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Evaluation Role of vitamin k and many physiological parameters in women with chronic kidney disease in Kirkuk city

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Abstract

The current study was conducted in order to find out the changes in a number of physiological and biochemical parameters, including Matrix G1a protein (MGP), osteocalcin hormone levels , urea and creatinine concentration that are associated with vitamin K deficiency in women with chronic kidney disease in Kirkuk city. The study was designed with 60 women attending Kirkuk General Hospital and Azadi Teaching Hospital in Kirkuk city, whose ages ranged between (45-65) years, and were distributed among 20 women in the control group and 40 women in the chronic kidney group. Blood samples were collected from patients attending the hospital for the period from November 2022 to February 2023, The results of the study showed a significant decrease ($p \leq 0.05$) in the concentration of vitamin K in the blood serum of the chronic kidney patients compared to the healthy control group. There was also a decrease ($P \leq 0.05$) in the matrix Gla protein (MGP) in chronic kidney patients compared to the healthy control group. The chronic kidney patients showed a decrease in osteocalcin concentration and an increase in urea and creatinine concentration in blood serum , compared to the healthy group.

Key words : vitamin k , Matrix Gla protein , Osteocalcin , Urea, Creatinine.

Introduction

chronic kidney disease (CKD), It is usually defined as a decrease in renal function (destruction of the tiny capillaries in which blood is filtered in the kidneys), and a glomerular filtration rate (GFR) less than 60 mL/min per 1.73 m^2 that present at least 3 months. These changes are often identified by increased serum levels of creatinine, cystatin C, or blood urea nitrogen (Kalantar-Zadeh et al., 2021).

The VK vitamin family consists of a group of fat-soluble molecules that share the (2-3)-methyl-1,4-naphthoquinone groups. Vitamin K exists in 3 main forms, K1 and K2 which are the natural form, and K3 or menadione which is the synthetic form of the vitamin. Vitamin k1, also known as phylloquinone, is found in vegetables, while vitamin k2, also known as menaquinone, is found in fermented foods or produced by intestinal flora (Fusaro et al., 2020). Vitamin K plays an essential role in many physiological processes as the only cofactor for the enzyme γ-glutamyl carboxylase (GGCX) that catalyzes the activation of vitamin K-dependent proteins (VKDPs) involved in bone formation, prevention of tumor growth, inflammatory reactions and many other biologically important functions(Fakhree et al., 2021).

The mechanism of action of vitamin K is add a carboxylic acid functional group to the amino acid glutamate (Glu) residue of a protein, by the enzyme gamma-glutamyl carboxylase (GGCX) to form gamma-carboxyglutamate (Gla). GGCX is located in the endoplasmic reticulum and is expressed in various tissues, including the liver, brain, heart, kidney, lung, pancreas, and skeletal muscle (Alonso et al., 2022). This posttranslational change of a protein referred to as the "Gla protein" requires a propeptide and three co-substrates: vitamin K, CO2, and O2. The presence of two −COOH (carboxylic acid) groups on the same carbon within the gamma-carboxyglutamate residue results in chelation of calcium ions. In this way, the binding of calcium ions takes place, which often affects the action or binding of protein Gla(Fakhree et al., 2021). Concurrently, vitamin K is converted in the cell into a reduced form known as vitamin K hydroquinone, which acts as a cofactor for GGCX, which is converted into a VK-2,3 epoxide, then reduced to the respective quinone by the enzyme VK epoxide reductase and, finally, it is converted back to hydroquinone and it is not clear whether VKOR itself catalyzes the conversion of vitamin K to reduced vitamin K or this is achieved by a separate enzyme. Then the cycle begins again (Alonso et al., 2022).

