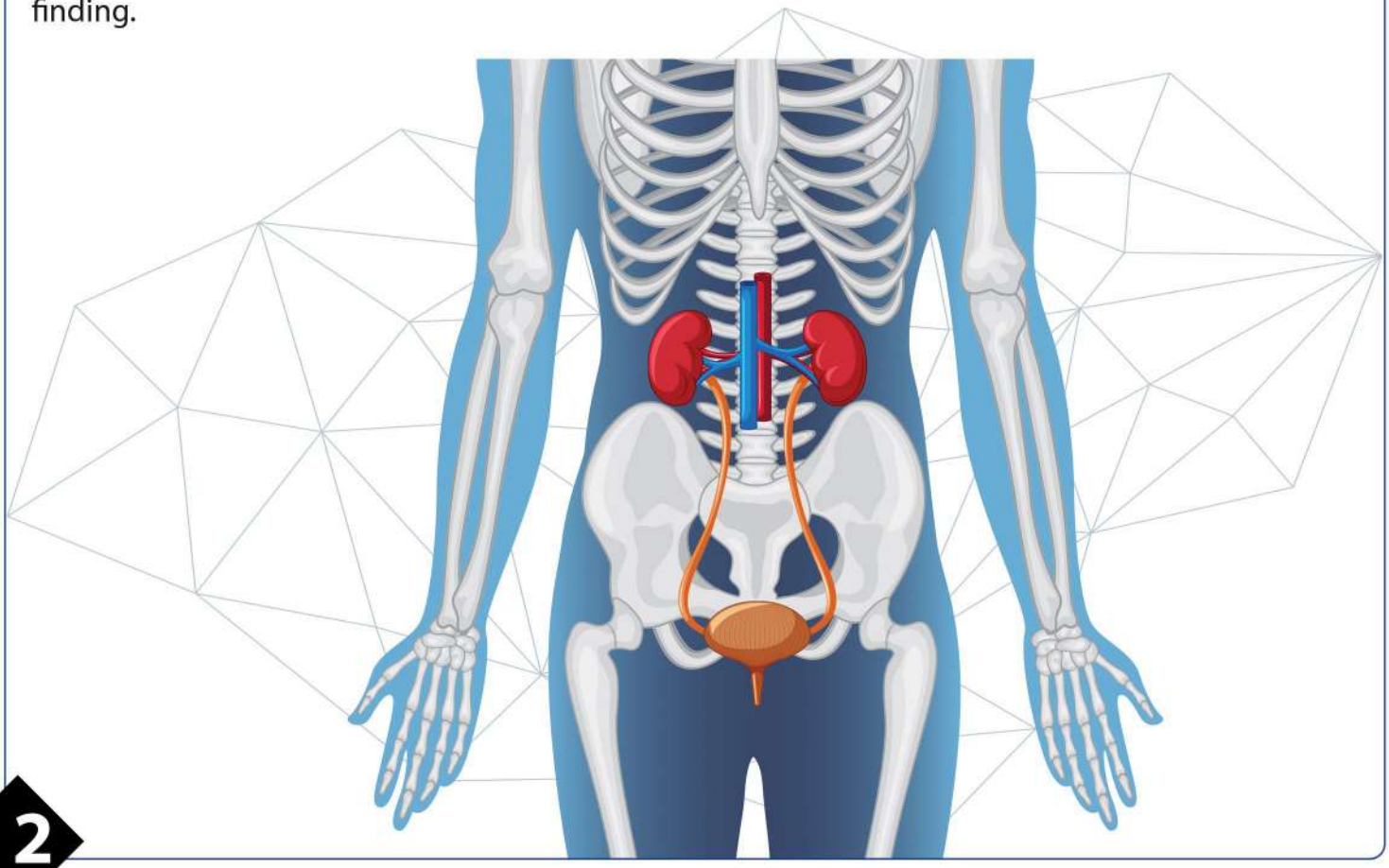
Conclusion

There are some evidences show that GE has some good effect on reducing oxidative stress, injury in renal tissue and reducing inflammatory markers such as (TNF-α, IL-1, IL-6, IL-8, T-cell, interferon-α and IL-2) that prevent CKD; However more documents are needed to prove our finding.



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The Effect of L-arginine on CKD Patients

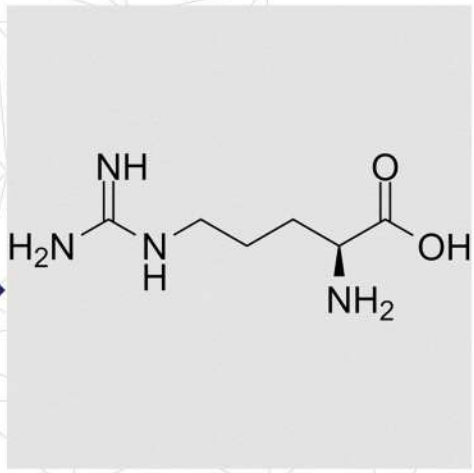
Introduction

Chronic Kidney Disease (CKD) is increasing worldwide and became a public health problem (1). CKD is a condition in which the kidneys are damaged and cannot filter blood as well as they should. Because of this, excess fluid and waste from blood remain in the body and may cause other health problems, such as heart disease and stroke (12).

The global estimated prevalence of CKD is 13.4% (11.7-15.1%), and patients with End-Stage Kidney Disease (ESKD) needing renal replacement therapy is estimated between 4.902 and 7.083 million. Patients with CKD are a very high-risk group for Cardiovascular Disease (CVD) and consequently, mortality. CKD could progress to an ESKD, which is the worst complication in renal function since it requires treatment with dialysis and transplant (1).

L-arginine, a main substrate for nitric oxide (NO) production, is involved in many physiological processes related to metabolic disorders and cardiovascular disorders. L-arginine is synthesized endogenously in the kidney using L-citrulline (2). A dual role of L-arginine on kidney has been reported in previous animal studies; increasing glomerular filtration rate (GFR) due to its potential to production of agmatine and stimulating glucagon release (2, 3). Conversely, L-arginine may induce adverse effects on kidney function due to enhanced inducible NO synthase activity, overproduction of NO, generation of polyamine and proline and consequently, promotion of proliferation and collagen formation (2). Short-term beneficial properties of L-arginine administration have been reported in some pathologic conditions including hypertension, hypertensive kidney disease and CVD (2, 4); however, the role of L-arginine in the pathogenesis and treatment of kidney disease is not completely understood. L-arginine could modify animal models of ischemic acute kidney failure and CKD. In fact, patients with CKD showed a reduced production of L-arginine by kidneys and this reduction seems to be correlated with the progression of CKD and mortality (1).

To the best of our knowledge, the association of L-arginine intakes from usual diet and the risk of kidney dysfunction is currently an important gap of knowledge. Therefore, we aimed to evaluate the association of total dietary L-arginine intake with the incidence of CKD in a national representative population.



Literature review

Zahra Bahadoran et al. published the result of a clinical trial in 2017 in Iran. They evaluated 1780 people participated in the Tehran Lipid and Glucose Study, followed for a median of 6.3 years. Dietary intakes of total L-arginine as well as animal- and plant-derived L-arginine were assessed using the validated semi-quantitative food frequency questionnaire, at baseline. Demographics, anthropometrics and biochemical variables were evaluated at baseline and again after a 3-year and a 6-year follow-up. The incidence of CKD was assessed across tertiles of L-arginine and its categories using multivariable logistic regression models. In the fully-adjusted logistic regression model, the highest compared to the lowest intakes of animal-derived L-arginine increased the risk of CKD. Animal-derived L-arginine was negatively associated with changes of estimated glomerular filtration rate and creatinine clearance rate during the follow-up. There was no significant association between total or plant-derived L-arginine intakes and the risk of CKD after 6.3 years of follow-up (2).

An interventional animal study by Michel Kendy Souza et al. was done in 2019 in Brazil investigated that L-Arginine supplementation blunts resistance exercise improvement in rats with CKD. Their study demonstrated that 10 weeks of Resistance Training (RT) improve the muscle strength, inflammation, arginase metabolism and renal function, besides protecting against renal fibrosis in an experimental model of CKD. However, the supplementation of L-arginine alone didn't improve muscle strength, had no effect on inflammatory system and didn't impair CKD progression (1).

