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Mini Review

# An Update on Etiology of Chronic Kidney Disease with Role of Associated Vitamin K Deficiency in Prevention of Vascular Calcification and Cardiovascular Risks and Avoid Mortality: A Minireview

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## Abstract

Vitamin K possesses numerous significant role in human health. More recently researchers have a established that healthy diet consumption possessing good fats, Vitamins, minerals, polyphenolics possesses anti-inflammatory actions can act in antiaging role. Earlier the belief was that Vitamin K acts basically as an anticoagulant, besides part in calcium homeostasis. Having reviewed the etiology in chronic kidney disease (CKD), Diabetic Kidney Disease (DKD)with those patients presenting with DKD- CKD or end stage renal Disease (ESRD), in addition to details of associated Vascular calcification, acute kidney injury here we tried to further update knowledge regarding role of Vitamin K deficit in deterioration of CKD in particular the ones associated with Vascular calcification (VC). Vitamin K plays a significant role as a co- factor in transformation of glutamate to Gla. This has a significance in hampering of VC. CKD patients both on dialysis as well as not on dialysis generally possess Vitamin K deficiency. Enhancement of uncarboxylated matrix Gla protein [MGP] (uc MGP) indirectly points to Vitamin K deficiency as well as correlated with a greater chance of generation of the cardiovascular processes. It has been pointed that greater Vitamin K consumption might cause avoidance of development of VC, besides reduction in CV risk. Thus we did a minireview utilizing the search engine pubmed, google scholar and other sutilizing the MeSH terms like DKD; CKD; Vitamin K ; Growth arrest specific protein 6 (Gas6); VC; hemodialysis (HD) patients from 2000 till date in 2022. We found s total of 65 articles with regards to CKD, Vitamin K, out of which we chose50 articles for this minireview. Despite all the research till date role of supplementation of Vitamin K with dosage, kinds still not clear that is varying from country to country as well as source VK1 or2. Still greater large RCTs are required to settle that query.

**Keywords:** Vitamin K; uc MGP; CKD; VK Supplementation; VC; Gas61

## Introduction

Aging represents an event with numerous factors being implicated, that worsens the physiological functioning amongst organs inclusive of brain, musculo skeletal, cardiovascular well as immune system that result in numerous pathological situations correlated with escalation of mortality along with morbidity. Oxidative stress (OS) as well as chronic inflammation represent the pathophysiological modes implicated in aging propagation [1].

With the enhancement of human life expectancy, age correlated diseases would enhance also. More recently the studies corroborated the significance of factors that can get modulated, lifestyle factors inclusive of diet in the amelioratation of pathological alterations in mature adult [2]. Healthy fats, Vitamins, minerals, polyphenolics possessinganti inflammatory action, can result in enhancement of the quality of life along with impact the aging event, amongst which Vitamin K (VK) has assumed significant role [3].

It is well that known that VK is implicated in the generation of certain blood clotting factors (k for coagulation in german). VK is a fat soluble family of constituents possessing a chemical structure that is shared, a 2, methyl, 4- naphthoquinone ring along with an aliphatic side chain possessing variability. This aliphatic side chain gets differentiated into 2isoforms VK 1 or phylloquinine (PK), Vitamin K2 (VK 2) or generally known as menaquinone (MK). MK is existent in numerous structure that might be differentiated by the number of isoprenyl units along with saturation in the side chain (MKn)where n represents the number of isoprenyl units [4]. Utilization of these compositions get reciprocally right through this manuscript in case of this Vitamin (Figure 1) [5].

