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Research Article

Evaluating the effect of vitamin D3 supplementation on DKK-3 serum for third-stage chronic kidney patients

Hiba R. Kamal[1], Thikra A. Allwsh[1]

1 *Department of Chemistry, Collage of Science, University of Mosul, Mosul, Iraq*

Corresponding author: Thikra Allwash (thekraaliallwsh@uomosul.edu.iq)

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Abstract

Vitamin D3 helps to reduce oxidative stress levels, as does Dickkopf-3 (DKK-3) glycoprotein, which is released in the kidney's tubular membrane during stress and helps promote tubulointerstitial fibrosis. The aim is to investigate how vitamin D supplementation affects serum DKK-3 levels and biochemical indicators of renal function in CKD patients in stage III. The study had inclusion criteria for 180 participants of both sexes, aged between 20 and 35 years. They were divided into 3 groups: 60 healthy participants as control, 60 CKD patients in stage III (without vitamin D3 supplements), and 60 others (with three months of 5,000 IU of weekly vitamin D3 supplements). DKK-3 levels in serum, vitamin D3, and parathyroid hormone were examined, and kidney function was tested. Findings indicated a significant increase in levels of DKK-3 serum for patients in the 2 and 3 groups with CKD compared with control. Additionally, outcomes revealed significantly lower DKK-3 (41%) in the third group of patients who took vitamin D compared to the second group (120%) without vitamin D supplements. There was also an improvement in several kidney functions for the third group, and the relationships revealed a significant inverse association between the levels of vitamin D3 and serum DKK3. Also, there is a significant inverse association with urea and creatinine levels; additionally, there is a significant positive association with glomerular filtration rate and calcium. In conclusion, DKK-3 may be a potential biomarker for the development of CKD. Furthermore, vitamin D administration improved kidney function and DKK-3 levels in individuals with stage III CKD. As a result, vitamin D can assist in reducing the development of chronic kidney disease.

Keywords

CKD, DKK-3, parathyroid hormone, renal function, vitamin D3

Introduction

Chronic kidney disease is described as an irreversible illness that lasts for at least three months and is brought on by a progressive loss of renal function (Altamura et al. 2023). A glomerular filtration rate (GFR) consistently less than 60 ml/minute/1.73 m^2 (G3 stage) indicates chronic kidney disease (CKD). The GFR is the best kidney function estimate, reflecting excretory function. It can decrease due to reduced blood flow or fewer nephrons. It determines acute or chronic kidney damage and disease progression (Jančič et al. 2022).

The progressive reduction in glomerular filtration rate is connected with vitamin D3 insufficiency (Kim and Kim 2014; Ganimusa et al. 2024), which showed that the level of vitamin D3 drops below 30 ng/ml in 71% of individuals

with chronic renal disease (stage 3), 84% of patients in the fourth stage of eGFR (15 to 29 /min/1.73 m^2), and 89% of people in the fifth stage, where their eGFR is below 15 ml/min/1.73 m^2 (Valdivielso et al. 2023). Patients with chronic kidney disease frequently have deficiencies in vitamin D3, and vitamin D3 supplementation may be essential to improve this condition. It also shows a link between better survival and the use of vitamin D3 treatment in individuals with chronic kidney disease (Ganimusa et al. 2024). Additionally, it was found that vitamin D3 supplementation may improve blood vessel function in kidney patients (Kumar et al. 2017). A negative relationship was also observed between glomerular filtration rate and vitamin D3 metabolite levels (Teumer et al. 2018).

It has been demonstrated that the renal cells in the stressed tubular epithelium release a glycoprotein called Dickkopf-related protein DKK-3 (Fang et al. 2020). This multifunctional protein, DKK3, belongs to the DKK family and is involved in several cellular processes, such as the differentiation of cells, proliferation, and programmed death of cells. One of the main pathways that leads to kidney illness is this one (Lipphardt et al. 2019). Dickkopf-related protein 3 activates the Wnt pathway by blocking the antagonistic impacts of the protein DKK1 attaching to LRP5/6, whereas DKK1 inhibits canonical Wnt/β-catenin signaling. It has also been found that DKK3 causes fibrosis of the kidneys through the pathway of Wnt signaling (Fang et al. 2020).