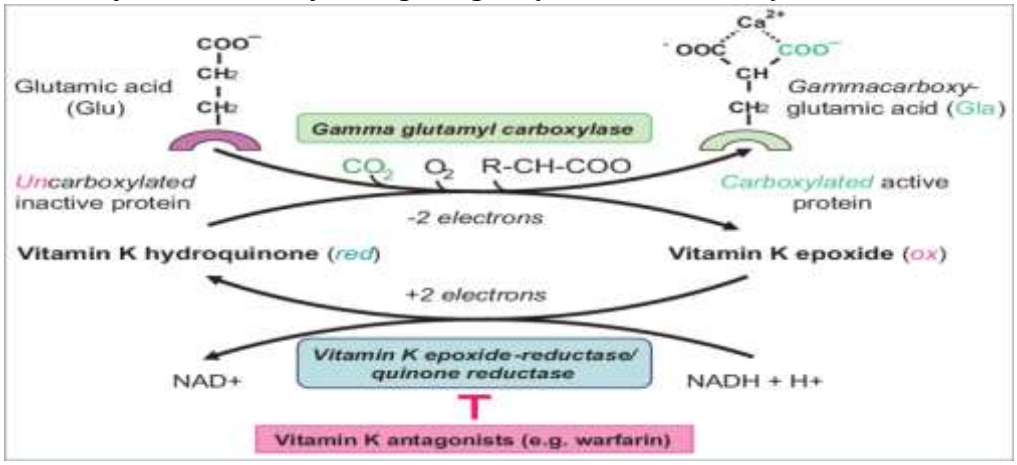

Figure (1) : In the vitamin K cycle, vitamin K-dependent gamma-carboxyglutamic acid (Gla) proteins are carboxylated and activated.
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Among the VKDPs, the major proteins involved in vascular and bone function are matrix Gla protein (MGP) and osteocalcin (OC), which belong to a large and distinct group of vitamin K-dependent proteins.

MGP It is a 10.6 kDa protein that is secreted into the extracellular interstitial substance mainly by vascular smooth muscle cells (VSMCs) and chondrocytes, which specifically exerts the role of an inhibitor of calcification. It is activated, in addition to the carboxylation process, by a three-site serine acid phosphorylation process. Thus, phosphorylation also determines the state of activity: phosphorylated (pMGP) is the active form and dephosphorylated (dpMGP)is the inactive form. (Fusaro *et al.*, 2020).

MGP acts as an inhibitor in the deposition and crystallization of calcium in the vascular wall. MGP carboxylate inhibits extracellular mineralization by fusing with calcium crystals, thereby inhibiting their growth, and also acts by binding to and inhibiting bone morphogenetic protein (BMP-2) that prevents VSMC differentiation into osteogenic cells, which is the pivotal step in the development of vascular calcification (Wallin et al., 2000).

Osteocalcin is the most important non-collagen protein in the interstitial substance of bone. It is a protein composed of 49 amino acids with a molecular about 5800 Daltons. Osteocalcin is produced by osteoblasts and osteocalcin contains three glutamic acid residues. This residue in OC is beta-carboxylated , in the presence of vitamin K and becomes decarboxylated osteocalcin, which binds to calcium ions in hydroxyapatite (calcium hydroxyl phosphate), the Glu-carboxylated amino acid residue present in γ-carboxylated OC has a calcium-binding site, where it attracts calcium ions. Therefore, the compound is able to bind to calcium ions and incorporate them into the hydroxyapatite crystals that form the interlayer of bone (Zoch et al., 2016).

Urea, commonly referred to as blood urea nitrogen (BUN) when measured in blood, is a product of protein metabolism. Amino acids derived from the breakdown of protein are deaminated to produce ammonia. The ammonia is then converted into urea by liver enzymes. Therefore, urea concentration depends on protein intake, the body's ability to catabolize protein, and adequate excretion of urea by the renal system, (Salazar, 2014). BUN levels are significantly increased in patients with CKD, reaching in patients with end-stage renal disease, pre-dialysis concentrations that can reach 10-fold or more than the upper limit of the normal range (Almeras & Algires, 2009).

Plasma or serum creatinine is the most commonly used diagnostic marker for estimating glomerular filtration rate (GFR) in routine settings (Herget-Rosenthal et al., 2007). It is an end product of catabolism (the breakdown product of dietary meat and creatine phosphate found in skeletal muscle). Creatine circulates throughout the body and is converted to phosphocreatine through the process of phosphorylation in skeletal muscle and brain. The majority of creatinine is produced in muscles. Serum creatinine (Scr) is produced at a relatively constant rate and is eliminated mostly by glomerular filtration, but it is

also affected by several factors other than glomerular filtration such as diet and diseases (Salazar, 2014).