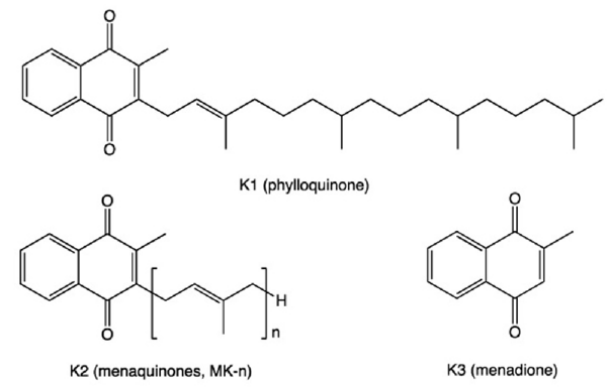


**Figure 1:** Courtesy ref no-5-Vitamin K chemical structures. Vitamins K1 (VK1), K2 (VK2), and K3 (VK3) share the naphthoquinone ring; VK1 has a phytyl sidechain; VK2 has a sidechain with a varying number of isoprenyl units; VK3 has no sidechain.

The commonest, source for the dietary PK are green leafy vegatables (like collards tunip, broccoli, spinach, kale), 70-700µg/100g along with different fruits (like dried prunes, kiwifruit, avocado, blueberries, grapes)-15-70 µg/100g, along with certain nuts (pine nuts, cashews, piostachio) 10-75 µg/100g [6]. Conversely the major sources of VK 2 are fermented foods, cheeses, eggs as well as meat [7].

Despite, the dietary PK in vegatables represents the major sources of the VK 2 consumption (80-90%), just 5-10% absorption takes place while MK's are obtained from dairy products, get practically totally absorbed. PK, having tight binding with chloroplasts in addition to PK that gets digested with certain phytochemicals (like saponins, tannins, fibers, phylates) observed in pulses possesses lesser bioavailability in human. Despite, PK obtained from collards as well as broccoli possesses greater bioavailability in contrast to PK from spinach [8].

VK 1 or VK 2, both have received recognition for acting as co factor for enzymes γ-glutamyl -carboxylase (GGCX) that causes transformation of glutamic acid (Glu) to a new aminoacid γ-carboxy glutamic acid (Gla), in a VK dependent proteins (VKDPs)fashion at the time of their bio generation [9]. Carboxylation is the requirement, of VKDPs for getting biological activation, as well as the negatively charged γ-carboxy glutamic acid residues possessing a greater rapport for the positively charged calcium ions [10].

Classification of VKDPs is feasible as hepatic as well as extrahepatic. The hepatic VKDPs are generally implicated in blood coagulation. The extra hepatic VKDPs conducted variation of actions, osteocalcin (OC), regulation of bone generation along with mineralization, the matrix Gla protein (MGP) acts by robust hampering of vascular calcification (VC) nephrocalcin is implicated, in kidney functions, the Gla protein growth arrest specific protein (Gas6) in the generation along with differentiation of nervous system [11]. Furthermore, certain extra hepatic VKDPs (proteinC as well asS) hamper coagulation by inactivation of particular coagulation factors essential for the formation of blood clots [12] see figure 2 [24].

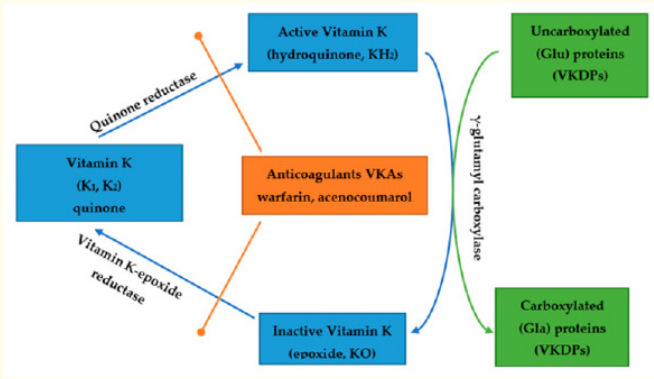


**Figure 2:** Courtesy ref no-24-The vitamin K cycle and action. VKAs-vitamin K antagonists, VKDPs-vitamin K-dependent proteins, Glu-glutamate, Gla-γ-carboxyglutamate, KH2-vitamin K hydroquinone, KO-vitamin K.