It is important to understand the effects of vitamin D3 intake on DKK-3 and renal function. Thus, this study aimed to examine how vitamin D3 supplementation affected DKK-3 and biochemical markers of kidney function in individuals suffering from Iraqi chronic kidney disease.

Materials and methods

Study design

The period of conduct for this prospective case-control research was September 2022 to February 2023 at the Department of Chemistry, College of Sciences, University of Mosul. Mosul/Iraq

Inclusion criteria

Participants in the research had to be between the ages of 30 and 45, of both sexes, and they had to have undergone a rigorous screening process to be divided into three groups.

Group 1: comprised of 60 healthy participants

Group 2: comprised 60 patients with clinical indicators visiting the Ibn Sina Teaching Hospital Department of Nephrology, all exhibiting initial evidence of third-stage chronic kidney disease, noting that the patients were diagnosed by specialized doctors. Patients' information was recorded according to the questionnaire paper.

Group 3: 60 chronic kidney patients with oral vitamin D3 supplements at a dosage of 5000 IU capsules (Madama Company, Warsaw, Poland) per week for three months.

Participant exclusion criteria

Participants with pregnant women, high blood pressure, diabetes mellitus, and any inflammation cases were excluded from this study.

Study procedures

Participants underwent a comprehensive clinical assessment encompassing a detailed medical history and physical examination. All participants were estimated for blood pressure and body mass index (BMI). Furthermore, laboratory investigations included assessments of renal function (serum creatinine, urea, GFR, uric acid, cystatin C, total protein, and albumin). Additional laboratory parameters included parathyroid hormones, calcium, and phosphate.

Outcome measures

Serum DKK-3 assessments: The primary outcome measure in this study was the determination of DKK-3 levels, which were meticulously compared between the patients and the control group.

Secondary outcome measures comprised the assessment of the effect of vitamin D3 on DKK3 serum. The objective was to discern whether notable disparities in outcomes existed between these three distinct cohorts.

Ethical approval

The research protocol completed an accurate ethical approval procedure and was authorized by the Iraqi Ministry of Health (Nineveh Health) on July 9, 2022 (No. 2022140). Every participant provided consent. This clearance confirms that the study follows accepted ethical norms and guidelines.

Secrecy and privacy

The study adhered to patient confidentiality and privacy at all stages of the research process. Strict security measures were in place to protect research participants' private data.

Blood collection and storage

Using a sterilized syringe, 10 milliliters of venous blood were extracted. The serum was separated by centrifugation at 4000 revolutions per minute for 13 minutes and then used to calculate the necessary amounts. Clinical Variables Measurements of the serum were used to estimate the clinical variables.

ELISA was applied to determine the concentration of DKK-3 using a kit provided by Sun Long Biological

(China)24. parathyroid hormone and vitamin D3 were measured using an electrochemiluminescence (ECL) kit with Cobas e411 analyzers. Cystatin-C was determined by the VEDALAB Easy Reader+® immunochromatographic rapid method using a kit (France). Also, phosphate and calcium were estimated using a BIOSYSTEM kit (Spain). The enzymatic colorimetric method was used to estimate serum urea, uric acid, total protein, albumin, and creatinine using a BIOLABO kit. while GFR levels were determined using the modification of diet in renal disease (MDRD) equation, which is suitable for adults with CKD. GFR (mL/min/1.73m^2) =175× (S Cr) $^{-1.154}$×(age) $^{-0.203}$× (0.742) if female × (1.212 if black) where S Cr = serum creatinine in mg/dL

Information management and analysis

Results data

Data from healthcare histories, clinical testing, and outcome evaluations was coded carefully.

By using Microsoft Excel, this coded information was easy to administer and methodically.

Evaluation of data statistically

The information collected in Microsoft Excel was then sent into the SPSS variant 20.0 statistical package for analysis. The results were provided as counts and ratios, while qualitative information was stated as mean values with a standard deviation. Mathematical tests, including Pearson's correlation, were meticulously utilized to differentiate between two groups and assess the significance of the statistical data. It judged a P value < 0.05 statistically significant, while a P value < 0.01 was declared extremely significant.

