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Possible Correlations between Vitamin D and Inflammatory Markers among Hemodialysis Patients

Mahmoud Hosny Zahran, Adel Abdelmohsen Ghorab, Abdul-Rahman Mahmoud Abdelhady Bayoumi, Tamer Mohamed Goda
Internal Medicine Department, Faculty of Medicine, Zagazig University, Egypt

abdohassan8830@gamil.com

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Abstract: Some experts have defined vitamin D deficiency as a serum 25(OH)D level <20 ng/mL and insufficiency as between 21 and 29 ng/mL: a target of >30 ng/mL is suggested for optimal health. However, this remains controversial because of the lack of a consensus regarding the optimal range for serum 25(OH)D. Nevertheless, there is a common understanding that low serum 25(OH)D levels cause a negative calcium balance, secondary hyperparathyroidism (SHPT), and bone disease. Impaired metabolism of vitamin D is a common feature of chronic kidney disease (CKD). Renal dysfunction is associated with impaired conversion of 25(OH)D to 1,25(OH)2D. Therefore, supplementation with active vitamin D [1,25(OH)2D] is commonly practiced in patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD). However, recently it has been shown that 25(OH)D can be converted to 1,25(OH)2D at sites other than the kidney, including the prostate, breast, colon, and macrophages. Patients on hemodialysis have increased level of inflammatory mediators including C-reactive protein, tumor necrosis factor and IL6, as it plays major role in malnutrition, inflammation and atherosclerosis as well as overall mortality rate in these patients. Leukocytes are considered among the classic inflammatory markers due to their role in pathogenesis of atherosclerosis and its complications by mediating several biochemical pathways. The association between inflammatory markers and cardiovascular events, coronary artery disease and its complications occur with high frequency in patients with ESRD; and substantially is contributing to cardiovascular morbidity and mortality in this population. Elevated levels of serum CRP is linked to the development of coronary artery disease even in the absence of dyslipidemia. Serum CRP level measured by conventional method is a predictor of mortality in hemodialysis patients.

Keywords: Vitamin D, Inflammatory Markers, Hemodialysis

Introduction: Vitamin D plays a vital role in maintaining healthy bones and calcium levels. A lack of vitamin D leads to hypocalcemia and defects in bone mineralization. Although rare, too much vitamin D can result in life threatening hypercalcemia. Vitamin D toxicity should always be considered as a differential diagnosis in patients with hypercalcemia. Several international guidelines often refer to 25(OH)D concentrations >150 ng/mL posing a

significant risk of vitamin D toxicity; Individuals prescribed high doses of vitamin D should be regularly monitored **(1).**

Vitamin D promotes calcium absorption in the gut and maintains adequate serum calcium and phosphate concentrations to enable normal bone mineralization and to prevent hypo calcemic tetany (involuntary contraction of muscles, leading to cramps and spasms). It is also needed for bone growth and bone remodeling by osteoblasts and osteoclasts. Without sufficient vitamin D, bones can become thin, brittle, or misshapen. Vitamin D sufficiency prevents rickets in children and osteomalacia in adults. Together with calcium, vitamin D also helps protect older adults from osteoporosis **(2).**

Vitamin D has other roles in the body, including reduction of inflammation as well as modulation of such processes as cell growth, neuromuscular and immune function, and glucose metabolism. Many genes encoding proteins that regulate cell proliferation, differentiation, and apoptosis are modulated in part by vitamin D. Many tissues have vitamin D receptors, and some convert 25(OH)D to 1,25(OH)2D **(3).**

Vitamin D Deficiency

Some experts have defined vitamin D deficiency as a serum 25(OH)D level <20 ng/mL and insufficiency as between 21 and 29 ng/mL: a target of >30 ng/mL is suggested for optimal health. However, this remains controversial because of the lack of a consensus regarding the optimal range for serum 25(OH)D. Nevertheless, there is a common understanding that low serum 25(OH)D levels cause a negative calcium balance, secondary hyperparathyroidism (SHPT), and bone disease **(4).**

People can develop vitamin D deficiency when usual intakes are lower over time than recommended levels, exposure to sunlight is limited, the kidneys cannot convert 25(OH)D to its active form, or absorption of vitamin D from the digestive tract is inadequate. Diets low in vitamin D are more common in people who have milk allergy or lactose intolerance and those who consume an ovo-vegetarian or vegan diet. In adults and adolescents, vitamin D deficiency can lead to osteomalacia, in which existing bone is incompletely or defectively mineralized during the remodeling process, resulting in weak bones. Signs and symptoms of osteomalacia are similar to those of rickets and include bone deformities and pain, hypo calcemic seizures, tetanic spasms, and dental abnormalities **(5).**