More recently an innovative part of Vitamin K has been documented in the form of an antioxidant along with anti inflammatory substance that is independent of GGCX co factor action [13]. The antioxidant characteristics are dependent on the protection effect against the oxidative cellular injury along with cell demise by i) direct Reactive oxygen species (ROS) uptake [13], ii) the restriction of free radicals intracellular accrual [14], in addition to iii) hampering of 12-lipoxygenase [15].

Research established, that VK further possesses anti inflammatory effect, a key part in variabile chroic aging diseases [16]. VK causes hampering of nuclear factor κB (NFκB) as well as hence causes reduction of generation of proinflammatory cytokines 13]. It has a significant along with inverse correlation with the unique biomarkers along with inflammatory events injury in view of its anti inflammatory actions [17]

The reference consumption/day of VK is dependent maximum on bleeding correlated studies, besides variation as per country. US Guidelines advocated 90 as well as120μg for women along with men respectively, whereas in United Kingdom it was 1 μg/kg/d [8]. Nevertheless, these advocated concentrations are not enough for the induction of total carboxylation of all the VKDPs. Just MK -7 possessing greater bioavailability along with longer half life, corroborated that they possessed the capacity of γ carboxylation of extrahepatic VKDPs whereas at the present advocated concentrations of, PK along with MK -4 have been demonstrated, to result in reduction of γ carboxylation of VKDPs [18].

Dependent on the determined dietary intake, PK contributes to50%, MK -4 to10% along with MK -7. -8, -9 for40% of the full VK absorption [19]. VK gets absorbed from the small intestine in view of it being a fat soluble Vitamin, in the existence of fat in the diet. A vital modulator of intestinal VK absorption is Niemann Pick C like1 (NPCiL1) protein, that is what causes transportation of cholesterol along with phytosterol by the observation of the transporter that is present in the erythrocytes as well as hepatocytes [20]. Subsequent to the absorption, PK transportation to the liver occurs, besides other tissues, Its utilization might occur without any alteration or it might get metabolised by some kinds of microbiota into VK2 or into menadione in the human intestinal cells. Partially menadione gets converted to MK -4, that is the predominant MK kind in case of animal tissues [rev inref 5]. as well as Nevertheless, tissue particular VK spread ways. observation of PK in all tissues with comparatively greater concentrations in the liver, heart, however lesser in brain, lung along with Kidney. in contrast to PK, MK 's apparently are of greater significance with regards to extrahepatic tissues [rev inref 5]. MK concentrations were greater in brain as well as Kidney, lesser in liver, heart, along with lung. The escalation of MK concentrations in brain pointed that this K Vitamin is the active kind of VK in this area [2]. escalation of validation has recommended that MK -4 possesses numerous biological effects, inclusive of facilitation of growth factor of neuron like cells modulation of apoptosis in different Cancer cells, regulation of glucose homeostasis [rev inref 5]. In the central nervous system (CNS), MK -4 causes regulation of the actions of proteins implicated in renewing of tissues, regulation of cell growth, myelination, mitogenesis, chemotaxis, neuro protection [rev inref 5]. The medium along with long side chain of MK's were removed mainly from liver samples [rev inref 5]. Both MK -4 as well as MK -7 resulted in enhancement of collagen formation along with Bone mineral density, thus facilitation of Bone quality as well as strength [13]. Since VK 1, MK -4 as well as MK -7 possess unique bioavailability along with biological effects, their advocated amounts need to be decided dependent on their comparative effects [rev inref 5].

With the advocated dietary consumptions are dependent on their dosage needed for avoidance of bleeding innovative results pointed that the advocated amounts requirement is with regards to intake of VK has to be established [rev inref 5]. As bioavailability from foods along with endogenous formation of VK are less, VK supplementation needs to be taken into account for numerous chronic disorders in particular amongst older individuals [rev inref 5].

Despite, numerous publications advocated the greater advantageous actions of VK in numerous chronic disorders, it is tough to detail the supplementation amounts. However, numerous preclinical in addition to clinical studies corroborated the safety of VK intake. In numerous studies greater dosage in contrast to the determined dietary consumption did not demonstrate any toxicity in case of experimental animals [rev inref 535]. In case of clinical studies considerably high dosages of MK -4 got utilized for the therapy of osteoporosis with no adverse actions [rev inref 5].

