

REVIEW ARTICLE



Chronic Kidney Diseases: Role of Vitamin-K and Vitamin-D

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Abstract

Chronic kidney disease is the most common form of kidney disease and high blood pressure is the most common cause the pressure on the glomeruli increases due to high blood pressure which can prove to be very dangerous. Lack in VITAMIN D isn't restricted to the dynamic chemical, calcitriol (25-hydroxycholecalciferol) is likewise insufficient in many patients with constant kidney sickness (CKD), free of their fundamental renal capacity. Diminishes in calcitriol happen generally right off the bat in the movement of kidney illness and may originate before the increment in PTH. These progressions in calcitriol and PTH add to the upkeep of moderately ordinary serum and calcium fixations until the glomerular filtration rate (GFR) diminishes to <20–25%; nonetheless, the outcome is the potential advancement of bone and vascular sickness. Vitamin K intake and long-term vitamin K status are expressed by a high percentage of undercarboxylated OC (uOC). Vitamin D, which is needed for uOC development, and parathyroid hormone (PTH), which is often elevated in patients with CKD, are also affected by osteocalcin levels. Therefore, elevated serum uOC is present in patients with chronic kidney disease (CKD) with hyperparathyroidism, but this does not generally mean that they are deficient in vitamin K.

Keywords: Vitamin K, Vitamin D, CKD, GFR, PTH

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1 | INTRODUCTION

Nutrient D receptors assume a significant part in transforming Vitamin D into its dynamic structure, calcium and phosphorus ingestion in our body are observed by initiated Vitamin D and manages Parathyroid chemical. At the point when kidney can't deliver the enacted nutrient D, the control to calcium and phosphorus levels will be lost and PTH will attempt to over redress and leave range. In CKD the PTH organ will detect the less calcium in blood and produce the overabundance parathyroid chemical, which hauls the calcium out of the bone into the circulation system. Also, overabundance measure of PTH may prompt optional hyperparathyroidism which is answerable for bone misfortune or feeble bones and patients will be more inclined to crack. All the patients with CKD build up a high PTH, to manage high PTH enacted nutrient D is given to suppress PTH creation. Hemodialysis patients will be given a professionally prescribed medication intravenously during their dialysis treatment. Those not on dialysis or on peritoneal dialysis will be endorsed an oral type of initiated nutrient D or nonexclusive calcitriol. PTH levels are checked routinely to ensure the portion of the medication is right and that PTH is satisfactorily smothered yet not over-stifled. It's an almost negligible difference that the specialist, attendant and dietitian are observing. On the off chance that an individual has a high blood level of phosphorus or calcium, the doctor will frequently decide not to treat the high PTH with initiated nutrient D in light of the fact that there is an expanded danger of calcium-phosphorus stores in the delicate tissues. It's significant for all kidney disappointment patients to keep phosphorus and calcium blood levels inside an ordinary reach. A renal dietitian routinely works with individuals on dialysis to guarantee that they aren't eating such a large number of food sources wealthy in phosphorus or calcium and to ensure phosphorus covers are taken accurately (1).

Lack in VITAMIN D isn't restricted to the dynamic chemical, calcitriol (25-hydroxycholecalciferol) is likewise insufficient in many patients with constant kidney sickness (CKD), free of their fundamental renal capacity. Diminishes in calcitriol happen gen-

erally right off the bat in the movement of kidney illness and may originate before the increment in PTH. These progressions in calcitriol and PTH add to the upkeep of moderately ordinary serum and calcium fixations until the glomerular filtration rate (GFR) diminishes to <20–25%; nonetheless, the outcome is the potential advancement of bone and vascular sickness. Notwithstanding the immediate aggravations in bone and mineral digestion related with calcitriol insufficiency, there are expanding epidemiological information recommending that nutrient D insufficiency may assume a part in general dismalness and mortality related with CKD (2).

Vitamin K acts as an enzyme substrate for vitamin K-dependent carboxylase, which, by adding CO₂, transforms unique glutamic acid residues of a small number of proteins to glutamic carboxyl (Gla) residues. In order to generate Gla residues; vitamin K is required to insert carboxyl groups into residues of glutamic acid in blood coagulation factors (II, VII, IX, X); proteins containing Gla include osteocalcin (OC) synthesised by the osteoblasts in bone, and matrix Gla protein (MGP) produced by chondrocytes and vascular smooth muscles which plays a major role in mineralization of bone and Inhibition of vascular calcification, respectively (3).

Data suggests that patients with CKD suffer from a subclinical deficit in vitamin K, indicating that this group is at risk for any symptoms of low vitamin K status. This deficiency can be caused by vitamin K fatigue due to its high need to prevent calcification by vitamin K-dependent proteins. However, this deficit may be further exacerbated in CKD patients, due to their diets low in potassium (less leafy green vegetables rich in K1) and low in phosphate (fewer dairy products rich in K2) (3).