Material & Methods : Blood samples were collected from women with chronic kidney disease attending Azadi Teaching Hospital and Kirkuk General Hospital, aged between 45-65, for the period from October 2022 to February 2023. The blood was separated to obtain blood serum using a centrifuge and the serum was kept at -20 degrees Celsius for biochemical analysis later. An analysis of the concentration of vitamin K in the blood serum of the studied samples was carried out using the ELISA kit with the immunoassay of the enzyme competitive inhibition. The analysis of the Matrix Gla protein and the osteocalcin hormone was performed for the studied samples performed by using the ELISA kit on the principle of the enzyme sandwich immunoassay, where the concentrations were determined All by comparing the OD of the samples with the standard curve. The analysis of urea and creatinine was carried out for the studied samples performed by using a spectrophotometer, and the results were extracted by applying the equation that included the proportion of the standard solution .

Result & Discussion :

1-The results of the current study as shown in Figure (2) , there was a significant decrease at ($p<0.05$)level in the concentration of vitamin K1 in the blood serum of infected patients in chronic kidney failure (1618.47 ± 473.20 pg/ml) in compared with the healthy control group (1838.97 ± 307.61pg/ml).

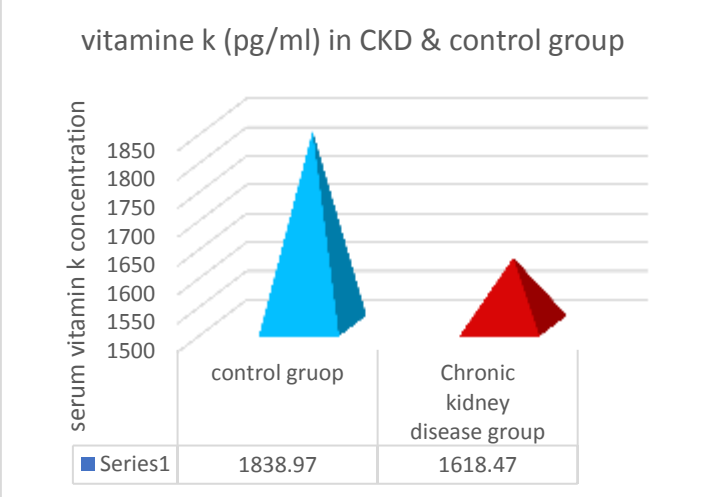

Figure (2) The average concentration of vitamin K in the serum of the studied samples

The low concentration of vitamin K in chronic kidney patients agreed with the results of the study by Krueger et al (2009) that showed vitamin K deficiency in chronic kidney patients due to its contradiction with anticoagulants, which may stimulate vascular calcification in chronic kidney patients. In another study, evidence shows that patients with CKD have a higher risk of subclinical vitamin K deficiency. This deficiency may be due to vitamin K consumption due to a higher requirement for vitamin k dependent proteins (VKDPs), which are lost due to bone turnover. and the environment o uremia. However, dietary

recommendations for CKD patients, such as diets low in green vegetables (rich in phylloquinone (K1)) and low in dairy products (rich in menaquinone (K2)), appear to play the major role in promoting this deficiency (Cozzolino et al., 2019).

2-The results of the current study as shown in Figure (3) a significant decrease ($P<0.05$) in the concentration of matrix Gla protein (MGP) in the blood serum of infected patients with chronic kidney disease (5.62 ± 2.95 ng/ml) when compared with the healthy control group (7.05± 3.89 ng/ml).