Vitamin D deficiency symptoms include abnormal bone mineralization and deformities (i.e., rickets in young, and osteomalacia in adults), hypocalcemia, and high circulating titers of PTH. Additionally, since vitamin D receptors are present on hair follicles, vitamin D deficiency can promote hair loss. In addition to hereditary, dietary, and behavioral causes (e.g., lack of UV light), liver and/or kidney disease may also result in a 1,25(OH)2D deficiency. Also, lead (Pb) appears to block intestinal 1,25(OH)2D-stimulated Ca++ absorption, yet

vitamin D supplementation enhances Pb uptake. As with vitamin A, normal hepatic stores of vitamin D are generally thought to be capable of supporting vitamin-deficient diets for several months. Therefore, deficiency symptoms usually manifest themselves slowly **(6).**

Groups at Risk of Vitamin D Inadequacy

Few foods contain sufficient vitamin D. Therefore, without daily sunlight exposure or fortified food, an important risk for vitamin D deficiency exists. Thus, climate, location, aging, lifestyle, and skin pigmentation affect vitamin D production **(7).**

Older adults

Older adults are at increased risk of developing vitamin D insufficiency, partly because the skin's ability to synthesize vitamin D declines with age. In addition, older adults are likely to spend more time than younger people indoors, and they might have inadequate dietary intakes of the vitamin **(8).**

People with limited sun exposure

Homebound individuals: people who wear long robes, dresses, or head coverings for religious reasons; and people with occupations that limit sun exposure are among the groups that are unlikely to obtain adequate amounts of vitamin D from sunlight. The use of sunscreen also limits vitamin D synthesis from sunlight. However, because the extent and frequency of sunscreen use are unknown, the role that sunscreen may play in reducing vitamin D synthesis is unclear **(9).**

Vitamin D deficiency in hemodialysis patients

Impaired metabolism of vitamin D is a common feature of chronic kidney disease (CKD). Renal dysfunction is associated with impaired conversion of 25(OH)D to $1,25(OH)_2D$. Therefore, supplementation with active vitamin D [$1,25(OH)_2D$] is commonly practiced in patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD). However, recently it has been shown that 25(OH)D can be converted to $1,25(OH)_2D$ at sites other than the kidney, including the prostate, breast, colon, and macrophages **(10).**

Local production of $1,25(OH)_2D$ may be important for several biologic functions in these tissues; thus, circulating 25(OH)D levels may be relevant even when supplementation with active vitamin D is carried out, as in patients with CKD with low renal production of $1,25(OH)_2D$. Levels of 25(OH)D below 30 ng/ml are associated with increased parathyroid hormone (PTH) levels, low bone mineral density (BMD), and increased risk of hip fractures. According to the latest Endocrine Society guidelines, serum levels of 25(OH)D between 20 and 30 ng/ml indicate vitamin D insufficiency and levels less than 20 ng/ml indicate vitamin D deficiency. Severe deficiency is defined as a 25(OH)D level less than 10 ng/ml. The recently

published KDIGO (kidney disease: improving global outcomes) guidelines recommend that the serum level of 25(OH)D should be maintained over 30 ng/ml in patients of all stages of CKD **(11).**

Hemodialysis patients often have limited exposure to sunlight, which is a crucial source of vitamin D synthesis in the body. This can be attributed to factors such as spending long hours indoors or limited outdoor activities. Additionally, the use of protective clothing, sunscreen, and geographic location can further decrease sunlight exposure **(12).**

Impaired renal function is another significant factor contributing to vitamin D deficiency in hemodialysis patients. The kidneys play a crucial role in converting inactive vitamin D (vitamin D3) to its biologically active form (calcitriol). In patients with end-stage renal disease, the kidneys are unable to perform this conversion efficiently, leading to low levels of active vitamin D. Furthermore, hemodialysis itself can contribute to vitamin D deficiency. During the hemodialysis process, vitamin D-binding proteins and active vitamin D are removed from the blood, further reducing the available levels of vitamin D in the body **(11).**