Indirect functional tests to detect vitamin K levels, such as prothrombin time or measurement of under-carboxylated proteins OC and MGP that are more

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sensitive than prothrombin time to detect subclinical vitamin K deficiency, can be assessed. This calculation is possible because, in the presence of vitamin K deficiency, vitamin K-dependent proteins

(VKDP) do not achieve their carboxylation state (and stay undercarboxylated); which causes their ability to bind calcium to be lost, so that bone metabolism may be compromised and the vascular calcification mechanism may be increased (4).

2 | METHODOLOGY

This review includes data related to role of Vitamin-K and Vitamin-D in Chronic kidney diseases. Analyzing the effect of both vitamin for improving and promoting the quality of the health care system. The information was collected through a computerized search from various research article, review article and various guidelines related to role of various vitamin in chronic kidney diseases.

3 | KIDNEY DISEASE

Maintenance of kidney health is an international priority. This is been shown that the important role that the kidneys play like maintaining fluid by filtering blood and electrolyte balance and take away waste (including the process of medicines), cathartic hormones to manage blood pressure (BP) and stimulate red blood cell creation (and so reduce the risk of cardiovascular disorder and anemia), and maintain bone health by activating ergocalciferol (5).

4 | CHRONIC KIDNEY DISEASE

Chronic kidney disease is the most common form of kidney disease and high blood pressure is the most common cause the pressure on the glomeruli increases due to high blood pressure which can prove to be very dangerous. The kidney function starts deteriorating to the point where the kidney can no longer function properly. Another major cause of chronic kidney disease is diabetes. The blood vessels in the kidney gets damaged over time due to the

increase of sugar levels in the blood hence causing the kidneys from filtering the blood. When the body starts to accumulate the toxins, the kidney starts to fail (6).

CKD is outlined because the existence of kidney damage, displayed by abnormal simple protein excretion or reduced kidney operation, quantified by measured or calculable glomerular filtration rate (GFR) that persists for over 3 months. Creatinine clearances may be calculated from water creatinine concentration measured in a 24-hour water assortment and an associated serum creatinine concentration, a more practical approach in the office is to estimate GFR (estimated GFR or eGFR) from the serum creatinine concentration, victimisation either the Cockcroft-Gault or the Modification of Diet in nephritic sickness Study estimating equations (5).

In addition, early intervention can additional ordinarily scale back serious CKD sequelae and slow CKD progression. To facilitate assessment of CKD severity and, the National Kidney Foundation developed criteria, as part of its Kidney Disease Outcomes Quality Initiative (NKF KDOQI™), stratify CKD patient (5).

1. Stage one: traditional eGFR \geq ninety mL/min per 1.73 m² and persistent albuminuria
2. Stage two: eGFR between sixty to eighty-nine mL/min per 1.73 m²
3. Stage three: eGFR between thirty to fifty-nine mL/min per 1.73 m²
4. Stage four: eGFR between fifteen to twenty-nine mL/min per 1.73 m²
5. Stage five: eGFR of < fifteen mL/min per 1.73 m² or end-stage renal disease

CKD in medical care is may be and commonly asymptomatic, and the pathology underlying its development is commonly not discovered (as no nephritic diagnostic tests is probably achieved). It is identified and defined by the presence of an irregularity of kidney structure or function (or both) present for at least 3 months. It is classified by

the degree of nephritic harm, as measured by the estimated glomerular filtration rate ([eGFR] derived from serum creatinine using standard estimating equations) and by the existence and non-existence of structural nephritic abnormality or by other evidence of chronic kidney damage, particularly albuminuria (6).

Pathophysiology

The nephritic structural and physiological characteristics, as well as the theories of nephritic tissue necrosis and tissue repair has to be taken into concern in order to understand the pathophysiology (6).

There are four stages of chronic renal damage:

1. Reduction in Excretory Function

The consequence of an accumulation of endogenous and extraneous substances is caused by breakdown of excretory function. Due to this it will cause changes in pharmacokinetics and a rise in the concentration of various drugs. Breakdown happens once the remaining glomeruli are opposed by a far more waste yields, resulting to osmotic diuresis. There is a reduction in the peak concentrating capability of the urinary organ. So as to filter the physical quantity of dissolved substances, the nephrons manufacture between three and four times the maximum urine during nephropathy, leading to a gathering of waste substances (6).

2. Reduction in Incretory Renal Function

The kidney plays a role in the instruction of many important hormonal series of cycles, chronic kidney disease also has endocrinal consequences. Through a shortage of glycoprotein, there is a discount in corpuscle synthesis, that results to renal anaemia; uraemia then leads to a reduction of functional erythrocytes due to haemolysis or haemorrhages (6).