Results

This comprehensive study investigated the levels of DKK3 and clinical variables in a group of patients with chronic kidney disease following two months of oral vitamin D3 supplementation at a dosage of 5000 IU per week. Their results were compared with those of healthy individuals and patients with chronic kidney disease without vitamin D3 supplements. Analyses revealed several significant findings across demographic and laboratory parameters. Identification of the three groups' characteristics based on Table 1 shows that all participants control (G1) and third-stage chronic kidney patients with the treatment vitamin D3 supplementation (G3) and nontreatment with vitamin D3 supplementation (G2) showed a significant rise in BMI and blood pressure (BP) in group (G2) when contrasted to both groups (G1 and G3) at the P ≤ 0.01 level.

The results indicate in Table 2 that the studied kidney function biomarkers include GFR, urea, creatinine, uric acid, cytostatine C, albumin, and total protein. Bone indicator tests include calcium, phosphate, vitamin D3, and parathyroid hormone.

Table 1. Demographical data for the three groups.

Variables	G1 Mean ± SD	G2 Mean±SD	G3 Mean± SD
No. of subjects	60	60	45
Age (years)	25.34±4.5	28.51±6.6	27.81±5.4
Sex, M/F	28/32	34/26	34/26
SBP (mm Hg)	125.3 ± 13.1a	141.2± 14.5 b	133.6 ± 11.8 a, b
DBP(mm Hg)	78.4 ± 7.9 a	91.5 ± 6.1 b	83.3 ± 8.1 a, b
Smoking	No	No	No
Genetic predisposition	No	No	No

G1: Controls; G2: Patients without vitamin D3 supplement; G3: Patients with vitamin D3 supplement. Different letters indicate significance at the level of P ≤ 0.01.

Table 2. The biomarkers of kidney function and bone indicators in the participants for the three groups.

Variables	G1 Mean±SD	G2 Mean±SD	G3 Mean ± SD
GFR ml / min	114±12.67 a	45 ± 9.87 b	60 ± 6.87 c
Urea (mg/dl)	33.32±5.88 a	86.00 ± 7.79 b	60.34 ± 5.76 c
Creatinine (mg/dl)	0.68±0. 14 a	1.46 ± 0.42 b	1.13 ± 0.35 c
Uric acid (mg/dl)	4.36±1.11 a	6.60 ± 1.56 b	5.93 ± 1.76 b
Cystatine C (mg/l)	1.22±1.03 a	4.62 ± 1.12 b	2.97 ± 1.54 c
Albumin (g/dl)	5.25±0.76 a	2.57 ± 1.02 b	3.45 ± 1.56 b
Total protein (g/dl)	7.54±2.11 a	5.93±1.11 b	5.87 ±1.98 b
Calcium (mg/dl)	8.3 ±1.23 a	6.01±1.16 b	9.84 ± 1.76 c
parathyroid hormone (pg/mL)	31.91±4.99 a	65±3.14 b	57.87 ± 3.34 c
Phosphate(mg/dL)	3.13±0.90 a	4.91±0.87 b	5.67 ± 0.56 bc
Vitamin D3(IU)	54.56±2.80 a	20.29 ± 5.69 b	37.65 ± 6.76 c

G1: Controls; G2: Patients without vitamin D3 supplement; G3: Patients with vitamin D3 supplement. Different letters indicate significance at the level of P ≤ 0.01.

The results of creatinine, urea, and cystatine C indicated an increase in those levels (p-value < 0.01), and GFR levels were significantly decreased before (G2) and after (G3) the supplement of vitamin D for third-stage chronic kidney patients when compared with the (G1) group. Albumin, total protein, and uric acid indicated no differences in those levels before and after vitamin D supplementation for third-stage chronic kidney patients.

Calcium, phosphate, and parathyroid hormone results indicated differences in those levels (p value < 0.01) before and after vitamin D supplements for third-stage chronic kidney patients. We also found a significant rise in levels of vitamin D3 in the group (G3) when compared with the (G2) group (p < 0.01).

In this study, the level of DKK-3 was also measured in patients with third-stage chronic kidney disease before and after they received vitamin D3 supplements. The results in Table 3 revealed an increase in levels of DKK-3 in the serum of the patient group without vitamin D3 supplement (G2) (27.03±1.40 ng/ml) compared to the control group (G1) (12.13±1.67 ng/ml) by 125%. while the levels of DKK-3 increase after receiving the supplements vitamin D (G3) (16.767 ± 3.76 ng/ml) by 41% compared to the (G1).