Vitamin D deficiency is a prevalent issue in hemodialysis patients due to reduced sunlight exposure, impaired renal function, and the dialysis process itself. Recognizing and addressing vitamin D deficiency is crucial to prevent complications and optimize the health outcomes of hemodialysis patients. Regular monitoring and appropriate supplementation are key components of managing vitamin D deficiency in this population **(10).**

Cardiovascular disease (CVD) is on the list of the leading causes of mortality in CKD patients. Nevertheless, the exact etiology linking CKD with CVD remains poorly understood and consequently, therapy nowadays is regarded as being unsatisfactory. A chronic low-grade systemic inflammation in addition to dyslipidemias is believed to play a major role **(13).**

Both cardiovascular diseases and infection are linked to inflammation and ESRD has recently been considered a state of chronic inflammation, which is the cornerstone of pathogenesis of atherosclerosis, is increased in ESRD patients compared to normal population. It is thought that early detection of inflammation might improve the quality of the life of those patients and decrease the rate of morbidity and mortality **(14).**

Patients on hemodialysis have increased level of inflammatory mediators including C-reactive protein, tumor necrosis factor and IL6, as it plays major role in malnutrition, inflammation and atherosclerosis as well as overall mortality rate in these patients. Leukocytes are considered among the classic inflammatory markers due to their role in pathogenesis of atherosclerosis and its complications by mediating several biochemical pathways **(15).**

Chemokine ligand-16 (CXCL16) is a small cytokine categorized as being a part of the CXC chemokine family. It combines scavenger receptor functions with properties of an inflammatory chemokine. It exists in a transmembrane as well as a soluble form. The transmembrane form is comprised of a chemokine domain, a mucin-like stalk, a transmembrane domain, as well as a cytoplasmic tail. The soluble form results from cleavage at the cell surface and is composed of an extracellular stalk and chemokine domain. The transmembrane form functions as an adhesion molecule for CXCL16 expressing cells and as a scavenger receptor for pathogenic oxidized low-density lipoproteins (oxLDL). The soluble form is regarded as a chemoattractant that enhances the migration of CXC chemokine receptor type 6 (CXCR6) expressing cells including T cells, monocytes, and myeloid fibroblasts. Trans membrane CXCL16 has been found to be present on glomerular and tubular cells during renal injury **(16).**

Approximately 30 to 50% of CKD cases have been found to have noticeably raised levels of serum inflammatory biomarkers including C-reactive protein (CRP) and interleukin-6 (IL6). The etiology of inflammation in this case is multifaceted and involves patient-related causes, such as underlying disease, comorbidity, oxidative stress, infections, obesity, genetic or immunologic factors, or on the other hand, hemodialysis-related factors, mainly concerning the dialysis membrane biocompatibility and dialysate quality **(17).**

Secondary hyperparathyroidism is known to be another cause of morbidity and mortality in patients with end stage renal disease. Growing evidence implies that higher levels of parathyroid hormone may be accompanied by low-grade inflammation, but this association remains uncertain. Parathyroid hormone encourages interleukin-6 (IL-6) production by osteoclast and liver cells. Other studies showed elevated levels of C-reactive protein (CRP), tumor necrosis factor-a and other inflammatory markers in hyperparathyroidism patients **(18).**

In addition, high levels of other related parameters of inflammation like ESR, hepcidin, and ferritin may be seen in patients with ESRD whereas, by contrast, serum albumin, LDL and HDL cholesterol levels decrease with inflammation. A number of these markers may be used for the prediction of kidney function variations. For example, higher levels of CRP and soluble tumor necrosis factor receptor 2, were shown to be associated with faster kidney function loss **(19).**

Cardiac troponin and hs-CRP may be used in predicting future mortality. In hemodialysis patients with history of coronary artery disease, higher troponin levels were associated with higher mortality as compared with those without coronary disease. While in patients without a history of coronary artery disease hs-CRP>3 mg/L was associated with significantly higher mortality. However, IL-6 may be a more reliable predictor of cardiovascular diseases and mortality in patients with ESRD **(20).**

The advantages of CRP test are lower cost and availability particularly in developing countries. Serum CRP concentration does not change with the changes in kidney function but in the early stage of kidney disease, serum CRP may be related to serum albumin levels which is affected by inflammatory response **(21).**

It appears that elevated serum CRP may be more associated with thrombotic risk rather than the degree of atherosclerosis. Because serum CRP changes in response to the development of cardiovascular complications; so, it cannot be considered as an independent factor of atherosclerosis. However, hs-CRP has greater predictive ability for primary prevention of cardiovascular risk. The risk prediction role of hs-CRP has been advocated in several studies. In general, serum blood levels at 1, 1-3, and>3 mg/ml corresponds to low, moderate, and high vascular risk across all levels of LDL-C. **(22).**