Vitamin D production is additionally impaired, and phosphate excretion is reduced. Secondary glandular disease and also the associated renal osteopathy ("high-turnover" osteopathy) develop as a result of hyperphosphatemia. Along with this, other path mechanisms lead to a disturbance in bone metabolism: osteocalcin occurs due to a disruption of mineralization, and dynamic bone disease occurs due

to a decrease in osteoactivity (specifically in dialysis patients) (6).

3. Water Intoxication and the Disturbance of Electrolyte Balance

As long as the glomeruli will manage to compensate, diuresis and fractional sodium excretion rise. If the capillary filtration rate perceptibly drops, then the ability to compensate is exhausted, resulting to exaggerated retention of water and electrolytes (6).

Hypertension, pulmonary dropsy, and peripheral dropsy result from over hydration. Water and salt excretion are thereby inextricably connected. Diuretics will aid in water and salt excretion where critical glomerular damage is present. Early loss of salts as a result of the disturbance within the biological process can really be created worse by the employment of diuretics (6).

Thus, because the glomeruli adapt to compensate, the hollow transport mechanisms additionally adapt so as to forestall hyperkalaemia through exaggerated potassium secretion. Hyperkalaemia solely develops as a result of hyper stimulation of the reabsorption capability. As several patients are treated with calcium-sparing diuretics due to previous conditions, it is important to see to a patient's treatment history and adapt the treatment set up consequently (6).

Acidosis gradually rises along with hyperkalaemia. The kidneys will not sufficiently eliminate accumulating protons because of a powerfully reduced capillary filtration rate (6).

4. Harmful Organ Damage as a Result of Retention of Urinary Excreted Metabolites

Toxic organ injury can be explained beneath the umbrella term "uremic syndrome." The increase in urinary excreted metabolites in the blood is named uraemia. These metabolites embrace urea, creatinine, beta-2 microglobulin, and parathyroid hormone, along with others. Uremic syndrome (uremia) primarily describes a general disruption of all organ functions, particularly the cardiovascular system, central nervous system, blood, and membranes. Clinically, several symptoms of chronic nephrosis will be detected via the skin. Patients typically have macules ("café au lait" spots), are prominently pale, and have a grey, dirty-looking complexion. They

often complain of itching. Internal membranes are also affected, resulting to pericarditis, peritonitis, and inflammatory disease (6).

Uremia also can lead to haematolysis with anaemia. Thrombocyte and leukocyte disfunctions can happen.

Patients with chronic kidney failure have a specifically increased risk of atherosclerosis with an increased heart risk. This will cause the media calcification formed due to calcium phosphate and calcification through inflammatory influences and cholesterol plaques (5).

- High blood pressure
- Other family members with ckd.
- Elderly.
- Abnormal kidney structure.
- Smoking.
- Obesity.
- Cardiovascular disease.
- Family history of kidney disease (6).

5 | KIDNEY STONES

Another common type of kidney disease are kidney stones. Solid masses are formed when minerals and other substances in the blood crystalizes in the kidney (6).

Glomerulonephritis

Inflammation of the glomeruli is called Glomerulonephritis. The main cause of Glomerulonephritis is congenital abnormalities, infections or drugs (6).

Polycystic kidney disease

A genetic disorder that causes numerous cysts to grow in the kidneys is called polycystic kidney disease. Kidney failure can be caused due to the interference of cyst with the kidney functions (6).

Urinary tract infections

Bacterial infections of any part of the urinary system urinary tract infections (UTIs). The infections are most common in the bladder and urethra. They can be easily treated. If it is left untreated for prolonged time it causes kidney failure (6).

6 | RISK FACTORS

The most common risk factor for developing kidney disease is diabetes.

Other risk factors are -

7 | VITAMIN K

Vitamin K is a vitamin that is fat-soluble, and is best known for its blood coagulation function. In 1939, Henrick Dam discovered and named the molecule 'vitamin K' after the Danish term for blood clotting coagulation.

Vitamin K is a non-polar molecule; which is solubilized by bile salt and pancreatic juice following its intestinal absorption, and is then packed into chylomicrons that are secreted into the lymphatic system. Lipids, particularly triglycerides, interfere with the estimation of vitamin K for this reason (7, 8).

There are two sources of vitamin K in our diet: vitamin K1 (phylloquinone) found primarily in green leafy vegetables and vitamin K2 (menaquinones) found mostly in animal foods, fermented milk items such as yogurt, and natto (fermented soy beans). Vitamin K2 contains a multitude of sources of vitamin K and varies in its side-chain length and degree of saturation from vitamin K1. The most biologically active source of vitamin K2 has a longer half-life than vitamin K1 (days vs. hours) (9, 10)

Menaquinones could be more potent than phylloquinone in activating extra-hepatic vitamin K-dependent proteins. However, existing dietary reference values (DRV) for vitamin K are solely focused on phylloquinone and its coagulation function. In addition to its role in coagulation, there is growing

concern in the possible health benefits of vitamin K. Several studies have documented roles beyond the classic role of vitamin K, including improving bone quality and reducing vascular calcification and cardiovascular risk. Nonetheless, when designing nutritional guidelines for vitamin K, menaquinones are usually not included. The current dietary vitamin K guidelines are specified for phylloquinone intake only and are based on the median phylloquinone intake in some regions, such as North America. The effects of phylloquinone on coagulation have also been accounted for in some cases. Adequate intakes of vitamin K range from 55 to 90 $\mu\text{g}/\text{d}$ for adult women and 65 to 120 $\mu\text{g}/\text{d}$ for adult males, for healthy individuals (11).