An open-label study conducted by S. K. Annavarajula et al. in 2012 in India aimed to check the effect of L-arginine on arterial stiffness and oxidative stress in CKD. Total duration of the study was 17 weeks which included a 1-week run-in period and 4 weeks of follow-up. The drugs were administered for 12 weeks. The drugs were at the result of this study response to L-arginine was identical in both diabetics and nondiabetics and NO levels increased significantly. The systolic, diastolic, mean and pulse pressure of aorta and brachial artery also showed a significant decline with L-arginine necessitating a reduction in the dose of antihypertensive drugs in 19 of the 25 patients during the study period (5).

Hansongyi Lee et al. examined a study about amino acid metabolites associated with CKD in 2020 in Korea. This study used data drawn from the second follow-up of the Ansan-Ansung population cohort. They analyzed a total of 2579 subjects (with metabolite information) in the cross-sectional study (6, 7). In that study, single metabolites including branched-chain amino acids, alanine, arginine, asparagine, citrulline, glycine, histidine, methionine, phenylalanine, proline and their ratios were cross-sectionally associated with reduced estimated Glomerular Filtration Rate (eGFR). However, some amino acid metabolites related to oxidative stress (methionine sulfoxide/methionine) or nitric oxide production (citrulline/arginine), which were previously reported to be associated with CKD, were not found to be associated with a decline in kidney function (6, 8).

Discussion

The data on the effects of L-arginine in humans are conflicting. Therefore we will consider experimental studies in animal models (5).

Endothelial cells maintain a sufficient intracellular concentration of L-arginine to satisfy the Km of endothelial Nitric Oxide Synthase

(eNOS), treatment with exogenous L-arginine has been shown to cause improvements in endothelial NO synthesis. This has been referred to the "L-arginine paradox" and suggests that NO is derived from extracellular sources of L-arginine. Classified as a semi essential amino acid, the body is normally capable of producing sufficient quantities of L-arginine to sustain homeostasis; however, the synthesis of L-arginine occurs primarily in the kidneys and is impaired in CKD. Supplementation with exogenous L-arginine would therefore be highly beneficial to patients with CKD. To that end, L-arginine has been shown to prevent the progression of renal and endothelial dysfunction in rats when treatment was initiated immediately following renal mass reduction (9).

In the other hand in a randomized trial involving 25 normotensive children with CKD, Kathy et al. had shown an increase in plasma arginine concentration but with no improvement in endothelial dysfunction. In contrast, a clinical benefit with L-arginine was shown by Maxwell et al. in a randomized study of 36 patients with angina. The mean level of NO at the start of our study was lower than the levels seen in healthy population. Plasma levels of NO in CKD patients with type 2 diabetes mellitus were lower than in patients without diabetes. We could show a significant increase in the plasma levels of NO from a mean of 13.55 µM/L ± 7.49 to 30.22 µM/L ± 9.8 ($P < 0.001$) with L-arginine therapy and this effect was significant both in patients with or without diabetes. This increase in the plasma NO levels may help to retard the progression of CKD as shown in experimental studies in mice (5).

Another study demonstrated that 10 weeks of RT improve the muscle strength, inflammation, arginase metabolism and renal function, besides protecting against renal fibrosis in an experimental model of CKD. However, the supplementation of L-arginine alone did not improve

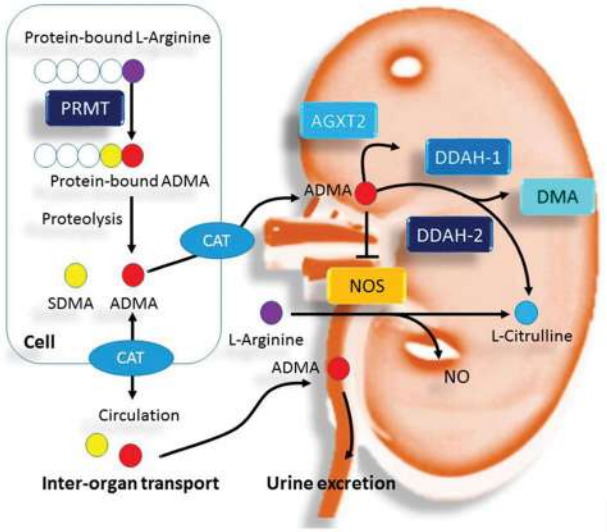


Figure 1: NOS and L-arginine mechanism in chronic kidney disease (10).

muscle strength, had no effect on inflammatory system and did not impair CKD progression. The combination of L-arginine supplementation to RT prevents the benefits observed by the RT performed exclusively (2).

Conclusion

Generally L-arginine supplement alone would not be as beneficial as combination of L-arginine with RT. In addition, high concentrations of baseline amino acids and their ratios were associated with CKD incidence. Multiple amino acid metabolites showed higher predictive ability than single metabolites. It is determined that amino acid levels and their ratios differed according to inflammation or proteinuria status and as underlying drivers of CKD pathology, can be used as biomarkers of CKD due to their modified metabolism. Absolute quantification of amino acid metabolites and their regulatory enzyme activities is needed to design CKD treatment strategies (11).

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Zinc Supplementation in Hemodialysis Patients

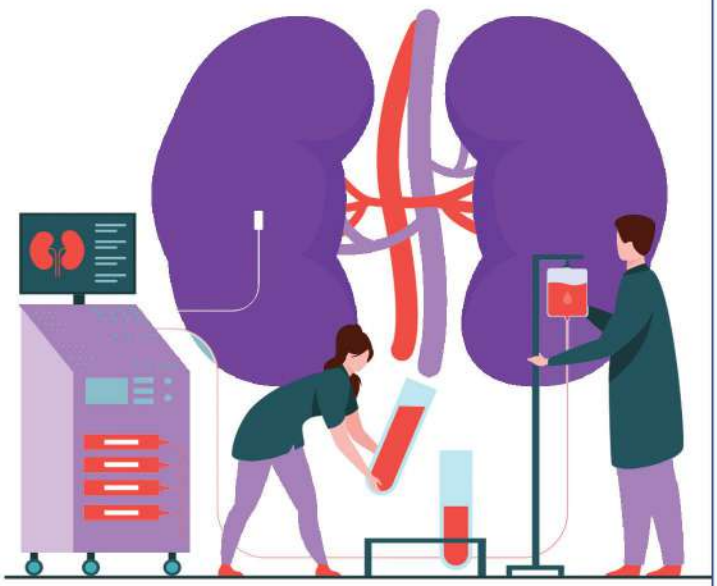
Introduction

Chronic Kidney Failure (CKF) is caused by progressive and irreversible destruction of nephrons, in which the body's ability to maintain metabolism and balance of water and electrolytes is lost and uremia occurs. Hemodialysis (HD), peritonea dialysis and kidney transplant are among the treatment methods for kidney failure. The annual prevalence of this disease in Iran is about 29,000 people, of which 14,000 people are treated with HD. HD is a treatment method for patients with acute and CKF, which is used to correct the imbalance of water, electrolytes and blood chemicals. In HD patients, the concentration of systemic inflammatory factors and vascular inflammatory factors increases. Hypotension is the most common acute side effect of HD (1).

CKF is one of the major public health problems in the world, which affects 8-16 percent of the population worldwide. In Iran, the prevalence of End-Stage Renal Disease (ESRD) has increased by 14.9% and 5.3%, annually in periods of 1995–2004 and 2005–2014. HD reduces uremic toxins by equilibration of plasma and dialysate across a semipermeable membrane. Substances which have higher concentrations in blood than in dialysate tend to be cleared by dialysis. Although this can exert beneficial effects on the clearance of the uremic toxins, it may cause a diminution of essential elements. Due to continuous removal of trace elements by dialysis and low dietary intake that results from uremic-related anorexia as well as dietary restrictions, HD patients are at increased risk of trace element deficiency (2).

ESRD and CKF have become one of the world's major problems that increase morbidity and mortality in the world and putting pressure on health systems. The prevalence of zinc deficiency in HD patients is reported to be 40-78%. Previous studies have confirmed that zinc deficiency may be a predisposing factor for insulin resistance, impaired glucose tolerance, increased lipid profile, atherosclerosis and cardiovascular diseases (3).

The present study aimed to investigate the effect of zinc supplementation on HD patients. Zinc is an essential trace element for human nutrition and its deficiency is associated with growth retardation, anorexia, insulin resistance and impaired immune systems. Patients undergoing HD have been reported to have low serum concentrations of zinc due to inadequate dietary intake, reduced gastrointestinal absorption and zinc removal during HD sessions (5).