The results indicate a decrease in high DKK-3 from 120% to 41% after receiving supplements for vitamin D in chronic kidney disease patients.

Table 3. The serum DKK-3 levels in the participants for the three groups.

Groups	DKK-3 (ng/ml) Mean ± SD %
G1	12.13±1.67 0
G2	27.03±1.40* 120
G3	16.767±3.76* 41

* Significant difference at ($p \leq 0.01$).

The results in Table 4 demonstrated a significant inverse association between the levels of vitamin D3 and serum DKK3 levels in kidney patients (G3) who received vitamin D3 supplements. Also, there is a significant inverse association between vitamin D3 levels and urea and creatinine levels, but there is a significant positive association with glomerular filtration rate and calcium at $P \leq 0.01$.

Table 4. The relationship between vitamin D3 and DKK-3, kidney function, and bone indicators after taking vitamin D3 supplements.

Parameter	r - value	p-value
DKK-3	-0.658	0.01
GFR ml / min	-0.543	0.01
Urea)mg/dl(	+0.489	0.01
Creatinine)mg/dl (	+0.546	0.01
uric acid)mg/dl (	0.654	0. 11
Cystatine C)mg/l(	0.289	0.21
Albumin (g/dl)	0.534	0.64
total protein (g/dl)	0.689	0.521
Calcium (mg/dl)	+0.857	0.01
parathyroid hormone	0.657	0.41
(pg/mL) Phosphate (mg/dL)	0.456	0.34

Discussion

This study proved a significant rise in BMI and blood pressure (BP) in chronic kidney patients and no important effects of vitamin D supplementation on BMI and blood pressure (BP). It has been noted that patients suffering from chronic kidney disease suffer from a severe deficiency in vitamin D, which worsens over time due to the decreased ability of the kidneys to convert vitamin D into its active form (Fayoumi et al. 2023). Also, the development of chronic kidney disease and many cardiovascular complications may be related to vitamin D deficiency. The role of vitamin D appears to change kidney function and the work of the renin-angiotensin system, which is a hormonal system that balances both blood pressure and water in the body. Since people who suffer from high blood pressure may experience a change in kidney function and may suffer from a defect in the renin-angiotensin system, the effect of vitamin D does not appear to lower blood pressure (McMullan et al. 2017).

Also, vitamin D deficiency in people with a high body mass index is linked to an increase in their body mass, which causes lower levels of vitamin D in their bodies. Vitamin D enters fat cells from the bloodstream, so people with a high body mass index often suffer from vitamin D deficiency. The impact of vitamin D on the kidney indicator test was investigated, and patients who took vitamin D3 supplements had an increase in glomerular filtration rate and decreased blood serum levels of urea and creatinine. This indicates that vitamin D improves kidney function and performance by filtering the blood of nitrogenous waste (Feng et al. 2022). Vitamin D3 supplements improved kidney function and reduced inflammation in the kidney, which led to an increase in the rate of glomerular filtration (GFR) and improved renal filtration capacity, as cystatin C is considered a sensitive biomarker to detect changes in glomerular filtration rate and kidney disease. It has other properties, so it is found in fixed concentrations in plasma and is not secreted by tubular cells. It is less affected by the effects of non-renal factors such as gender, age, muscle mass, and interfering substances during its measurement (Tapper et al. 2021). In addition, vitamin D3 regulates the thyroid gland and, thus, inhibits the synthesis of cystatin C by this gland, as it is easily secreted as a result of slight changes in the function of this gland. The result is a decrease in cystatin C in the group that received D3 supplementation (Wiesli et al. 2003).

We note from our current study the effect of vitamin D3 on bone marker tests for patients before and after receiving treatment with vitamin D3 supplements for two months. The results showed a significant increase in calcium in the patient, which is consistent with [16]. The intake of vitamin D3 supplements in patients has enhanced vitamin levels in the serum and enhanced absorption of intestinal calcium, thus increasing its percentage in the blood. This means that vitamin D3 supplements have led to improved hypocalcemia and increased bone density (Feng et al. 2022).