8 | ROLE OF VITAMIN K IN CKD:

Vitamin K intake and long-term vitamin K status are expressed by a high percentage of undercarboxylated OC (uOC). Vitamin D, which is needed for uOC development, and parathyroid hormone (PTH), which is often elevated in patients with CKD, are also affected by osteocalcin levels. Therefore, elevated serum uOC is present in patients with chronic kidney disease (CKD) with hyperparathyroidism, but this does not generally mean that they are deficient in vitamin K (12).

The inactive type of MGP is a good alternative to determining vitamin K status, even though inactive MGP can only reflect vitamin K status at vascular level and not at bone or liver level. Indeed, randomized controlled trials have shown that treatment with vitamin K lowers levels of undercarboxylated unphosphorylated MGP (uc-dp-MGP); Anti-vitamin K (AVK) therapy, on the other hand, increased the amount of inactive uc-dp-MGP and reduced uc-dp-MGP by stopping treatment. All of these data show that uc-dp-MGP may be a strong vitamin K status marker (13).

Functional vitamin K deficiency can lead to a high vascular calcification (VC) burden in haemodialysis patients, given that vitamin K is necessary for the activation of matrix Gla protein (MGP), a powerful inhibitor of tissue calcification; a mechanism by which

minerals pathologically accumulate into larger blood vessels, primarily large elastic and muscular arteries like aorta, carotid, coronary, and the peripheral arteries. The involvement of VC in dialysis patients is closely linked to elevated cardiovascular morbidity and mortality (14).

Thus, in an experimental model of CKD, vitamin K plays a significant role in altering pathways relevant to the sensitivity of arteries to calcification (15).

In addition to presenting a higher risk of developing vascular calcification due to secondary hyperparathyroidism, patients with haemodialysis are frequently treated with vitamin K antagonists, mainly to prevent atrial fibrillation stroke, potentially compounding the risk of cardiovascular disease in these patients who are already vulnerable (15).

In control rats and rats with CKD, K2 greatly improved matrix Gla protein carboxylation. At calcification and neointimal hyperplasia sites, arterialized human vein samples contained inactive matrix Gla protein, suggesting local vitamin K deficiency. Vitamin K antagonists therefore have negative effects on AVF remodeling, whereas K2 decreased neointimal hyperplasia and vasoprotective effects demonstrated by calcification. In order to avoid neointimal hyperplasia and calcification in arterialized veins, administration of K2 can therefore be useful (15).

Recently researchers have concentrated on understanding the function of vitamin K in chronic renal disease. Patients develop mineral and bone defects from the early stages of CKD onwards (CKD-MBD). This constitutes a severe, life-threatening complication marked by calcification of soft tissue, osteodystrophy, irregular homeostasis of minerals, and hormonal imbalances. Dietary limits on potassium and phosphate translate into a low intake of green leafy foods, dairy products and meat as part of CKD treatment, all though they are high in vitamin K. These 3 drawbacks lead to low levels of serum vitamin K measured in CKD patients (16).

In patients with CKD, there is evidence of a high risk of vascular calcification and calciphylaxis associated with the use of vitamin K antagonists. CKD may lead to the expression of a unique clinical condition linked to vitamin K deficiency for all the reasons described above. Vitamin K modulation has emerged

as a potential therapeutic alternative, but no effective therapies are currently available to minimize vascular calcification and improve bone volume and mineralization. A body of scientific research has highlighted the essential roles of vitamin K in bones and vessels that are substantially impaired in the course of CKD (17).