Literature review

In placebo-controlled, double-blind and randomized trial study in 2019 in Iran, Halim et al. investigated associations between the high prevalence of insulin resistance and zinc deficiency among hemodialysis patients. After 60 days of intervention in the experimental group, Fasting Blood Sugar (FBS) and insulin significantly (all $p<0.05$) decreased compared to the placebo group. Additionally, there was a significant reduction in serum triglycerides ($P<0.001$) and LDL-c concentrations ($P<0.001$) after the administration of zinc supplements compared to placebo (3).

In 2020 Fukasawa et al. was accomplished a research which involved 87 hemodialysis patients in Japan. Evaluating the Impact of Serum Zinc Levels on Abdominal Fat Mass in Hemodialysis Patients, was aim of this study. Their findings suggest that serum zinc levels could play a vital role ($p<0.01$) in determining abdominal fat mass in hemodialysis patients (5).

In the prospective study in 2021 Garagarza et al. analyzed the relationship between zinc intake and mortality in HD patients in Portugal. This multicenter study with 582 HD patients from 37 dialysis centers, discovered that there is a high prevalence of HD patients with an inadequate zinc intake, which is related to worse nutritional, body composition parameters and with a higher mortality risk (6).

In the single-blind randomized clinical trial by Sadeghi et al. in 2019, 61 HD patients were examined for 60 days. Evaluating the effect of zinc supplementation on weight and dietary intakes in hemodialysis patients, was aim of this study. As a result, after two months zinc supplementation, a significant improvement ($P=0.046$) was observed in the weight of the patients compared to the control group (2, 7, 8).

Discussion

Zinc, as an essential trace element with vital roles in human body, is reported to be deficient in HD patients. Zinc supplementation could positively affect dietary intakes and weight of HD patients. This effect may be exerted through various mechanisms (9).

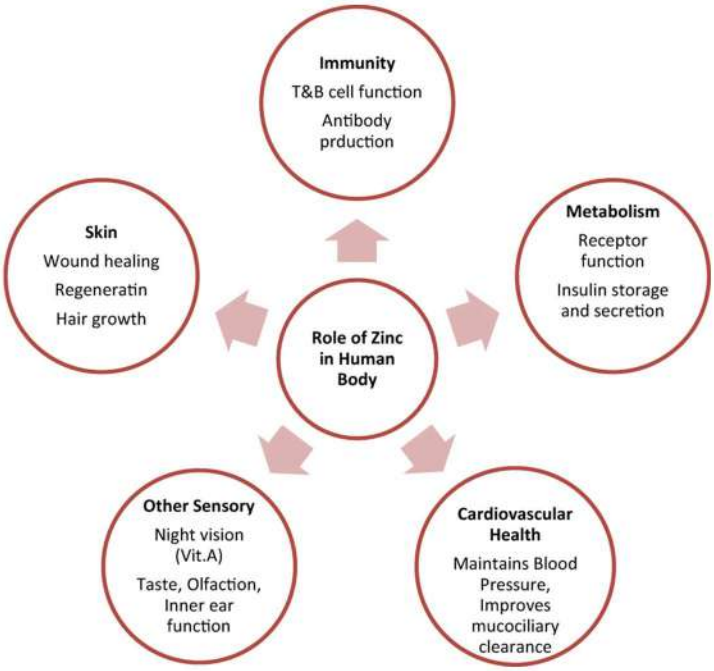
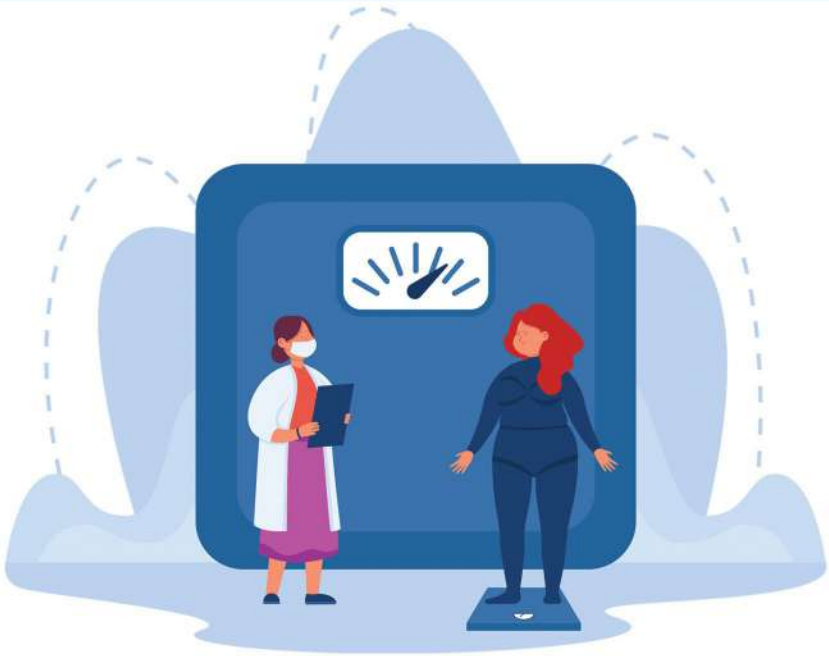


Figure1: The role of zinc in human body (4).

First of all, it has been suggested that zinc supplementation could prevent taste changes which occur in HD patients because of the accumulation of uremic toxins (7).

Second probable mechanism is the positive effects of zinc supplementation on hormones involved in appetite control like leptin and gain weight control like ghrelin (10). Previous studies have shown that zinc has an important role in stabilizing insulin hexamers and the pancreatic storage of insulin as it can increase insulin binding to hepatocyte membranes (11).



Khan et al. in their study demonstrated that 50mg of elemental zinc as zinc sulfate supplementation for 12 weeks in type-2 diabetes with microalbuminuria patients has resulted in a significant decrease in triglycerides, Very Low-Density Lipoprotein cholesterol (VLDL-c) and a significant rise in High Density Lipoprotein cholesterol (HDL-c) levels (12). Serum zinc levels may be a predictor of visceral fat areas in the abdomen of HD patients. Adipose tissues in subcutaneous fat obesity might function normally with the expected release of anti-inflammatory adipocytes, whereas adipose tissues in visceral fat obesity release an increased amount of pro-inflammatory adipocytes and suppress the secretion of anti-inflammatory adipocytes, thereby creating low-grade inflammation which contributes to systemic metabolic and cardiovascular diseases (13,14).

It remains unclear whether the difference of abdominal fat distribution plays a role in the risk for mortality and how zinc in the serum affects abdominal fat distribution in HD patients. Further studies are needed to answer these enigmas. There is a high prevalence of HD patients with an inadequate zinc intake, which is related with worst nutritional and body composition parameters and with a higher mortality risk. Food sources that most contribute to increase zinc consumption are also rich in protein, which is also an extremely important nutrient for these patients (20).

Conclusions

In conclusion, serum zinc levels are significantly and positively correlated with abdominal fat areas in HD patient and can improve weight of HD patients. Also, it has beneficial effects on glycemic status parameters, triglycerides and LDL-c levels.