The association between inflammatory markers and cardiovascular events, coronary artery disease and its complications occur with high frequency in patients with ESRD; and substantially is contributing to cardiovascular morbidity and mortality in this population. Elevated levels of serum CRP is linked to the development of coronary artery disease even in the absence of dislipidemia. Serum CRP level measured by conventional method is a predictor of mortality in hemodialysis patients **(23).**

Serum CRP has been shown as a strong independent risk factor for cardiovascular disease. Patients with higher baseline CRP will have significantly a greater risk of coronary artery event one year later. In one study of hemodialysis patients, serum CRP levels greater than 0.6md/dL increased the odds of cardiovascular diseases by 1.73 times. In a study of hemodialysis patients, CRP level determined the outcome more than LDL-cholesterol. Other cytokines alone or in combination with CRP may be also considered for predicting future cardiovascular or noncardiac complications **(24).**

The level of serum CRP increases with declining serum albumin concentration. The reduction of serum albumin in the early stage of nondiabetic kidney diseases is associated with inflammation and increased risk of cardiovascular diseases. In one study, serum CRP level>0.6 mg/dl was associated with decrease in serum albumin level by 70 mg/dl. In diabetes type 2, CRP and tumor necrosis factor-alpha may be considered as independent risk factors for progression of chronic kidney disease **(25).**

Several studies have revealed that elevated neutrophil count was strongly associated with malnutrition and inflammation and that decreased lymphocyte count had a weaker association. Increased neutrophils and decreased lymphocyte count were also independent predictors of mortality in hemodialysis patients. Recently, neutrophil – to- lymphocyte ratio is considered a novel cheap and available indicator, which reflects the extent of inflammation and atherosclerosis and predicts the clinical outcome and estimate survival in cardiac and non-cardiac including ESRD. The neutrophil to lymphocyte ratio is obtained by dividing the

absolute neutrophil count by the absolute lymphocyte count. It is a marker of poor prognosis in several disorders like malignancies, chronic kidney disease and myocardial function **(25).**

As novel inflammatory factors, neutrophil-to-lymphocyte ratio (NLR), which is a calculated ratio obtained by dividing the absolute neutrophil count by the absolute lymphocyte count in the blood. The NLR has been recognized as a marker of systemic inflammation and has been studied in various clinical conditions, including hemodialysis patients. It has been shown that NLR can be used as an independent risk factor for predicting renal failure in patients with stage 4 chronic kidney disease. Under the stimulation of inflammation, megakaryocytic hyperplasia can be induced to increase the count of platelets, which will interact with endothelial cells and leukocytes to produce inflammatory factors, resulting in a vicious cycle. The onset of many diseases is associated with the increase of platelets **(26).**

It has been investigated the association between NLR and various outcomes in hemodialysis patients. Elevated NLR levels have been found to be associated with increased cardiovascular events, mortality, and overall worse outcomes in these patients. Higher NLR values reflect an imbalance between pro-inflammatory neutrophils and anti-inflammatory lymphocytes and may indicate a state of chronic inflammation and immune dysregulation **(26).**

The NLR has also shown potential as a predictor of nutritional status in hemodialysis patients. It has been associated with markers of malnutrition, such as low serum albumin levels and decreased body mass index (BMI). This suggests that NLR may have a role in assessing the overall health and nutritional status of hemodialysis patients. Furthermore, the NLR has been investigated as a tool for monitoring the response to therapy in hemodialysis patients. Changes in NLR over time may reflect changes in the inflammatory state and response to interventions, such as adjustments in dialysis prescription, use of anti-inflammatory medications, or nutritional interventions **(27).**

The Relationship Between Vitamin D and Inflammatory Markers in Hemodialysis Patients

The deficiency of vitamin D3 is commonly associated with chronic kidney disease (CKD), and the prevalence of this hypovitaminosis increases as kidney function declines. Several factors, such as aging, loss of appetite, and other factors affecting cutaneous synthesis, such as low sun exposure and skin pigmentations, have consistently been associated with low 25-hydroxyvitamin D [25-(OH) D3] levels in the general population. Therefore, it is common in the elderly, malnourished individuals, and some societies **(28).**