Having reviewed the etiology of in Chronic Kidney Disease (CKD) along with Diabetic Kidney Disease (DKD)with those patients pre-

senting with DKD- CKD or end stage renal Disease (ESRD), in addition to details of associated Vascular calcification, acute kidney injury [21-23], here we tried to summarize the proof with regards to VK for avoid of age correlated in mature adults, besides specifically concentrating of role of Vitamin K in cardiovascular disease (CVD) along with renal actions diseases as well as enhancement of effectiveness of certain medical treatments.

## Vitamin K, risks correlated with cardiovascular as well as vascular calcification

Deficiency of VK represent an in dependent anticipator of cardiovascular disease (CVD) along with supplementation of Vitamin K might slow this event as well as result in avoidance of Atherosclerosis along with CVD in addition to stroke [5].

Vascular calcification (VC) represents a dynamic event where the promoters along with inhibitors of calcification participated while currently no specific treatment is existent [5,25]. The mode of this event implicated matrix Gla protein (MGP), that possesses the maximum robustness of hampering arterial calcification that is a part of the Gla possessing proteins alias Gla-rich protein (GRP) [18,25-27,29] are based on Vitamin K that is a co- factor for the transformation of glutamate into Gla [29]. MGP represents a small protein that possesses a molecular weight of12 kDa, that possesses 84 amino acids, 5 glutamate (Glu) as well as 3serine residues [16]. MGP liberation takes place from Chondrocytes, arterial medial vascular smooth muscle cells (VSMC), fibroblasts along with endothelial cells [25-27,31]. MGP results in hampering arterial calcium ($Ca^{2+}$). Furthermore, it can get directly correlated with the Circulating calcium molecule along with hydroxyapatite crystals which are existent in the vessel wall generating inactive complexes [29].

MGP liberation takes place in its inactive state with its activation occurring by a VK based carboxylation that is essential for a robust hampering action on calcification [5,28]. Binding of active MGP takes place to calcium with high harmony along with hampering the event of elastic fiber injury as well as VC [5,28]. Noticeably, MGP is the lone existent factor that is possessing the capacity of reversal of the event of VC [5]. Considerable basis was seen amongst deficiency of VK along with enhancement of uncarboxylated VK- based protein amounts in addition to hepatic protein whose induction takes place by Vitamin K absence-II (PIVKAII) along with extra hepatic dephosphorylated uncarboxylated matrix Gla protein (dp-ucMGP) [5]. The observation was that VK impacts the plasma amounts of dp-ucMGP along with the robustness of VC, cardiac function as well as long term mortality [5]. An independent correlation was observed amongst escalation of plasma amounts of dp-ucMGP, lesser amounts of full uncarboxylated matrix Gla protein (t-uc MGP) in addition to robustness of peripheral arterial calcification in case of diabetic patients possessing greater CV risk [5]. Moreover an independent correlation was observed amongst greater dp-ucMGP values, besides carotid, femoral pulse wave velocity (cfPWV)in diabetic along with patients of chronic kidney disease (CKD), that might result in arterial with stiffening [5,30].

Three separate kinds of MGP are existent; t-uc MGP- that is the circulating variant that possesses in major amounts of phosphorylated ucMGP (p- uc MGP), dephosphorylated uncarboxylated matrix Gla protein (dp-ucMGP) that is undergoing transformation to dephosphorylated carboxylated (dp-cMGP) [30]. It has been pointed that dp-ucMGP might be an anticipator of peripheral arterial calcification that is independent of age, gender, prior CVD as well as t-uc MGP amounts [31]. Furthermore, dp-ucMGP is associated positively with peripheral arterial calcification. Moreover, the association was demonstrated amongst greater amounts of dp-ucMGP with aortic calcification in patients existent at variable stages of CKD [31].