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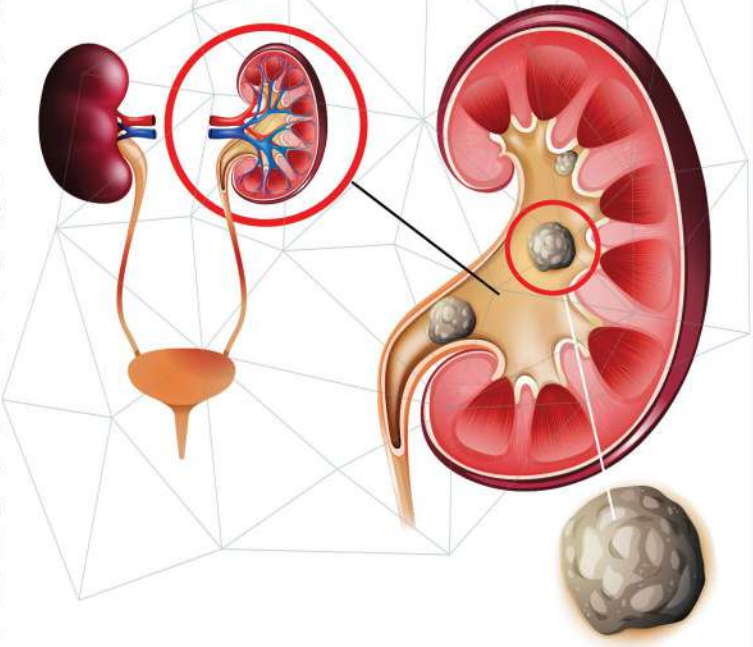
Nephrolithiasis and Caffeine

Introduction

Nephrolithiasis, referred to as kidney stones, is the most common chronic kidney condition, after hypertension (1). Stones typically develop in the kidney and pass through the urine. Nephrolithiasis is an acutely painful and often recurrent condition that affects all ages, races and genders. Nephrolithiasis presents as acute flank or abdominal pain with nausea and vomiting. Noncontracted computed tomography scan is first-line to diagnose kidney stones in nonpregnant adults. Ultrasound is first-line in children and pregnant women. According to the study, kidney stone prevalence was 10.6% in men and 7.1% in women, with an overall prevalence of 8.8%. This increase has occurred across all ages, races and genders. In male individuals, kidney stone incidence begins to rise after age 20 and peaks between 40-60 (2).



3 large cohort studies have been used to investigate risk factors for nephrolithiasis occurrence and recurrence. In All 3 studies associations was found between nephrolithiasis and weight gain, Body Mass Index (BMI) and diabetes mellitus. Both a higher baseline BMI and a 35 pound or more weight gain since early adulthood significantly increased the risk of developing a kidney stone and the increased risk was higher in women than in men. A history of type 2 diabetes mellitus also increased risk for kidney stone development, independent of diet and body size. Several other nondietary risk factors exist: family history (a family history of kidney stones increases risk by 2.5 times), systemic disease (primary hyperparathyroidism, renal tubular acidosis and Crohn's disease increase risk), history of gout (increases the likelihood of forming both uric acid stones and calcium stones), working (or living) in a hot environment. Urine composition is influenced by dietary composition and the high or low intake of several nutrients are linked to an increased risk of kidney stone formation. High urinary excretion of substances such as calcium, oxalate, cysteine and uric acid promote stone formation, whereas substances like citrate and magnesium are protective (2).

Knowing the factors which result in nephrolithiasis, it can be treated depending on the type of stone. Fortunately, most stones are excreted without surgery but many of them are not excreted on their own and require pharmacotherapy. About 90% of stones can be excreted through consumption of liquids. Surgery is required when: stones are large or growing that they are not excreted after the expected time, pain is permanent and stable, stone prevents urine excretion, The existence of urine infection and Kidney tissue is destructed. Finally, if it results in kidney fluctuations, kidney should be dialyzed and if it does not get better, kidney transplant is the last solution (3).

In this study, we investigated the effect of caffeine on kidney stones, and we concluded that according to the studies, caffeine consumption has protective effects against the formation of urinary stones (4).

Literature review

Shuai Yuan conducted a Mendelian Randomization (MR) analysis study in 2021 in UK. In this study, MR analysis was used to determine the relationship between coffee and kidney stones, and genetic factors were also investigated. Based on the analysis that was done, they concluded that there is an inverse relationship between coffee consumption and kidney stones (4).

A matched case study was conducted from June 2017 for six months with the aim of investigating the relationship between the consumption of carbonated drinks and the formation of kidney stones at Liaquat National Hospital Karachi, Pakistan by Maria Adeel. In this study, nephrolithiasis patients who were hospitalized in the nephrology department were selected. The sample size was 186 people, 93 were cases and 93 were controls and the average age of the samples in this study was 34.92 years. Multivariate logistic regression analysis was used. In multiple analyses, we failed to find a significant association between carbonated beverage consumption and kidney stones. People who have a history of kidney stones in the past are more exposed to this disease. As a result, this study did not show a significant relationship between the consumption of carbonated drinks and kidney stones and more studies are needed in this field (5).

A systematic review was preformed using the Medline, Cochrane library and Scopus databases by Yazeed Barghouthy in 2021 that aimed to investigate the effect of tea and coffee on the risk of nephrolithiasis. The major findings show that caffeine increases urinary excretion of calcium, sodium and magnesium, in addition to a diuretic action with consumption approximately four cups of coffee, this beverage might have potential protective effects against the formation of urinary stones (6).

People who had a history of passing at least one kidney stone from 2007 to 2014 were examined by Yao Fei Sun in 2019 in the national health and nutrition survey aimed to investigate the effect of caffeine intake on recurrent kidney stone. The results showed that caffeine intake was independently and linearly associated with a higher risk of recurrent kidney stones among adults especially for women and non-white race (7).

Discussion

There are several underlying mechanisms supporting inverse associations of coffee and caffeine consumption with kidney stones. Caffeine exerts diuretic properties by adenosine receptors in the kidney. Adequately compensated by water intake, the caffeine contained in coffee beverages results in an increase in urine flow, which represents an important protective factor against the development of kidney stones. Caffeine can also reduce calcium oxalate crystal adhesion on the apical surface of renal tubular epithelial cells (5).

Caffeine is essentially 100% bioavailable and is rapidly absorbed into the blood circulation after oral intake; absorption in the stomach and small intestine occurs 45 min after ingestion. Caffeine is then distributed to almost all tissues and body fluids, with the plasma concentration peak reached 15–120 min after intake. The half-life of caffeine in plasma is

Coffee and Caffeine Consumption and Risk of Kidney Stones

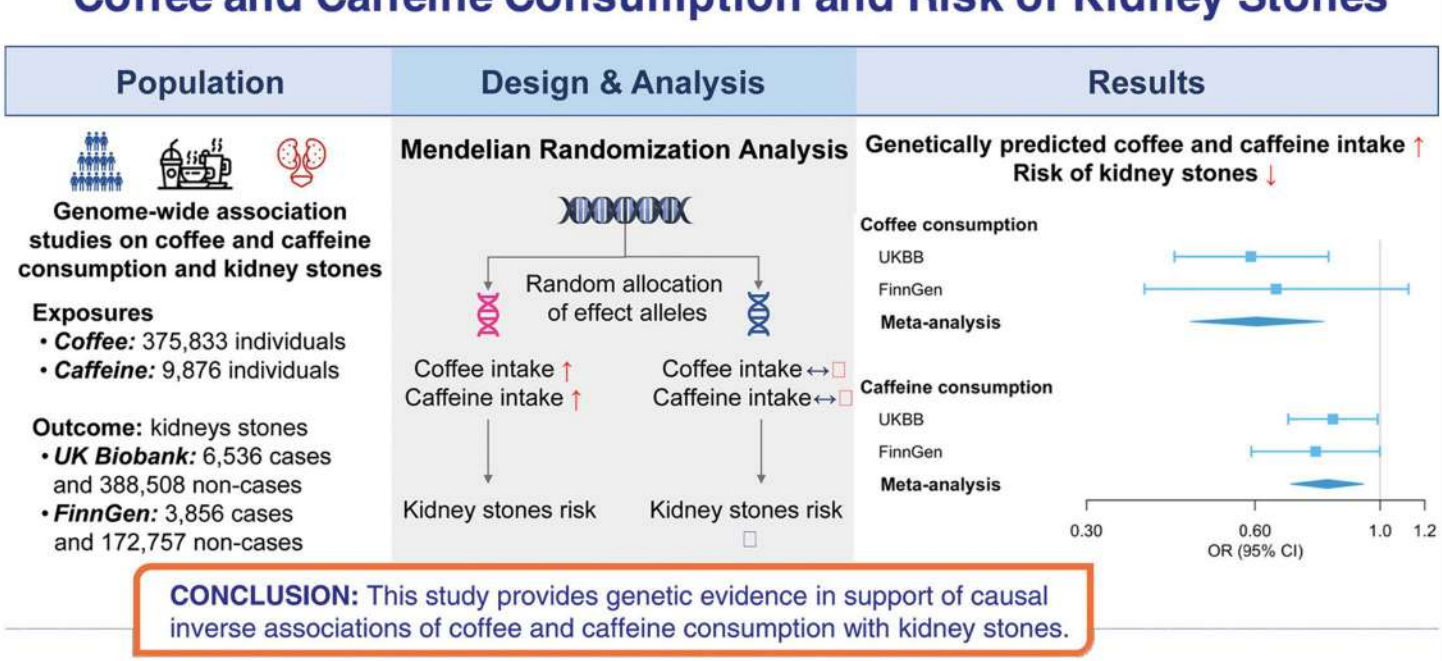


Figure1: The relationship between caffeine and nephrolithiasis and its outcome (4).