Foods high in vitamin K1, such as vegetable oils, green vegetables (e.g., cabbage, lettuce, Swiss chard, Brussels sprouts, parsley, watercress and broccoli), and animal livers, are the major dietary sources of vitamin K in humans. The bacteria found in the intestinal or fermented food microbiota like yogurt, curds, and Japanese soybean "natto" can synthesise Vitamin K2), but little is understood about the bioavailability of vitamin K2 from the gut (18). Propionibacterium, for example, found in Swiss emmental cheeses, produces menaquinone-9. Menaquinone-4 is abundantly found in tissues such as the cortex, kidney, pancreas and salivary gland, possibly due to local biosynthesis (19). The conversion in the kidney HEK-293 kidney cell line and in primary cultures of mouse cerebral hemispheres has been shown in several preclinical studies. The daily consumption of vitamin K in the Western diet is estimated to be between 80 and 210 μg per day, while the recommended daily dose for total vitamin K is 1 $\mu\text{g}/\text{kg}/\text{day}$. However, this daily intake tends to be inadequate to sufficiently carboxylate extra-hepatic Gla-proteins (e.g., OC and MGP) - especially when the metabolism of vitamin K is compromised, as in the condition of CKD (20). Vitamin K is emulsified by bile salts after food is digested, then absorbed by enterocytes (through chylomicron receptors), incorporated into triacylglycerol-rich lipoproteins containing apolipoprotein-A and apolipoprotein-B48, and secreted into the blood and lymphatic system (21). Both vitamin K variants, in particular vitamin K1 and menaquinone-7, are consequently absorbed by the liver. Chylomicrons are entered into the hepatocytes in the liver by endocytosis, whereas apolipoprotein-B100, before returning to circulation. The numerous vitamin K molecules are transported by LDL cholesterol particles and caught by target cells and tissues through LDL receptors, such as arteries, cartilage and bone, after addition and removal of apolipoprotein particles from the circulation (22).

The primary physiological function of vitamin K is to serve as a cofactor for the γ -glutamyl carboxylase enzyme in gamma-carboxylation reactions that add carboxyl groups to Glu residues in proteins. Vitamin K is oxidised into the vitamin K epoxide by Gamma glutamyl carboxylase enzyme, extracts a proton from the residue of Glu, and then adds CO_2 to it, resulting in the production of new carboxylated residues in such proteins called Gla domains. This approach turns inactive (uncarboxylated) proteins into active (carboxylated) proteins and makes it possible to bind them to calcium. For bone mineralization and in combating vascular calcification, adequate calcium binding is a crucial physiological step. The body's vitamin K reserves are small, and vitamin K is recycled effectively through a sequence of redox reactions. Using a vitamin K antagonist (e.g. warfarin) that prevents vitamin K epoxide reductase and quinone reductase is a cause that can hinder the recycling mechanism. There is also evidence that uremia interferes with the recycling of vitamin K in certain tissues by modifying the mRNA expression of vitamin K oxidoreductase (VKOR) and γ -glutamyl carboxylase. Impaired recycling of vitamin K in uremia can be boosted - at least partly - by vitamin K supplementation. Finally, vitamin K oxidative catabolism takes place in the liver and produces predominantly metabolites of glucuronide excreted in bile and urine (23).

9 | MECHANISM OF ACTION OF VITAMIN K

For clotting blood, vitamin K is important. Vitamin K facilitates the synthesis of hepatic coagulation factors II, VII, IX, X, X (the exact mechanism is unknown). In terms of the recent carbanion model that mimics proton abstraction from the gamma position of protein-bound glutamate, the mechanism of action of vitamin K can be explored. This is the crucial step leading to carboxylation and the activation of blood-clotting proteins. The model involves oxygenation that is consistent with the forming of carbon-carbon bonds, as is the oxygenation of vitamin K hydroquinone to vitamin K oxide (24, 25).

The mechanism of inhibition of carboxylase by HCN, which functions as an acid-base inhibitor rather than a metal-complexing inhibitor, can also be supported by a model hypothesis. The new model posits a dioxetane intermediate that describes the existence, a second atom of ^{18}O (from $^{18}\text{O}_2$) integrated into vitamin K oxide in the course of enzymatic carboxylation. Finally, the chemistry developed here was used to describe the vitamin K hydroquinone active site as the neighboring carbon-carbon bond to the methyl ring (24, 25).

Vitamin K is now considered to serve as a mandatory cofactor for an important carboxylase that stimulates seven blood-clotting cascade protein components. In addition, for the carboxylation of two proteins necessary for proper bone metabolism, osteocalcin and Gla matrix protein, vitamin K is required (24, 25).

10 | BIOCHEMICAL ROLE OF VITAMIN K IN BLOOD COAGULATION

Vitamin K was originally thought to be involved in mitochondrial electron transport and oxidative phosphorylation due to its chemical composition, but it was not possible to show the uncoupling of oxidative phosphorylation in vitamin K deficient animals and birds. Nevertheless, in mycobacterial and plant photosynthesis, vitamin K was later found to be involved in electron transport. Vitamin K has been known to play an important role in the synthesis of prothrombin and blood coagulation factors VII, IX and X for a long time, but the vitamin's mechanism of action remained unclear. A significant discovery in the 1960s found that plasma prothrombin was immunologically normal but non-functional in people and cattle administered with warfarin-type anticoagulants. This indicated a vitamin K post-translational alteration of prothrombin. The amino acid sequences of the amino-terminal ends of prothrombin, factor VII and factor IX and the Factor X light chain displayed marked homology, especially in the Gla residue positions. In the first exons that encode the signal peptide, propeptide and the area of the Gla residues (Gla domain), the genes for the vitamin K-dependent clotting factors are all homologous to each

other. V 10, 12 and 11 Gla residues per molecule are present in Factor VII, Factor IX and Factor X. In blood coagulation, the Gla residues are essential in the activation of the proenzyme types of the clotting factors that can only occur when the proenzymes are attached to phospholipid surfaces. This binding takes place through the residues of Gla and the calcium ions (26).