We also conclude from this study that the levels of phosphate in the blood serum of the group of patients after receiving treatment with vitamin D3 supplements increased compared to what they were before they took vitamin D3 supplements. The results are consistent with the results of the researchers (Akimbekov et al. 2022). Because vitamin D3 increases the absorption of phosphate in the intestine, it also facilitates their reabsorption through the kidneys, as vitamin D3 interacts with its receptor and increases the efficiency of the intestine in absorbing phosphate by approximately 80% of it. Therefore, patients will have increased phosphate levels after receiving vitamin D3 supplements.

Our results revealed higher DKK-3 levels in the patient group's serum due to the ongoing inflammation of the kidneys and the lack of oxygen access to them (kidney ischemia), which in turn will increase the expression of DKK-3 and its excessive secretion, which will later contribute to ongoing kidney damage through several different mechanisms. The result is increased levels of DKK-3 in the blood, as secretion of DKK-3 will initiate short-term activation of the Wnt/βcatenin pathway. It suppresses apoptosis and enhances tubular regeneration, protecting tubular cells (Schunk et al. 2021; Dziamałek-Macioszczyk et al. 2023). However, the continuous increase in its secretion from renal tubular

epithelial cells as a result of constant stress on the kidney and continuous activation of the Wnt/β-catenin pathway will lead to a change in the phenotype of thymic epithelial cells (TEC) and promote its transformation to a pro-fibrotic and pro-inflammatory phenotype, which in turn leads to EMT. , irreversible changes in kidney structure, and the development of chronic kidney disease (Lipphardt et al. 2018; Zewinger et al. 2018).

Our results also indicate that vitamin D3 reduced DKK-3 in patients after receiving vitamin D3 supplements. This means vitamin D3 improves renal function, reduces stress on the kidneys, and inhibits renal tubular cells from secreting DKK-3. (McCray et al. 2020) found in a study that sufficient vitamin D3 promoted organoid growth and accelerated differentiation by inhibiting canonical Wnt activity and suppressing the Wnt family member DKK-3. Wnt deregulation is a known contributor to aggressive prostate cancer, and thus findings further link vitamin D deficiency to fatal disease. (Ao et al. 2021) noted that the benefits of vitamin D3, which include immunomodulatory and anti-inflammatory effects as well as regulation of RAAS, may lead to further improvement in kidney function and thus reduce DKK-3 secretion and synthesis.

It was concluded from this study that there is a significant inverse relationship between vitamin D3 levels and DKK3 levels in kidney patients who receive vitamin D3 supplements. (McCray et al. 2020) indicated that vitamin D3 may inhibit canonical WNT signals and suppress the secretion and production of DKK3. (Sankaralingam et al. 2014) have also shown that vitamin D3 regulates the protein associated with low-density lipoprotein receptors (LRP5), which is the primary WNT receptor, and therefore this pathway, such as sclerostin and DKK1, which are inhibitors of DKK-3, prevents WNT signals and reduces the secretion of DKK3, thus increasing GFR and improving kidney function.

We also conclude from this study that there is a significant positive relationship between vitamin D3 levels in kidney patients who received treatment with vitamin D3 supplements and glomerular filtration rate. These results are consistent with the results of researchers (Fakhoury et al. 2019), who indicated that a severe deficiency in vitamin D3 will cause hyperfiltration in the kidneys and a decrease in the renal filtration rate.

Additionally, the data show that in patients treated with vitamin D3 supplements, there is a negative inverse association between vitamin D3 levels and urea and creatinine levels. This outcome aligns with the findings given by El Din et al. (2019). This is because vitamin D3 helps restore renal function, increases its workload, and excretes nitrogenous wastes from the body to a greater extent. As a result, vitamin D3 improves renal function and lowers serum urea levels in patients who take vitamin D3 supplements (Wang et al. 2021).

Conclusion

The dose of vitamin D taken by patients with chronic kidney disease can reduce the deterioration of kidney function by studying the levels of creatinine, urea, cystatin C, and GFR. Bone indicator tests include calcium, phosphate, vitamin D3, and parathyroid hormone. However, pathway analysis results indicate a relationship between vitamin D and DKK-3 levels. Vitamin D supplementation at a dose of 5,000 IU for two months can significantly reduce kidney function.

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