2.5–4.5 hours in young subjects and slightly longer in elderly subjects. Once in the circulation, 98% of circulating caffeine, a methylxanthine alkaloid, is metabolized in the liver by cytochrome P450 to its metabolites. The remaining ~ 2% of unmetabolized caffeine is directly excreted into the urine (7).

Conclusion

According to the studies that were conducted on the relationship between caffeine consumption and kidney stone formation, each of them showed different results. In some of them, it was said that there is no effective relationship, and another study, showed that the consumption of carbonated drinks could not have an effect on kidney stones. Although some studies have said that caffeine has a hypercalciuria effect, which increases urination after consumption, such as green tea, which has a protective effect on the formation of kidney stones. For people who experience kidney stones, caffeine consumption can have a negative, linear and independent effect.

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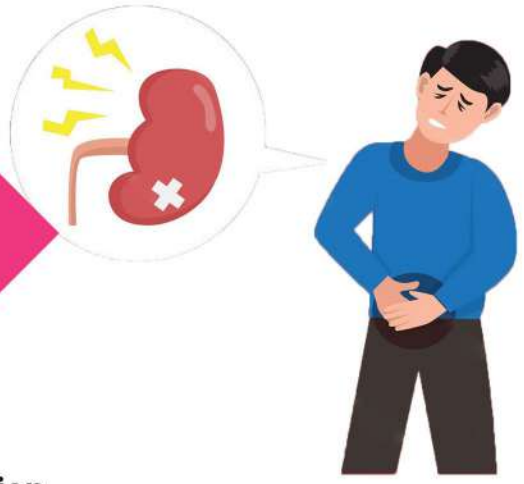
DASH Diet and Prevention of CKD



Introduction

Chronic Kidney Disease (CKD) is a worldwide concern that interferes with the body's physiological and biological mechanisms and it can lead to other health conditions. Based on The National Kidney Foundation (NKF), CKD is either a decline in Glomerular Filtration Rate (GFR) to <15 mL/min/1.73 m^2 or the presence of kidney damage persisting for at least three months. Most CKD patients are unaware of their condition due to a lack of apparent symptoms in early stages.

Medical nutrition therapy is important for CKD because it may slow the progression of the disease through careful monitoring of protein, calcium, phosphorus, potassium and sodium, relieving symptoms experienced in CKD patients while not restricting too many nutrients that would put the patient at high risk for malnutrition (3). The Dietary Approaches to Stop Hypertension (DASH) diet is one of approaches that has been considered in CKD patients since it lowers blood pressure. DASH diet is rich in fruits, vegetables, low-fat dairy products, and saturated and total fat are limited in this diet. The DASH diet lowers blood pressure and is recommended to manage hypertension and prevent Cardiovascular Disease (CVD) (1, 2).

Studies have shown the association between healthy dietary patterns and the primary prevention of major health conditions, including type 2 diabetes, CVD, hypertension and metabolic syndrome; however, the effect of a healthy diet on CKD is still unclear. Therefore, in this study, we will discuss the association between DASH diet, CKD and its progress (4).

Literature review

In the article written by Kalan L. Raphael in 2019 with the topic The Dietary Approaches to Stop Hypertension (DASH) diet in chronic kidney disease: should we embrace it? published, acknowledged that hypertension is a risk factor for CKD and its progression. It is possible that the DASH diet also preserves kidney function. The DASH dietary pattern is associated with lower serum uric acid levels and a lower risk of kidney stones. During 8 weeks, 459 people with systolic blood pressure less than 160 and diastolic blood pressure 80 to 95 mm Hg were tested. In the hypertension subgroup, the DASH diet, fruits and vegetables had a significant effect and systolic blood pressure /diastolic decreased by 11.4/5.5 and 7.2/2.8 mm Hg respectively (1).

In an article published in 2020 entitled Poor accordance to a DASH dietary pattern is associated with higher risk of End-Stage Renal Disease (ESRD) among adults with moderate chronic kidney disease and hypertension by a group of

group of authors under the supervision of Tanushree Banerjee, the result was that the increase in the level of dietary magnesium in the DASH score may lead to less production of inflammatory and proatherogenic cytokines in endothelial cells. Low adherence to the DASH diet, low base-stimulating foods such as K and Mg in the diet and acid-stimulating foods such as dietary protein may lead to metabolic acidosis, especially in patients with CKD. This may stimulate the secretion of aldosterone, which has adverse hemodynamic effects and causes renal fibrosis (2).

In a 2021 study by Tania Naber entitled CKD: Role of Diet for a Reduction in the Severity of the Disease, it was found that CKD is a growing health crisis in the United States. Diabetes and high blood pressure are the main causes of CKD. As the United States experiences an increasing prevalence of both, CKD is expected to remain an important national health issue. In ESRD, the kidneys have lost their ability to function and as a result, a series of disorders occur that lead to health problems and health outcomes. Medical nutrition therapy with registered dietitian is a critical aspect of intervention for CKD because it is almost exclusively through nutrition that helps delay disease progression and prevent comorbidities and mortality (3).

Katrina E. Bach et al. conclude that article Healthy Dietary Patterns and Incidence of CKD in 2019, on the importance of following a healthy diet rich in vegetables, fruits, legumes, nuts, whole grains, fish and low-fat dairy products and consuming less meat. Red and processed sodium and sugar-sweetened beverages emphasized to reduce the incidence of CKD and albuminuria (4).

Discussion

Hypertension is a hazard component for CKD and its progression. The DASH diet lowers blood pressure. The DASH diet is wealthy in fruits, vegetables, low-fat dairy, and saturated and total fat is limited in this diet. Fruits and vegetables are wealthy in potassium and bicarbonate, which may have defensive consequences on the kidney. A growth in dietary magnesium ranges in the DASH rating also result in a decreased manufacturing of inflammatory and proatherogenic cytokines in endothelial cells. Low adherence to the DASH diet low base-stimulating ingredients consisting of dietary potassium and magnesium and acid-stimulating ingredients consisting of dietary protein, may lead to metabolic acidosis, specifically in sufferers with CKD. This may stimulate aldosterone secretion and cause Kidney fibrosis. After the prognosis of ESRD, the patient either undergo dialysis for the rest of his existence or gets a kidney transplant (5).

Below is an example of a diet to prevent high blood pressure and kidney disease, which is a combination of the Mediterranean diet and the DASH diet (Fig1).

DASH diet		Mediterranean diet	
Food group	Daily servings	Food group	Recommendation
Whole grains	7 to 8	Whole grains, vegetables, fruits, seeds, olive oil, beans, nuts, legumes	Base every meal on these foods
Vegetables	4 to 5		
Fruits	4 to 5		
Dairy, low-fat or nonfat	2 to 3	Fish, seafood	Eat at least twice a week
Lean meats, poultry, fish	2 or fewer	Poultry, eggs, yogurt, cheese	Eat moderate portions daily to weekly
Nuts, seeds, dry beans	4 to 5 per week		
Fats and oils	2 to 3	Meats and sweets	Eat less often than other foods
Sweets	5 per week	Wine	Drink in moderation

Figure 1: Key features of the Dietary Approaches to Stop Hypertension (DASH) and Mediterranean diets (5).

Conclusion

Medical nutrition therapy for CKD slows disease development via cautious monitoring of protein, calcium, phosphorus, potassium and sodium. The DASH dietary sample related to decreasing serum uric acid levels and a decreased chance of kidney stones.