Significant reduction in the incidence of VC along with coronary heart disease (ChD) was observed on dietary consumption of greater VK2 in contrast to VK 1 [32,33]. The reason might be as VK 1 is implicated basically in carboxylation of VK based factors in the liver while VK2 participates in carboxylation of VKDPs in the extrahepatic tissues [5,32]. More recently in a 12mth prospective randomized trial conducted, the outcomes pointed that VK 1 might further take part in carboxylation responses in extrahepatic tissues along with result in post ponement of VC on administration in high dosage of2mg daily [33].

An intricate association was derived in a more recent study amongst Gas6 along with circulatory system [26]. Furthermore, Gas6 plasma amounts might be a prognostic factor of CVS risks [26]. Activation of Akt as well as PI3Kvia binding Gas6 to Axl receptor restricts the apoptosis of VSMC's [26]. Restoration of Gas6 expression, along with activation of downstream signaling by Axl, Akt as well asBcl2 that can results in hampering of calcification along with apoptosis of VSMC's [26]. Furthermore it was demonstrated

that significant liberation of Gas6 in VSMC's took place in atherosclerotic plaques in contrast to healthy blood vessels [26]. The anti inflammatory cytokines transforming growth factor beta (TGF-β), caused induction of liberation of Gas6 in VSMC's. Conversely Gas6 resulted in stimulation of VSMC's via repression of proinflammatory cytokinefactor Tumor necrosis factor alpha (TNFα) as well as intercellular cell adhesion molecule (ICAM)-1) [26] Hence one can believe that Gas6acts as a factor possessing the capacity of conferring protection in Atherosclerosis [26].

Gas6 further possesses the capacity of stimulation of endothelial progenitor cell (EPC) proliferation, along with *in vivo* migration through activation of the Akt signaling pathway [26]. EPC 's have a crucial part in the production of new blood vessels or in proliferation of the prior existent vasculature [26]. These observations might form the trial of more reendothelialialization with the utilization of autologous EPC transplantation [26]. The initial meta-analysis with regards to dp-ucMGP in the form of a risk factor in case of cardiovascular episodes along with mortality was conducted dependent on the outcomes obtained from 11 trials performed on 33289 patients [33]. Zhang., *et al*. [31], observed that the Circulating dp-ucMGP possessed a correlation with an escalation of risk of all-cause mortality (HR1. 77;95%CI1. 44-2. 18; p = 0. 476) as well as cardiovascular mortality (HR1. 84;95%CI1. 33-2. 55; p = 0. 896) however not with the risk of CVD mortality (HR1. 41;95%CI0. 94-2. 12; p = 0. 068). Hence greater dp-ucMGP amounts resulted in a 70% escalation of risk of all cause mortality along with 80% escalation of risk of CVD mortality. However, this meta-analysis documented that the dietary consumption of VK 1, besides not being correlated with risk of all cause mortality (HR0. 90;95%CI0. 73-1. 12;4studies) along with CVD mortality (HR0. 92;95%CI0. 53-0. 93; p = 0. 0644) [34].

One more meta-analysis dependent on the results derived from 21 articles detailed Clinical studies inclusive of 222592 recruiters [34]. A significant association was illustrated byChen., *et al*. [35] amongst VK1 consumption as well as a full CHD by Chen., *et al.* [35], (pooled HR0. 92;95%CI0. 84-0. 99;4studies) along with VK2 as well as full CHD (0. 70;95%CI0. 94-2. 12; 2studies). Nevertheless, no significant correlations were observed amongst a dietary intake of VK along with all-cause mortality, CVD mortality, or stroke. escalation of plasma dp-ucMGP was correlated with an enhancement of all-cause mortality (HR1. 84;95%CI1. 48, 2. 28;5studies) as well as CVD mortality HR1. 96;95%CI1. 47, 2. 61;2studies). Thus Che., *et al*. 's [35] conclusions were that a greater VK dietary consumption was correlated with a lesser risk of CHD, in addition to greater plasma dp-ucMGP amounts possessed an association with the escalation of risk of all-cause mortality, as well as CVD mortality.