It has been suggested that vitamin D has endocrine and immunoregulatory activity through its active metabolite 1,25-dihydroxyvitamin D3, which is produced by renal 1-alfa hydroxylase. In addition, autocrine and paracrine activity from local metabolism of vitamin

D through extrarenal pathway by tissue 1-alfa hydroxylase has an impact on cellular proliferation and differentiation and also inflammatory process in different tissues **(28).**

CKD and ESRD are thought to be a state of micro-inflammation which causes atherosclerosis, cardiovascular disease, and increased incidence of microbial infection; thus, inflammation is responsible for increased mortality and morbidity in these patients. Several inflammatory markers have been proposed to measure inflammation in CKD and ESRD patients, but most of them are costly and are unnecessary. High-sensitivity CRP (HSCRP) is a factor of poor prognosis and decreased survival in ESRD patients and is used for assessing inflammation and cardiovascular risk stratification in this group of patients. Recently, neutrophil-lymphocyte ratio (NLR) has been proposed as a representation of inflammation in different disorders **(29).**

The role of vitamin D in the metabolism of Calcium, Phosphor, parathyroid hormone, development of neurons and the development of the immune cells is well known. 25-OH Vitamin D3 is an inactive form of vitamin D which regulates the hemostasis of Calcium and Phosphor. The deficiency of vitamin D is a risk factor for infectious, autoimmune, neurodegenerative and cardiovascular diseases, as it is widely seen in patients suffering from diabetes, osteoporosis and cancer. Vitamin D deficiency is also observed in patients with end-stage renal disease (ESRD) who are under renal replacement therapy (RRT). The metabolism of vitamin D in patients on hemodialysis (HD) is severely disrupted and the deficiency of vitamin D is a common finding among these patients. Vitamin D is related to cardiovascular mortality as a result of heart failure, myocardial infarction, sudden cardiac death in both general population, and patients on RRT **(30).**

CKD is associated with oxidative stress and inflammation. The existence of cardiovascular diseases in patients without traditional risk factors suggests the role of non-traditional risk factors or pathogenic mechanisms such as inflammation, oxidative stress and hormone changes. Although with inconsistent reports, the low-grade inflammations and the low level of vitamin D were introduced as risk factors of cardiovascular diseases. Epidemiologic studies have shown that vitamin D has a potential anti-inflammatory effect by regulating the inflammatory mediators and has discrete relation with the increase of CRP **(11).**

Inflammation in hemodialysis patients can be measured using several markers, such as CRP, highly sensitive CRP, interleukin-6, tumor necrosis factor alpha, procalcitonin, albumin, ferritin, and cholesterol levels. Of these inflammatory markers, CRP is the gold standard in hemodialysis due to its proven accuracy, low cost, and availability. Recently, the use of these markers has been supplemented by inclusion of the neutrophil-to-lymphocyte ratio (NLR), the platelet-to-lymphocyte ratio (PLR), and the mean platelet volume (MPV) as inflammatory markers in different disorders. Current studies now indicate that the NLR and PLR, in

particular, can be used as reliable and cost-effective inflammation markers in hemodialysis patients **(31).**

Another potential inflammatory marker is vitamin D, a steroid hormone that plays a central role in bone-mineral metabolism. Vitamin D deficiency is related to cardiovascular disease, autoimmune disease, infections, renal disease, anemia, depression, cognitive dysfunction, and malignancies, which are all disorders associated with inflammation. The effects of increasing vitamin D on inflammation or, conversely, the effects of inflammation on vitamin D levels remain controversial, although several studies have shown that vitamin D and its analogues have potential anti-inflammatory activities catalyzed by multiple mechanisms. chronic inflammatory state is an important problem in the hemodialysis population. Interestingly, the vast majority of hemodialysis patients also show vitamin D deficiency. It has been shown that uremic toxins are capable of inducing an inflammatory response in patients with CKD. Uremic toxins can cause oxidative stress and stimulate the production of proinflammatory cytokines in this population. Several studies have reported a relationship between uremic toxins (mainly indoxyl sulfate, p-cresyl sulfate, and indole-3-acetic acid) and inflammation. The indoxyl sulfate has been described to activate NF-κB, NADPH oxidase, upregulated mRNA and expression of intercellular adhesion molecule-1 (ICAM-1) and is also capable to induce endothelial injury with the formation of microvesicles that contribute to endothelial cell progenitor's dysfunction. The p-cresyl sulfate and indole-3-acetic acid are associated with increased IL-6 and CRP, respectively, in patients with CKD **(32).**