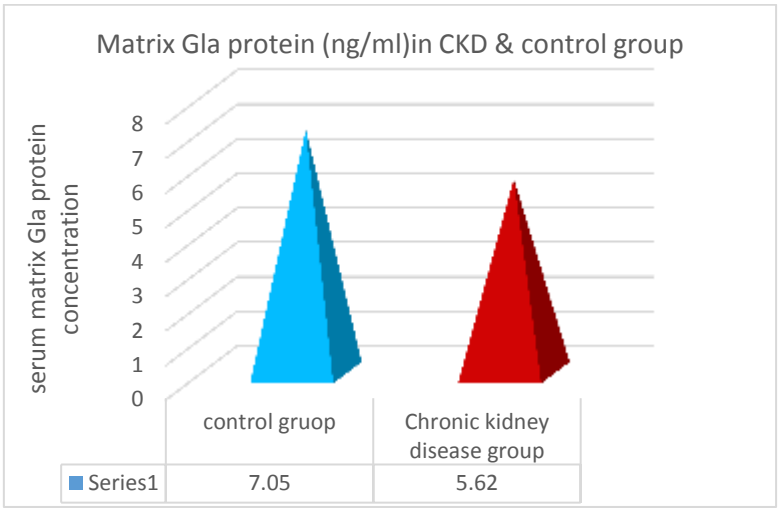

Figure (3) The average concentration of matrix Gla protein in the serum of the studied samples

In CKD patients, the decrease in serum MGP concentration was consistent with the Sevinc et al. (2021) which found that MGP levels were significantly lower in stages 2, 3, 4, and 5 of CKD compared to the healthy control group. She indicated the role of MGP in atherosclerosis in chronic kidney failure. Another previous study indicated that the level of MGP was inversely associated with progression in the stages of hemodialysis. Accumulating evidence indicates that vitamin K deficiency induced by diet or treatment with vitamin K-antagonizing drugs and deficiency in MGP may induce vascular calcification (VC) in particular endothelial and middle layer calcifications of atherosclerosis, which is a major contributor to mortality in CKD patients. (Krueger et al., 2009).

3-The results of the current study as shown in Figure (4) ,there was a significant increase at ($P<0.05$) level in the concentration of osteocalcin in the blood serum of patients With chronic kidney disease (0.32 ± 0.07 ng/ml) in compared with the healthy control group (0.61± 0.04ng/ml).

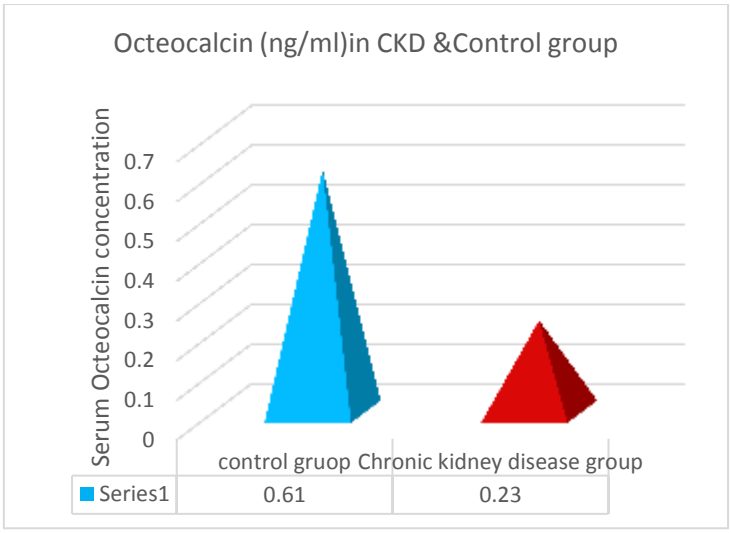

Figure (4) The average concentration of Osteocalcin in the serum of the studied samples

The decrease in osteocalcin concentration agreed with Fusaro et al. (2020) that estimate chronic kidney disease (CKD) had a decrease in blood OC levels. In a previous study, Guo et al. (2022) who explained OC and its relationship to lipid profile, renal function, and vascular function, they concluded that the decrease in OC may be due to disorders of lipid metabolism in patients with kidney disease.

Oral anticoagulants combined with vitamin K are another important variable in the bone disorder risk profile of hemodialysis-dependent patients. The mechanism by which these antibiotics may cause vitamin K deficiency is direct (inhibition of carboxylation of VKDPs, including osteocalcin) and indirect (reduced dietary intake of vitamin K-rich foods), thereby inhibiting γ-carboxyglutamyl synthesis, and causing poor bone health in patients with taking these drugs (Fusaro et al., 2022).