Thus, these outcomes corroborated the correlation amongst dietary VK consumption, plasma dp-ucMGP amounts in addition to cardiovascular risk. This pointed that a significant, part of VK in these events that needs greater research.

## Chronic kidney disease as well as vitamin K

Generally sub Clinical Vitamin K deficiency is an observation in Chronic Kidney Disease (CKD) patients might be correlated with an escalation of risk of mortality along with morbidity in this patients population [36]. The properties of Vitamin K deficiency is lesser amounts of Circulating Vitamin K along with greater inactive VKDP [26]. Lesser Vitamin K consumption in addition to decrease in the carboxylation event of VKDP comprise the major causes of this kind of status [26].

The VKDP action might get impacted by numerous factors in case of CKD patients [37]. Certain ofthese result in Vitamin K deficiency as well as reduction of VKDP action, like i) dietary restrictions that are correlated with lesser Vitamin K consumption, dysbiosis secondary to the uremic situations, haemodialysis (HD) treatment iv) sevalamer (phosphate binder) or Vitamin K analogue (Vitamin K antagonist s). Conversely certain factors might result in an escalation of VKDPi) calcimimetics administration, ii) utilization of Vitamin D (VD) analogue, iii) utilization of mycophenolate mofetil iv) Kidney transplantation [32]. More recently outcomes from a study pointed that treatment with statins might impact the Vitamin K metabolome in CKD patients [38].

Mice that had received feeding with VK 1along with simultaneous atorvastatinn, a41%decrease in MK-4 in Kidney was seen [32]. Ina Clinical study performed on patients on HD who got treatment with statins, a greater coronary artery calcification (CAC) in addition to greater propagation of calcification [38].

Documentation with regards to Gas6 amounts escalation in CKD patients in addition to patients going through HD was further done [26] In an animal study it was illustrated that Gas6 possessed the capacity of conferring protection against renal ischemia-reperfusion damage [28]. The observation was that Gas6 possessed an ad-

vantageous action on Acute Kidney injury in view of it having anti inflammatory along with immuno controlling characteristics [26]. It has been pointed that this action might be associated with endothelial action along with the inflammatory event in these patients [3]. It was demonstrated that disturbance as well as inflammation of Glomerular capillaries resulted in an escalation of Gas6 amounts [26]. Thus upregulation of Gas6 occurs in numerous inflammatory nepaphropathies [26].

An escalation of Gas6 amounts was illustrated in a mouse model of Acute Kidney injury in an experimental study conducted whose induction occurred secondary to sepsis that was correlated with enhancement survival in correlation with a reduction in serum urea nitrogen, creatinine in addition to apoptosis of renal tissues [26]. The researchers found a remarkable reduction in the liberation of proinflammatory cytokines, like TNFα) as well interleukin-12β (IL-1β) by the activation of Gas6 [33,39]. In its active form it got demonstrated that Gas6 resulted in VSMCs calcification by blockade of apoptosis along with avoidance, of apoptotic VSMCs vesicles calcification to act as nidus for the calcium -phosphate getting precipitated [37]. Hyperphosphatemia stimulated calcification of VSMCs has a correlation with the downregulation of expression of Gas6 in addition to hampering of calcification of VSMCs by VK2 by the restoration of this Gas6 anti apoptotic pathway [37] outcomes of Clinical studies pointed that an association amongst a lesser ucMGP amounts along with a reduction in eGFR in patients with CHD [5]. Nevertheless, albumin: creatinine ratio kept unaltered in this group of patients [25]. Conversely an escalation of dp-ucMGP amounts occurred slowly with a reduction in eGFR-determined renal function in patients possessing variability of renal impairment [30].