Fatemeh Rajabalizade [1]

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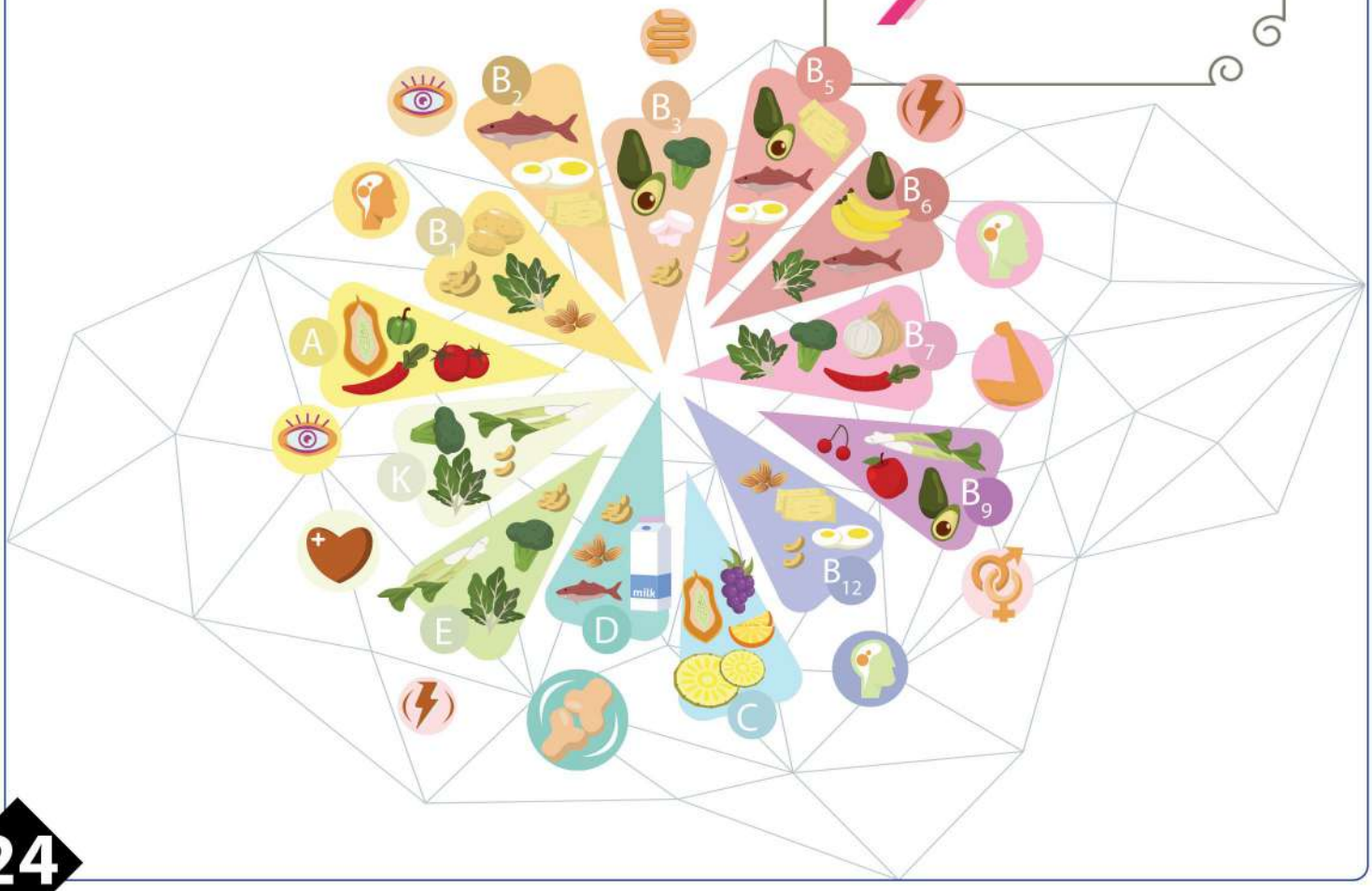
Mohadese Homaie far [1]



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The Effect of L-carnitine on Chronic Kidney Disease

Introduction

Nowadays, the world's disease profile is rapidly changing and chronic life circumstances account for most global morbidity and mortality. The number of Chronic Kidney Disease (CKD) patients is increasing worldwide. CKD encompasses a spectrum of pathophysiological processes associated with abnormal kidney function and progressive decline in glomerular filtration rate. This trend is related to the aging of the population, increasing prevalence of diabetes mellitus and hypertension, earlier detection of kidney disease and earlier referral of patients (1).

L-Carnitine (LC) has become of interest in End-Stage Renal Disease (ESRD) since loss during dialysis and reduced renal synthesis has been suggested as the cause of LC deficiency in patients on hemodialysis, which in turn has been associated with several symptoms frequently encountered in these patients (2).

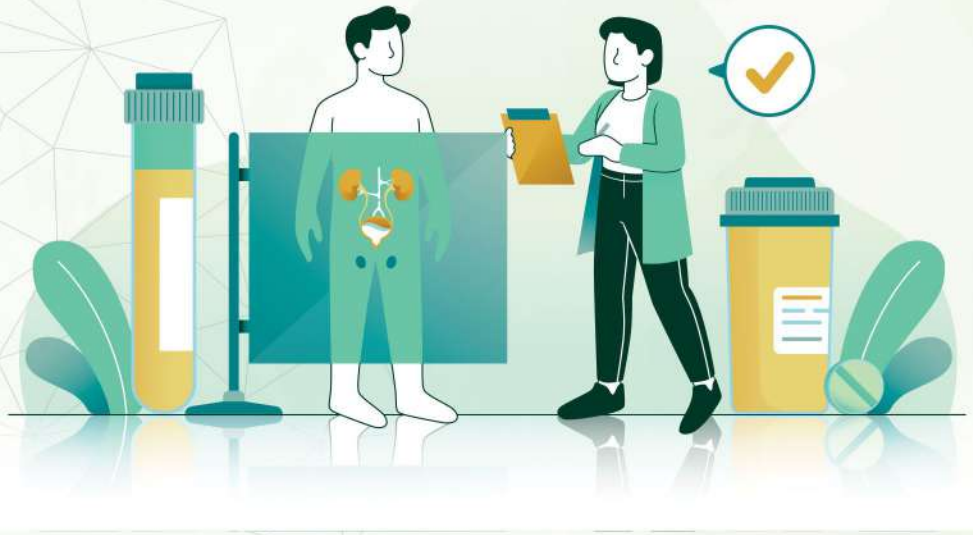
Carnitine is a naturally occurring compound involved in critical metabolic pathways in mammals. It is only active in the L-isomer form, LC; it is best known for its essential role in mitochondrial oxidation of long-chain fatty acid (3).

In this research, we evaluated the effect of LC on renal function.

Literature review

In 2021, Hai-lan Zheng conducted a study by the National Natural Science Foundation of China regarding the protective effect of LC against tacrolimus-induced kidney damage by reducing programmed cell death through PI3K/AKT/PTEN signaling. They investigated the protective effects of LC in a mouse model of chronic tacrolimus nephropathy (TAC). Sprague Dawley (SD) rats were injected with TAC (1.5 mg/kg/d-1, sc) for four weeks. The protective effects of LC were evaluated in terms of renal function, histopathology, oxidative stress, expression of inflammatory and fibrotic cytokines, programmed cell death (proptosis, apoptosis and autophagy), mitochondrial function and PI3K/AKT/PTEN. Nephropathy at the molecular level, TAC significantly increased the expression of inflammatory and fibrotic cytokines in the kidney. Which finally showed that LC has a protective role against various types of kidney damage (4).

The study aimed to investigate the side effects of 8 weeks of LC oral supplementation (0.3 and 0.6 g/kg) in male and female SD rats by Liu L in 2015 in China. LC decreased body weight and fat and lipid levels in serum, liver and kidney in rats. Also, hepatic fatty acid oxidation and lipid synthesis were impaired in mice. LC increased the production of reactive oxygen species in the serum and liver and, as a result, activated the NOD-like hepatic receptor 3 (NLRP3) inflammasome to increase the serum levels of interleukin (IL)-1 and IL-18 in mice. LC can disrupt kidney function by changing the renal organic ion transporter protein levels in rats (5).



Abu Ahmad conducted a study in 2016 to investigate the effects of LC treatment on kidney function and cognitive function in a progressive CKD mouse model. To assess the role of LC on CKD status, they estimated kidney function and cognitive abilities in a mouse model of CKD. They found that all CKD animals showed worsening renal function, as marked by elevated serum creatinine, Blood Urea Nitrogen (BUN) and histopathological abnormalities. LC treatment of CKD rats significantly reduced serum creatinine and BUN, reduced renal hypertrophy and reduced renal tissue damage. As a result, in a CKD mouse model, administration of LC significantly improved adrenal cognitive functions (6).