4- The results of the current study as shown in Figure (5 there was a significant increase ($P<0.05$) in the concentration of urea in the blood serum of CKD patients (44.57±14.06 mg/dl) ,When compared with the healthy control group (38.11±9.05mg/dl).

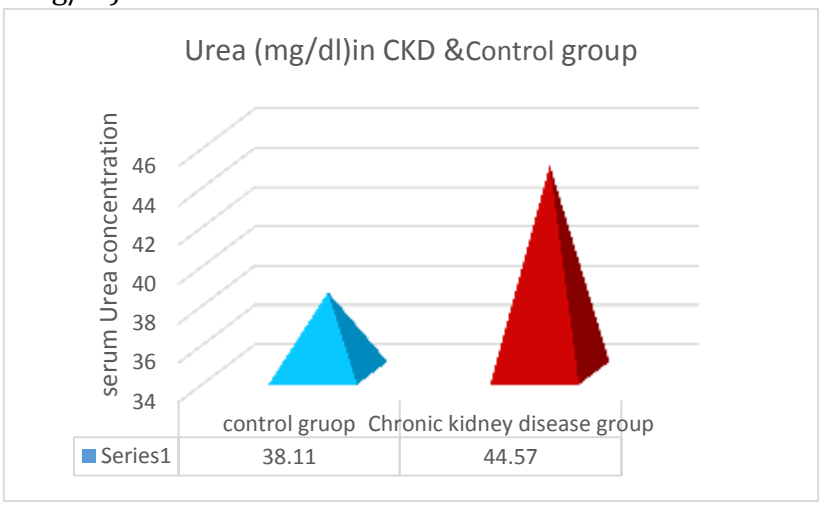

Figure (5) The average concentration of Urea in the serum of the studied samples

In patients with chronic kidney disease, an increase in their urea levels was consistent with previous study. Linking urea concentration independently with the development of chronic kidney disease (CKD) in patients with advanced stages of CKD, indicating that urea may be a useful marker to predict the progression of kidney disease (Seki et al., 2019).

Blood urea levels rise with a gradual decline in kidney function. Elevated concentrations of urea to levels above normal lead to the breakdown of the epithelial barrier of the intestine, leading to the transfer of bacterial toxins into the bloodstream and systemic inflammation. Urea induces vascular smooth muscle cell apoptosis as well as endothelial dysfunction, thus directly promoting cardiovascular disease (Lau & Vaziri, 2016).

5- The results of the current study as shown in Figure (6), s an increase ($p<0.05$) in the concentration of creatinine in the patients' blood serum.(1.25± 0.75mg/dl) ,When compared with the healthy control group (0.75 ± 0.71 mg/dl).

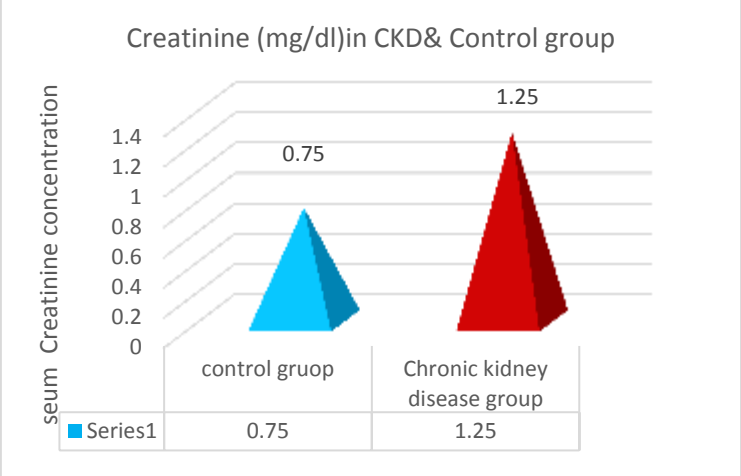

Figure (6) The average concentration of Creatinine in the serum of the studied samples

In chronic kidney patients, the high level of creatinine in the blood agreed with a study that indicated that high creatinine concentration was diagnostic and prognostic signs of chronic kidney disease. Creatinine is excreted in the urine by glomerular filtration and renal tubular secretion, so the sharp increases in serum creatinine are attributed to a decrease in the glomerular filtration rate (Shahbaz & Gupta, 2022)

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