A cohort study got performed by Dai., *et al*. [30], in 493 patients in stage 5 of CKD (CKD-5) [40]. assessment, of the correlation amongst functional deficiency of Vitamin K, besides all cause mortality along with if there was a modification of this correlation was done by Dai., *et al*. in the existence of VC in CKD-5. Every escalation of Standard deviation in dp-ucMGP had a correlation with an escalation of risk of demise from any of the etiologies (sub hazardratio (sHR)1. 17;95 and CI, 1. 01-1. 37), adjustment of age, gender, cardiovascular disease (CVD), DM, mass index (MI), inflammation in addition to HD treatment. This correlation was further significant, subsequentto adjustment for CAC as well as AVC in the sub assessment (sHR 1. 22, 1. 01-1, 48as well as;1. 27, 1. 01-1. 60 respectively). Hence Dai., *et al*. [30], illustrated that the functional deficiency of Vitamin K had a correlation with escalation of demise irrespective of the existence of VC in patients with ES CKD [40].

Diabetic nephropropathy is a usual complication that takes place in DM patients that resulted in end stage renal Disease (ESRD). Apparenthly Gas6 has a part in the etiopathogenesis. Nevertheless, the results derived with regards to the part played by Gas6 in this nephropropathy is debatable [26]. Hence. Nagai., *et al.* illustrated an escalation of glomerular expression of Gas6 along with Axl in streptozocin (STZ), induced Diabetic rats possessing glomerular nephropropathy [41]. Conversely Hung., *et al*. [42], conducted a study in type 2 diabetes mellitus (T2DM) patients found besides an enhancement of plasma Gas6 amounts in addition to its reduction [32]. Furthermore the amounts possessed an inverse association with fasting blood glucose (FBG), TNFα), interleukin-6 (IL-6), along with vascular cell adhesion molecule [VCAM]-1 [42]. Other researchers pointed to a reduction of Gas6 with the deterioration of proteinuria [43]. It was pointed that a complicated crosstalk amongst molecular charge as well as mass might have a part in the glomerular filtration rate (GFR) of Gas6 [25,26]. Furthermore Gas6 in addition to albumin share a common molecular weight along with charge, therefore might crosstalk with glomerular membrane [25,26]. Hence the plasma Gas6 amounts might alter in various stages of diabetes [25,26].

Diabetic patients possessing a greater CV risk an independent correlation amongst an escalation of dp-ucMGP in addition to the robustness of peripheral arterial calcification was illustrated [5,44]. Furthermore an independent correlation amongst greater dp-ucMGP amounts along with cfPWV)in diabetic along with patients of CKD was observed that can result stiffening of large arteries [5,30].

More recently a prospective study performed on 66 Diabetic patients with CKD illustrated that greater plasma dp-ucMGP amounts (> 656pM) had a correlation with all-cause mortality (HR = 2. 63, = 1. 7-5. 94; p = 0. 002), CV mortality (HR = 2. 82, 95%CI = 1. 07-7. 49; p = 0. 037) as well as propagation of CKD (HR = 4. 02, 95%CI = 1. 20-13. 46; p = 0. 024) [45]. These outcomes were in bargain with the outcomes derived from the prospective general population - based Prevention of Renal andVascular End Stage Disease (PREVEND) study that was inclusive of 4275 recruitment of patients [36] In case of 31% of the total study population functional, Vita-

min K deficiency (dp-ucMGP > 500pmol/l)was determined along with the incidence was much greater amongst, the older patients in addition to the ones with co- dp-ucMGP morbidities like T 2DM, Hypertension, as well as CVD. Riphagen., *et al*. [46], found a significant correlation amongst greater plasma dp-ucMGP amounts with all cause mortality (HR) 95%CI = 0. 20 (0. 12-0. 33), p < 0. 001); squared term 1. 14 (1. 10-1. 17), p < 0. 001); [46].

Chronic Kidney Disease (CKD) causes a predispositionto early vascular aging (EVA) that gets modulated bymedial VC [47]. The outcomes pointed that cellular aging along withinflammation secondary DNA injury could result in pathological situations, possessing the properties of exaggerated EVA. It was demonstrated, that nuclear factor, erythroid 2 related factor (NRF2) signaling in addition to VK possessed a significant part with regards to counteraction of Oxidative stress (OS), DNA injury, inflammation, Senescence. Hence it was suggested that NRF2 activation, besides supplementation of Vitamin K might give an innovative target for treatment in the context of EVA [47].