Yen-Cheng Chen conducted a study on the combined protective effects of oligo-fucoidan, fucoxanthin and LC on all mice with CKD in 2021 in Taiwan. They established a mouse CKD model by right nephrectomy with transient ischemic injury to the left kidney. CKD rats were fed the two compounds and LC to evaluate the effects of the combination on CKD. Oligo-fucoidan and fucoidan inhibited renal fibrosis and reduced serum creatine in CKD rats. LC had no measurable effect on renal fibrosis, but mixed oligo-fucoidan and fucoidan had a protective effect on kidney function in CKD rats. A two-month immunoassay showed that the combined mixture further improved renal function and did not increase the serum levels of aspartate aminotransferase and alanine aminotransferase in CKD rats. Also, the weight of CKD rats treated with this compound increased (7).

In 2014, Lorenzo Di Liberato researched the status of LC in patients with ESRD undergoing Automatic Peritoneal Dialysis (APD) in the Italian Society of Nephrology. They investigated carnitine levels in plasma from adult uremic patients treated for Continuous Ambulatory Peritoneal Dialysis (CAPD) or APD. Materials and methods plasma levels of carnitine and its esters by high-performance liquid chromatography/quadrupole tandem mass spectrometry in 14 patients with CAPD (3×1.5% glucose daily and icodextrin overnight), 16 patients with APD (method tidal), and eight patients measured in age. Abnormalities in plasma carnitine species were found in patients with Peritoneal Dialysis (PD) compared to the control group, mainly shown by a decrease in free carnitine and an increase in acetyl-carnitine, dicarboxylic and other carnitines. The main carnitine species (free carnitine, acetylcarnitine) were significantly lower in plasma from APD than in CAPD patients. APD patients tolerated LC supplementation well, laboratory, physical and dialysis. Considering the benefits of carnitine used in liquid PD, the solution bags containing LC in the treatment of APD should be further evaluated (8).

Discussion

The kidney is the main organ for synthesizing LC in animals. It also plays an essential role in LC's metabolism, excretion, secretion and reabsorption (9).

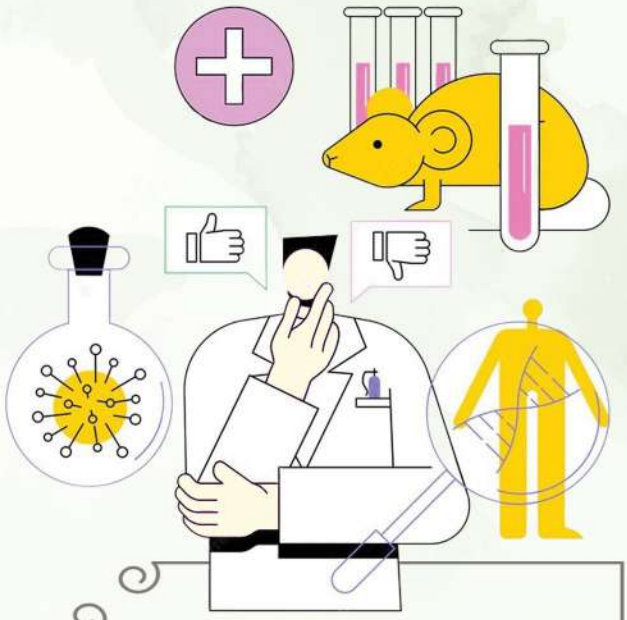
LC supplementation is usually applied to manage carnitine. LC possesses antioxidative and anti-inflammatory properties and may play diverse roles. LC attenuates myocardial injury after cardiopulmonary bypass in rheumatic valvular heart disease patients by mitigating inflammatory cytokine production and modulating oxidant enzymes (10). The benefits of LC have also been observed in fatty liver disease, metabolic disorders, and polycystic ovary syndrome (11). Moreover, LC reduces inflammation in hemodialysis patients with hyperlipoproteinemia and animal models of hypertension-associated renal fibrosis (12). CKD patients, especially those receiving hemodialysis, often suffer from a lack of LC (13).

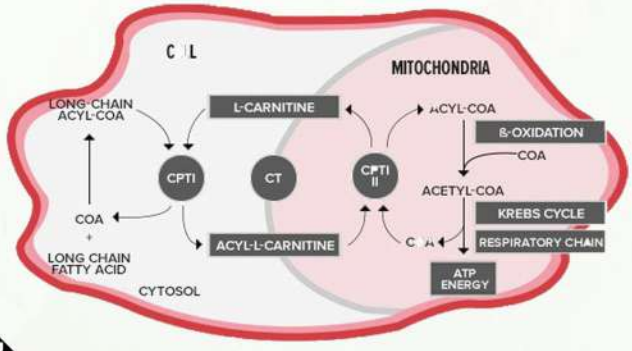
LC facilitates the entry of long-chain fatty acids into mitochondria for utilization in energy-generating processes (14). CKD is characterized by permanent loss of nephrons and an eventual reduced glomerular filtration rate (15). Progressive nephron loss is mainly due to stress-induced glomerular and tubular cell death (16). Severe nephron loss will eventually cause renal fibrosis; renal fibrosis is recognized as a critical determinant of progressive CKD due to the strong correlation between the degree of fibrosis and renal functional loss. Therefore, the prevention of both renal apoptosis and fibrosis will be beneficial for the treatment of CKD patients (17).

Conclusion

Our results indicate that prolonged administration of LC exerted significant renoprotective effects in a rat model by slowing the deterioration of renal function, decreasing undesirable kidney hypertrophy and ameliorating histopathological hallmarks of renal tissue damage and LC may be considered as a supportive treatment for CKD patients.

For the application of LC in food supplementation, more studies on LC supplementation-induced adverse side effects with lipid metabolism disorder and major organ function disturbance should be carried out.





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Vitamin D Deficiency in ESRD

Introduction

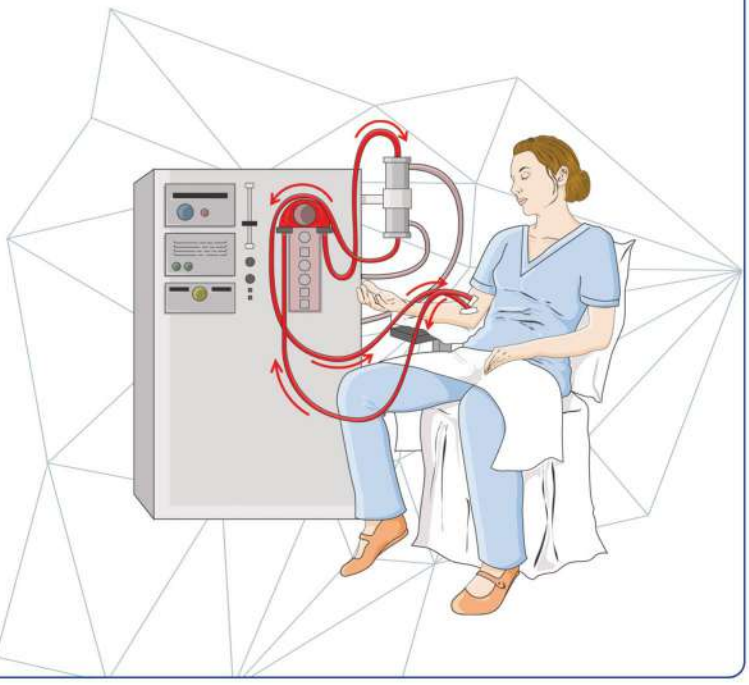
Vitamin D is a fat-soluble secosteroid that has a specific cytosolic receptor And it plays a central role in calcium and phosphate metabolism (1). The deficiency of vitamin D is a risk factor for diabetes, autoimmune disease, neurodegenerative, cardiovascular and renal diseases tuberculosis, depression and cancer (1, 2). Humans acquire approximatively 80% vitamin D from sunlight-induced dermal synthesis, the rest comes from diet and supplements, the main circulating form of vitamin D is 25-hydroxyvitamin D (25(OH)D). Some experts have defined vitamin d deficiency levels less than 20 ng/ml and insufficiency between 21 and 29 ng/mL, amounts above 30 are recommended for optimal health. The Workshop Consensus for Vitamin D Nutritional Guidelines estimated that more than 50% of the older population and the younger populations, even in sunny countries are vitamin D-deficient or vitamin D-insufficient (1, 3).