When renal function deteriorates to< 15 ml/min/1,73 m^2, patients usually need dialysis support. However, despite the technological advances in the dialysis procedures, three times weekly conventional hemodialysis is not able to remove all toxins, particularly those too large and/or protein bounded. Therefore, patients on dialysis still have serum circulating uremic toxins. Some studies have demonstrated a direct relationship between uremic toxins and inflammation and cardiovascular disease, which is the main cause of mortality in patients with CKD. Uremic toxins can cause immune activation with production of proinflammatory cytokines including TNF-α, IL-6 and MCP-1 mainly by monocytes. Although these proinflammatory cytokines enhance host defense, their excessive production leads to unresolved inflammation. The uremic toxins may induce the toll-like receptor (TLR) activation, resulting in the production of several inflammatory mediators. They reported that TLR4 expression is increased in neutrophils and monocytes obtained from hemodialysis patients that correlated with IL-6, reinforcing the role of TLR4 in the mechanism of inflammation **(33).**

Besides cytokines, 25-vitamin D has also been implicated as an inflammatory marker, participating in both innate and adaptive immunity. Hypovitaminosis D has been often reported in patients with CKD, reaching up to 80% of prevalence. Although the levels of 1,25-vitamin D are important, it is the circulating concentration of 25-vitamin D that determines

the vitamin D status of a given individual. Levels of serum 25-vitamin D from 20 to 60ng/mL are considered normal and values below 20ng/mL are considered indicative of vitamin D deficiency **(32).**

The vitamin-D receptor (VDR) and the enzyme 1α-hydroxylase (CYP27) are present in cells of the immune system. 25-vitamin D regulates the expression of cathelicidin, an endogenous antimicrobial peptide. This modulation occurs by activation of TLRs, which sign for increased expression of VDR and CYP27, the enzyme that converts 25-vitamin D to the active form, 1,25-vitamin D. This active form regulates the VDR that signs the HCAP18 encoding gene, which is a pro-protein that upon be cleaved releases cathelicidin to act against gram-negative and positive bacteria, viruses and fungi. Population with vitamin D deficiency has higher levels of inflammatory markers such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) compared to the sufficient group suggests a potential link between Vitamin D deficiency and increased inflammation **(34).**

Vitamin D deficiency can affect immune system function and result in dysregulation of the inflammatory response. Vitamin D plays a crucial role in modulating immune cell activity and suppressing excessive inflammation. In the absence of sufficient Vitamin D, immune cells may exhibit dysregulated responses, leading to increased production of inflammatory markers. Vitamin D deficiency has been associated with an enhanced inflammatory response. Insufficient Vitamin D levels may fail to properly regulate the immune system's inflammatory activity, leading to an overactive response and increased production of inflammatory markers. This dysregulation can result in higher levels of CRP, ESR, NLR, and PLR **(2).**

Vitamin D deficiency has been linked to increased oxidative stress. Oxidative stress can promote inflammation and contribute to elevated levels of inflammatory markers. Inadequate Vitamin D levels may impair the body's antioxidant defenses, leading to an imbalance between oxidative stress and antioxidant capacity, which can contribute to heightened inflammation. Vitamin D deficiency may disrupt feedback mechanisms that regulate inflammation. Vitamin D has been shown to interact with various signaling pathways involved in inflammation, including those related to the production and regulation of inflammatory markers. Insufficient Vitamin D levels may disrupt these feedback mechanisms, leading to an imbalance favoring increased inflammation and elevated levels of inflammatory markers. Approximately 30 to 50% of CKD cases have been found to have noticeably raised levels of serum inflammatory biomarkers including C-reactive protein (CRP) and interleukin-6 (IL6). The etiology of inflammation in this case is multifaceted and involves patient-related causes, such as underlying disease, comorbidity, oxidative stress, infections, obesity, genetic or immunologic factors, or on the other hand, hemodialysis-

related factors, mainly concerning the dialysis membrane biocompatibility and dialysate quality **(35).**

Secondary hyperparathyroidism is known to be another cause of morbidity and mortality in patients with end stage renal disease. Growing evidence implies that higher levels of parathyroid hormone may be accompanied by low-grade inflammation, but this association remains uncertain. Parathyroid hormone encourages interleukin-6 (IL-6) production by osteoclast and liver cells. Other studies showed elevated levels of C-reactive protein (CRP), tumor necrosis factor-a and other inflammatory markers in hyperparathyroidism patients **(36)**.

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