In the current decade greater attention has been paid to Vitamin K with regards to part of Vitamin K in calcification of arteries in particular in CKD patients [5,18,25-27,29]. In CKD patients, VC takes place broadly in early stages as well [48]. Like CAC took place in 13% of patients without renal disease, in 40% of nondialyzed CKD patients, in 57% of patients initiating dialysis, in addition to83% of CKD patients on long term dialysis [48].

MGP possesses a significant part in the form of hampering, calcium getting deposited besides crystallizing in the blood vessels wall [31]. MGP might retard propagation of VC in patients with CKD by binding hydroxyapatite crystals [33]. Thus interference with their getting deposited along with macrophages modulates facilitation of clearing [33]. Furthermore crosstalk, amongst MGP along with Bone morphogenetic protein (BMP2)causes hampering, of VSMC Osteoblasts conversion that possesses a key part in the generation of VC.

Deficientcy of Vitamin K results in formation of uncarboxylated MGP (uc- MGP). escalation of uc- MGP amounts on arterial walls are possessing acorrelation with the robustness of the VC [33]. Like observed in numerous studies the amounts of circulating dp-ucMGP enhances slowly in the following stages of (CKD [33]. Its amounts have got correlated with robustness of aortic valve calcification (AC) and Vascular stiffness [VS) [33]. Thus it has been pointed that dp- ucMGP amounts have a correlation with high risk or cardiovascular mortality in addition to all cause mortality [5]. Moreover dp- ucMGP amounts are further correlation with large arterial stiffness [30].

Calciphylaxis, VC or calcifying uremic arteriolopathy (CUA) are occasional conditions which might threaten life, taking place basically in patients with end stage renal disease (ESRD) [49]. This condition possesses the properties of calcification of cutaneous arterioles in addition to is fast propagating, correlated with robust painful ulcers of skin. VC is usually seen in patients on HD [48]. Greater plasma amounts of uncarboxylated MGP (uc MGP) as well as carboxylated MGP (c MGP) were seen in patients on HD with Calciphylaxis in contrast to patients on HD without Calciphylaxis [50]. correlation of VitaminK deficiency with a lesser amount of c MGP along with might be implicated in the pathogenesis of Calciphylaxis [50].

Further details of VitaminK in coagulation, BMD, see ref 5, 24.

## Conclusions

Utilization of Vitamin K has been posited with regards to supplementation along with conferring protection, in patients who possess, greater chances of formation of VC or bone situations in particular in case of patients with Chronic Kidney Disease (CKD). The outcomes derived till now are not incontrovertible. However no large scale randomized controlled trials (RCT) have been performed on patients with CKD, that pointed that Vitamin K supplementation for nephro protection depending on the generation of Vascular calcification in addition to the correlated mortality along with morbidity. Furthermore the query with regards to which VK utilization is to be done, VK 1 or2? Apparently VK 2 has greatsignificance might be for extrahepatic VKDP in addition to in all probabilityis without harm, besides economical [48]. Nevertheless, not properly conducted controlled trials are existent that valdated this reasoning. Conversely, as an alternative VK 1 might be of use since it gets converted to VK2, however in 10 fold greater dosage in contrast to VK2 [48].

One further hurdle is that the dosage advocated varies from country to country as well as source [28]. These days the dosage advocated dosage is 90µg daily for healthy adult women along

with65-120µg daily for healthy adult men [26] In the Institute of Medicine in US are 120µg daily for men as well as 90µg daily for women [18,28]. Conversely advocated dosage for the LARN from Italy (Reference Levels of Assumption Nutrients and Energy) are significantly greater along with based on age are140µg daily for 18-59 yr old; as well as 170µg daily for those > 60yrs [28]. Conversely advocated dosages in Belgian Conseir Supérieur de la Santé is 50-70 µg daily for VK1 for adult population [9]. Hence no uniform agreement is present [28]. Greater randomized studies depending on a large population are required to get conducted for ansering this query.

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