11 | BLOOD CLOTTING FACTORS AND OTHER VITAMIN K DEPENDENT PLASMA PROTEINS

It was soon after the discovery of vitamin, that the importance of vitamin K for prothrombin synthesis got established. In the 1950s, vitamin K was also found to be dependent on the formation of blood coagulation factors VII, IX and X. For a long time, the mechanism of vitamin K activity remained unclear, however after the observation that patients and animals treated with warfarin-type anticoagulants had immunologically reactive but non-functional prothrombin in their plasma, attempts were made to establish if the vitamin was involved in posttranslational alteration. Amongst the first 33 amino acids, all the 10 glutamyl residues containing prothrombin are normally carboxylated whereas at other locations of the proteins, the additional glutamyl residues are not. There are also 10-12 Gla residues near their amino-terminal ends in factors VII, IX, and X. To bind the proenzymes of vitamin K-dependent coagulation factors to phospholipid surfaces through calcium ions, the Gla residues are necessary. For activation of the proenzymes into active proteases, this binding to phospholipids is necessary. No proenzyme activation will occur in the absence of vitamin K action because the proper conformation necessary for the proenzyme and protease involved is not obtainable in a free solution. In blood coagulation, three additional identified vitamin K-dependent plasma proteins, protein C, protein S and protein Z, are not needed (27).

Carboxylation of Glutamate

Vitamin K is reduced by sulfhydryl-dependent reductase to its biologically active hydroquinone form,

vitamin KH₂, prior to the carboxylation of Glu. Protein-bound glutamate is carboxylated to Gla under the vitamin KH₂ and carboxylase departments, at the same time as vitamin KH₂ is transferred to vitamin K epoxide. For the transition of vitamin KH₂ to vitamin K epoxide and Gla, molecular oxygen is crucial. An epoxide reductase then returns vitamin K epoxide, completing the catalytic cycle, to vitamin K (28).

Facilitation of Calcium Binding

A posttranslational phenomenon occurring at the N-terminus of the nascent chain is carboxylation of Glu in the vitamin K-dependent zymogen precursors to the enzymes of the blood-clotting cascade. The 10 glutamates in residues 7-33 are carboxylated in prothrombin. None of the remaining 33 residues of glutamic acid in prothrombin is subjected to carboxylation after residue 33. In the clotting-cascade proteins, carboxylation transforms the chosen glutamates into Gla residues to allow calcium to be binded by the proteins. On the membrane surfaces of blood platelets and endothelial and vascular cells, the bound calcium forms ion bridges between blood-clotting enzymes and phospholipids. By allowing internal Gla-Gla binding, calcium binding also plays an important role in regulating the conformation of coagulation proteins. Blood coagulation factors VII, IX, and X, and proteins C, S, and Z also depend on vitamin K for carboxylation in addition to prothrombin (factor II) to allow calcium binding (29).

Vitamin K as a Cofactor

In animal cells, vitamin K serves as an enzyme cofactor for vitamin K-dependent carboxylase, which catalyzes the post-translational production of residues of γ -carboxyglutamyl (Gla) in particular proteins dependent on vitamin K. These proteins include four blood coagulation factors (prothrombin and Factors VII, IX and X), two bone proteins (osteocalcin or bone Gla-protein and matrix Gla-protein), two other plasma proteins (protein C, protein S and protein Z), and other proteins from the lungs, liver, spleen, testicles, placenta, and other tissues. The Gla residues are mandatory for the activation of the inactive proenzymes in the proteins involved in blood coagulation; this approach occurs on phospholipid surfaces to which the proenzymes are bound by Gla residues and

calcium ions. By oxidizing vitamin K hydroquinone to 2,3-epoxide of the vitamin, the energy required in the carboxylation reaction is extracted. Unique enzymes, vitamin K epoxide reductase and vitamin K quinone reductase, catalyze sequential processes in which vitamin K hydroquinone is regenerated, helping the vitamin K carboxylation molecule to continue to be used. Oral anticoagulants, 4-hydroxycoumarin and indan-1,3-dione derivatives, used as therapeutic agents in thromboembolic disease, are vitamin K antagonists which prevent the catalytic use of vitamin K by irreversibly inhibiting vitamin K epoxide reductase in carboxylations (30, 31).