The factors that affect vitamin D deficiency include age, sex, race and impaired vitamin D synthesis and metabolism. Because of 25(OH)D deficiency, the level of serum $1,25(OH)_2D$ decreases progressively, beside impaired availability of 25(OH)D by renal proximal tubular cells, high fibroblast growth factor (FGF)-23 and decreased functional renal tissue (1).

Infections are common and can be fatal in patients undergoing long-term dialysis, it's the second leading cause of death in patients with Chronic Kidney Disease (CKD). One potential reason for the heightened infection risk is an accession of vitamin D deficiency (4).

In patients with CKD, End-Stage Renal Disease (ESRD), even in dialysis patients, 25(OH)D3 deficiency is a common problem and also the inflammatory responses increase in these patients (1, 2).

Experts have recognized that vitamin D insufficiency and deficiency should be avoided in CKD and dialysis patients. Therefore, supplementation with active vitamin D, is commonly practised in patients with CKD and ESRD. However, recently it has been shown that 25(OH)D can be converted to $1,25(OH)_2D$ at sites other than the kidney, including the prostate, breast, colon and macrophages (1, 3).



In this article, we aim to investigate the effect of vitamin D deficiency and the cause of its decrease in patients with ESRD.

Literature review

A cross-sectional study was conducted in Kerman, Iran in 2019 by Abbas Etminan et al. The aim of this study was to evaluate the relation of 25(OH)D3 with the indirect inflammatory markers in patients on hemodialysis (HD) and peritoneal dialysis (PD). Patients was grouped according to the presence of HD (64 persons) and PD (21 persons) and Serum level of 25(OH)D3 was measured in each patient. This study showed that as the duration of Renal Replacement Theraphy (RRT) increases, the level of vitamin D also increases, which is not seen in PD patients (2).

The aim of a clinical study in 2012 in New Delhi, India that conducted by Beena Bansal et al. was undertaken to determine the vitamin D status of 45 Indian CKD patients on HD. 25(OH)D levels were measured with radioimmunoassay (Diasorin) method and parathyroid hormone (PTH) was measured using electrochemiluminescence immunoassay (ECLIA). However, severe vitamin D deficiency was seen in 64.4% of patients with serum 25(OH)D values below 10 ng/ml (3).

In 2019 in Oxford University, Guobbin Su et al. conducted a clinical trial. The aim of this study was to check the levels of serum 25(OH)D or use of vitamin D in long-term dialysis patients. When compared with those who did not use vitamin D, the pooled adjusted risk for composite infection was 41% lower in those who used vitamin D [RR 0.59 (95% CI 0.43–0.81)] (4).

A review study was conducted in 2017 in France by Guillaume Jean, et al. aimed to check the Effect of Native Vitamin D Supplementation on CKD and DP and published studies have shown that vitamin D deficiency is more common in CKD than in HD and PD and Native vitamin D supplementation should be the first line of treatment and prevention (1).

Discussion

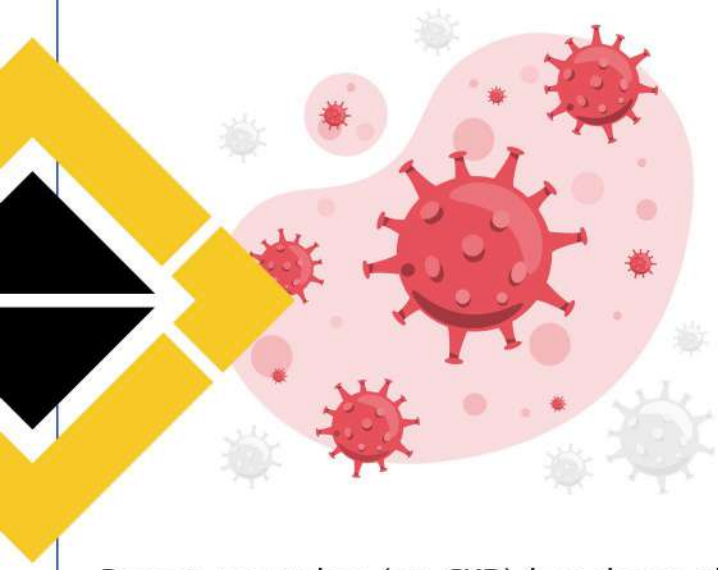
By examining the level of 25(OH)D3 in patients, we conclude that it is lower in PD patients than in HD patients and also we conclude that level of platelet and ESR are higher in PD patients (2).

Vitamin D has a potential anti-inflammatory effect and has a discrete relationship with the increase of C-reactive protein (CRP). Among other things needed to check is vitamin D deficiency and inefficiency in patients. Of the 85 patients (HD/PD) who entered the survey, 72 patients (72/94%) had vitamin D deficiency (20 ≥ng/dl) and 11 patients (12/94%) had vitamin D insufficiency (20-29 ng/dl), also we have

report that more than 50% of the older population are vitamin D-deficient or vitamin D-insufficient (1, 2).

Vitamin D deficiency is associated with insulin resistance. Vitamin D resistance has been reported in CKD patients before dialysis (1).

It is important to say that vitamin D related to risk of sudden death as a result of heart failure in both general population and patients on RRT (2).



Recent researches (on CKD) has shown that daily (or weekly) vitamin D3 doses are more efficient to reduce acute respiratory tract infections than monthly doses. It is reported that 10 ng/mL higher 25(OH)D level was associated with a decrease of 14% in mortality risk (1).

In patients undergoing PD, the risk of PD-related infections was 66% lower in those with high/normal levels of 25(OH)D than in those with low levels of 25(OH)D, with minimal heterogeneity. In patients undergoing HD, the risk of infection-related mortality was 12% lower in those with high/normal levels of 25(OH)D than in those with a low level, with minimal heterogeneity (4).

In other comparisons, calcium was lower in HD and alkaline phosphatase was lower in PD patients. there is a common understanding that low serum 25(OH)D levels cause a negative calcium balance, secondary hyperparathyroidism (SHPT) and bone disease (1, 2). According to figure 1, vitamin D deficiency has many side effects in the body and these side effects affect each other and ultimately cause high morbidity and high mortality (5).

Conclusion

Vitamin D insufficiency, which involves both serum 25(OH)D and 1,25(OH)D levels, is generally observed in CKD and dialysis patients. But vitamin D deficiency is more common in CKD patients than in HD and PD patients.

On HD patients, vitamin D deficiency is related to the increase of ESR as inflammatory markers, in these patients it is important to reduce inflammation due to vitamin D.

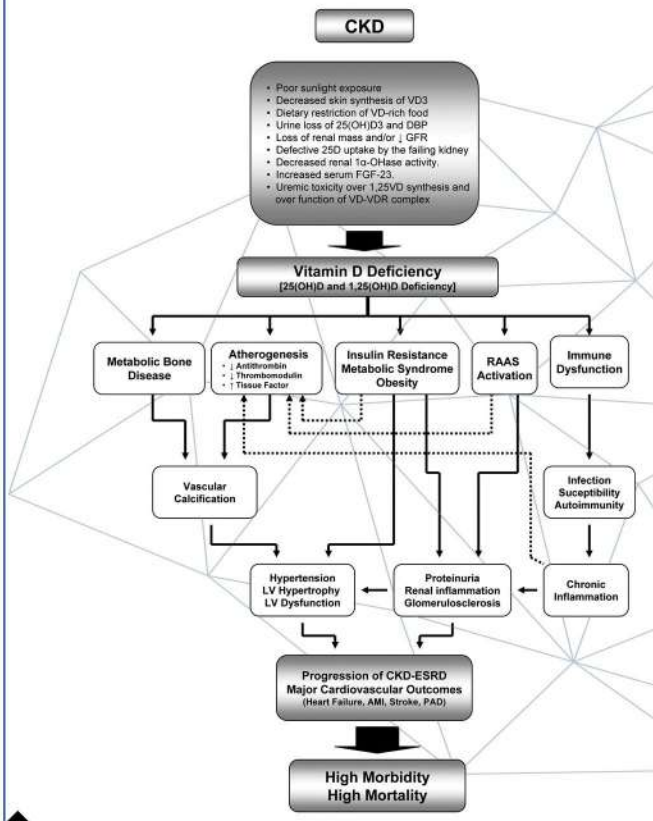


Figure 1 (5)

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