Vitamin K in Cardiovascular Health

In the process of gamma-carboxylation, vitamin K is necessary as a co-factor for many vitamin K-dependent proteins that transform inactive uncarboxylated proteins into active carboxylated forms to function. The hepatic coagulation factors prothrombin and factor X are the best-known vitamin K-dependent proteins. Other extra-hepatic proteins based on vitamin K have also been reported, however. Matrix gla (MGP) is a small extracellular matrix protein that binds Ca²⁺ ions in the vascular wall and serves as a potent promoter of vascular calcification, synthesized in smooth muscle cells. Vitamin K deficiency, a risk factor for vascular calcification and cardiovascular disease (CVD), results in the synthesis of under-carboxylated, biologically inactive gla proteins. These findings suggest that a high intake of vitamin K is correlated with an advancement in cardiovascular health. Self-reported food intake, however, is inaccurate and inherent in nutrient intake calculation constraints. By calculating the uncarboxylated fractions of some vitamin K-dependent proteins such as osteocalcin (a marker of bone formation) or MGP, which is the most studied vitamin K-dependent protein in the control of vascular calcification, vitamin K status may also be calculated. Since MGP is the key vitamin K vascular calcification status marker, experiments using osteocalcin concentrations as a cardiovascular-related vitamin K status marker have not been considered. Overall, observational findings suggest that, especially in high-risk and chronic kidney disease populations, vitamin K has a potential role in cardiovascular health. There are scarce vitamin K intervention findings

with subclinical cardiovascular endpoints. The mixture of vitamin D+K supplementation, which may have synergistic effects relative to vitamin K supplementation, has been studied in most clinical trials. Vitamin D can preserve protein activity dependent on vitamin K and can thus contribute to vascular health. In observational research and well-designed randomized trials, evaluating vitamin K status using various biomarkers will offer substantial insight into whether vitamin K is causally linked to vascular calcification and CVD (32).

TABLE 1: Sources of Vitamin K:

Food	Percent of DV per serving
Kale (cooked)	443%
Mustard Greens (cooked)	346%
Swiss Chard (raw)	332%
Collard Greens (cooked)	322%
Natto	261%
Spinach (raw)	121%
Broccoli (cooked)	92%
Brussels Sprouts (cooked)	91%
Beef Liver	60%
Pork Chops	49%
Chicken	43%
Goose Liver Paste	40%
Green Beans (cooked)	25%
Prunes	24%
Kiwi	23%
Soybean Oil	21%
Hard Cheeses	20%
Avocado	18%
Green Peas (cooked)	17%
Soft Cheeses	14% (33)

Calciphylaxis: Calciphylaxis which is also known as Calcific Uremic Arteriolopathy or Grey Scale. It is one of the rare painful syndromes of calcification of the small blood vessels situated in the fatty tissue and deeper layers of the skin. It occurs in people with end stage kidney disease and also early stages of CKD. About 1% of CKD patients can develop calciphylaxis. Approximately 50% of patients with

5D stage CKD (CKD5D) can develop calciphylaxis are on Vitamin K antagonists. When comparing with dialysis patients throughout the world, the number of calciphylaxis cases is nominal (34).

According to Krueger et al. Vitamin K, especially vitamin K2 supplement become necessary for the standard treatment of calcification-prone CKD patients (35).

Drug and Vitamin K-Dependent Protein: Fusaro et al. carried out a sub-analysis to estimate the relations between drug consumption and VKDP levels in 387 haemodialyzed patients (36). The VIKI study was performed in 387 adult patients of both genders was an observational study. It was designed to evaluate the prevalence of deficiency of Vit K and Vit K2 in dialysis patient. Concerning mineral and bone disorder treatment, the most common treatment was Oral Calcitrol and sevelamer (36).

Vitamin K supplement, Calcimimetics, and vitamin D analogues play a major role in conserving vitamin k dependent protein activity (34).

Vitamin K supplementation: According to Geleijnse J.M. et al. low vitamin k2 intake was linked with a higher incidence of severe aortic calcification and increased mortality. Daily vitamin k2 supplementation would expand the activity of vitamin k dependent proteins in CKD5D patients (37). A supplement in vitamin k in hemodialysis or peritoneal dialysis patient should be taken into account, by considering the low vitamin k status in CKD patients. The status of vitamin k plays a major role in kidney transplantation (34).

General management of CKD

Compared to the general population, people with chronic kidney disease (CKD) are at slightly greater risk of experiencing cognitive dysfunction, and both the reduced levels of glomerular filtration and the prevalence of albuminuria are correlated with cognitive impairment and impaired cognitive performance. In view of the excess vascular disease observed in people with CKD, the prevalent pathology causing these correlations is likely to be cerebrovascular disease, although compromised clearance of uremic metabolites, depression, sleep disruption, anemia, and polypharmacy may also contribute.

Modification of risk factors for vascular disease may be beneficial in reducing regression, but there is a lack of detailed knowledge (38).

In several countries around the world, cardiovascular disease (CVD), including coronary heart disease (CHD) and stroke, are also the leading cause of death and disease burden. Mounting research has shown that diet plays a major role in the growth of CVD and consequently death. Vitamin K contains both phylloquinone and menaquinone, a class of fat-soluble compounds (38).

The former, also referred to as vitamin K1, is derived mainly from dark green leafy plants, while the latter, also referred to as vitamin K2, is derived mainly from milk products, meat and eggs [6, 7]. The γ -glutamate carboxylation of both vitamin K-dependent proteins including matrix Gla protein (MGP) and osteocalcin can be catalyzed by both phylloquinone and menaquinone (38).

The latest recommendations for CKD are aimed at normalizing serum calcium, phosphate and parathyroid hormone levels to prevent bone defects and vascular calcification, it is not obvious, though, that there are advantages of normalizing these variables in the last years of life of patients being cared for conservatively. Instead, in patients already at high risk of protein malnutrition, there is the potential for harm in encouraging reduced protein intake. The emphasis is on encouraging QOL instead. This entails the maintenance of proper nutrition, the prevention of malnutrition and inflammation, and food liberalization. Furthermore, the levels of serum phosphorous, calcium, or parathyroid hormone do not seem to be significant factors behind uremic pruritus. We advocate not concentrating on normalizing biochemistry for these concerns, but rather stressing proper diet (39).

For many diseases, including CKD, plant-based diets provide a rising weight of evidence. Although data from the trial is limited to specifically metabolic acidosis, observational evidence suggests damage with red and processed meats whereas benefits in all stages of CKD with even minimal levels of plant food intake. Concerns over hyperkalemia and protein deficiency may be outdated and may have discouraged the pleiotropic properties of plant-based

diets from being used by patients and clinicians. In nephrology, healthcare professionals may recommend plant-based diets as an additional instrument in the prevention and treatment of patients with CKD (39).

In general, to produce a natriuretic reaction, higher doses of diuretics are required as GFR falls. In the late stages of CKD, diuretic dosing can be especially difficult as the risk of over diuresis and its subsequent acceleration of progression to dialysis outweighs the advantage of increased BP regulation. In patients with hypoalbuminemia, this is more aggravated as less protein-bound loop diuretics are available for tubular secretion. In general, in long-term BP regulation, the short-acting effect of certain loop diuretics hinders their effectiveness. On all these factors, clinicians have reconsidered the use of thiazide diuretics in advanced CKD (estimated GFR, 30 mL/min/1.73 m²) as an alternative or additional drug to the use of loop diuretics where they have traditionally been deemed unsuccessful (40).

In patients with ESRD, symptoms are caused by conditions linked to the disease process (metabolic derangements), comorbid conditions, and treatment-dependent factors, most commonly dialysis. While patients with ESRD who prefer a conventional, non-dialysis method do not have symptoms from dialysis, however may have a combination of symptoms that may culminate to a reduced quality of life (40).

12 | CONCLUSION:

From this study, we can conclude that Nutrient D lack grows ahead of schedule in the course of CKD. There is an expanding group of information recommending that VDR has a focal job in bringing down the horribleness and mortality seen in these patients through component including old style skeletal and non-traditional pathways. Hence in the absence of nutrient D receptor, PTH will get activated and utilizes the calcium from the bone and used by the heart to maintain myocontractability. The agreement among meeting members was that there is still a lot of work to be done to encourage our comprehension of how to utilize nutrient D in patients

with CKD stages 3 and 4. A worry that Nutrient D might be a proxy marker for chronic weakness status. The carboxylation of two proteins necessary for proper bone metabolism, osteocalcin and Gla matrix protein, vitamin K is required. Vitamin K deficiency, a risk factor for vascular calcification and cardiovascular disease (CVD), results in the synthesis of under-carboxylated, biologically inactive gla proteins. These findings suggest that a high intake of vitamin K is correlated with an advancement in cardiovascular health.

ABBREVIATIONS

CKD – Chronic Kidney Disease

PTH-Parathyroid Hormone

Gla- Glutamic Carboxyl

OC- Osteocalcin

MGP- Matrix Gla Protein

VKDP-Vitamin K-Dependent Proteins

BP-Blood Pressure

GFR- Glomerular Filtration Rate

eGFR- Estimated Glomerular Filtration Rate

NKF-National Kidney Foundation

NKFKDOQI-Kidney Disease Outcomes Quality Initiative

UTI-urinary tract infections

DRV-Dietary Reference Values

uOC – undercarboxylated Osteocalcin

AVK-Anti-vitamin K

VC-Vascular Calcification

VKOR-Vitamin K oxidoreductase

HCN-Hydrocyanic acid

CVD- Cardiovascular Disease

QOL-Quality of Life

CHF-Cardiac Heart Failure

NSAID- Nonsteroidal Anti-Inflammatory Drugs

ESRD- End Stage Renal Disease

VDR-Vitamin D Receptor

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