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CLINICAL STUDY OF DICKKOPF-3 SERUM IN MOSUL PATIENTS' CHRONIC RENAL

Hiba R. Kamal* and Thikra A. Allwsh

Department of Chemistry, Collage of Science, University of Mosul, Mosul, Iraq.

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***Corresponding Author: Hiba R. Kamal**

Department of Chemistry, Collage of Science, University of Mosul, Mosul, Iraq.

ABSTRACT

Introduction: Dickkopf-3 (DKK-3) participates in cell signaling pathways, inflammation, and tissue remodeling, secreted within the renal tubular membrane in response to stress and a gradual reduction in kidney function typifies chronic kidney disease. The study aimed to evaluate the Dickkopf-3 level in serum of Mosul Patients' Chronic Renal and the effect of many factors on its. **Methods:** The study established specific criteria for the participation of 150 participants, encompassing individuals of both sexes aged 30 to 70 years. The participants were categorized into 2 groups: 75 healthy individuals and 75 patients with CKD. Tests were conducted to assess the levels of renal function, DKK-3 in the serum, and qPCR for the DKK-3 gene. **Results** indicated chronic kidney patients demonstrated a significant increase in Age, blood pressure (BP), and BMI, in addition to renal function: GFR, creatinine, urea Cystatin-C, uric acid, Albumin, and total protein compared to a control group. An inverse relationship exists between BMI and age with DKK–3 serum and an increase in DKK–3 in smokers in control and patient groups. There was a significant increase in levels of DKK-3 in patients' group serum compared to the control group at ($p \leq 0.001$) depending on BMI, age, sex, and smoking. The study's results also showed an increase in the level of DKK3 in patients, which is considered one of the main reasons for the development of the pathological condition. **Conclusion:** The study suggests that DKK-3 correlates with decreased kidney function and clinical symptoms. The high DKK3 in the serum of patients may indicate the onset and progression of kidney disease. As a result, DKK-3 may be a potential target for treatment.

KEYWORDS: DKK3, BMI, Kidney disease, smoking, cystatin C, blood pressure, Albumin.

INTRODUCTION

Chronic kidney disease (CKD) is a chronic inflammatory disease that occurs due to gradual damage to the kidneys that may cause loss of kidney function so that they become unable to perform their functions in filtering the blood and purifying it from waste (Stevens et al., 2024). Over time, chronic kidney disease may increase and worsen and the kidneys stop working completely and the disease reaches its final stage (ESRD) and here the patient needs dialysis (Kopp et al., 2024). Chronic kidney disease is associated with and affected by many factors and diseases such as obesity, high blood pressure and cardiovascular diseases (Weerakoon et al. 2024).

In chronic kidney disease, the Wnt/β catenin pathway is activated, which is responsible for the increased secretion and expression of pro-inflammatory and fibrosis cytokines. This pathway also contributes to cell migration and proliferation (Xingn et al., 2023). The control and regulation of this pathway in the pathophysiology of chronic kidney disease is by the DKK family of proteins, including DKK3, a glycoprotein expressed in renal tubular epithelial cells as a result of the kidney being exposed to different conditions, pressure and stress (Li et al. 2021). Overexpression of this protein through continuous activation of the WNT/β-catenin pathway will lead to changes in the phenotype of TEC cells and convert them to a pro-fibrotic phenotype, which causes the activation and stimulation of EMT and finally causes an increase in the severity and progression of CKD due to the changes in the kidney structure resulting from this protein, and these changes are irreversible (Federico et al. 2016).

Patients with chronic renal illness may experience an indirect impact on prooxidant and antioxidant levels or activity due to DKK-3's participation in inflammatory and tissue remodeling pathways (Xu et al., 2020). However, the precise connection between DKK-3 and antioxidants is still unclear (Song et al., 2024).

This article aims to explore the relationship between chronic kidney disease and DKK-3, focusing on the significance of the effect of many factors on levels DKK-3 in understanding CKD progression.

MATERIAL AND METHODS

Study design

The participants in this study included two groups: patients with chronic kidney disease and the second group of healthy people who were not infected and did not show any clinical symptoms.

Inclusion criteria

The participants in this study were of both sexes and between the ages of 30 and 70 years, and they had to undergo a rigorous examination process to be divided into two groups.

Group 1: Consists of 75 healthy participants

Group 2: The number of patients was 75 individuals with clinical indicators who visited the Nephrology Department at Ibn Sina Teaching Hospital. All patients showed early signs of chronic kidney disease, and information about the patients was recorded using a questionnaire, knowing that the specialists were the ones who diagnosed the patients.

Criteria for Exclusion of Participants

Participants with diabetes mellitus, hypertension, pregnant women, and any history of inflammation were not allowed to participate in the study.

Study procedures

Comprehensive clinical assessments including physical examination and medical history were performed on all participants in this study. Blood pressure and body mass index (BMI) were estimated for all participants. In addition, renal function tests (serum urea, creatinine, glomerular filtration rate, cystatin C, uric acid, total albumin and protein) were performed.

Outcome measures

DKK-3 in serum measurement is the primary measurement measure used in the study. Based on some factors including age, sex, smoking status and obesity, DKK-3 results between patients and healthy individuals were compared.

Ethical approval

The Iraqi Ministry of Health - Nineveh Health approved the research protocol on July 9, 2022, after it completed an accurate ethical approval procedure (No. 2022140). Each participant gave consent. This approval attests to the study's adherence to recognized ethical standards and principles.

Privacy and Secrecy

The study complied with patient privacy and confidentiality regulations throughout the research procedure. Strict security protocols were used to safeguard the personal information of research participants.

Blood collection and storage

• For (biochemical parameters)

Ten milliliters of venous blood was drawn using a clean, sterile syringe, and serum was obtained by centrifugation at 6000 rpm for about 10 minutes.

Serum for measuring clinical biochemical variables

ELISA used with a kit from SUN LONG BIOLOGICAL (China) to measure the concentration of DKK-3. Cystatin-C was ascertained by employing a kit and the VEDALAB Easy Reader+® immunochromatographic fast technique (France). Additionally, blood urea, total protein, uric acid, albumin, and creatinine were estimated by used the enzymatic colorimetric technique using a kit from BIOLABO, and GFR levels calculated using (MDRD) equation.

Information Management and Analysis

Results Data

Careful labeling was done on data from clinical tests, outcome evaluations, and medical histories. This coding made it simple and systematic to administrate using Microsoft Excel.

statistical data analysis

After the data were obtained in Microsoft Excel, they were sent to Statistical Packaging (SPSS version 20.0) for examination. While the qualitative information was expressed as mean values with standard deviation, the results were presented as numbers and percentages. Careful mathematical tests, such as Pearson's correlation coefficient, were used to determine the difference between the two groups and the statistical significance of the data.

RESULTS

In this comprehensive study, DKK3 levels and clinical variables were examined in patients with renal failure and the results were compared with the healthy individuals. Several noteworthy findings regarding laboratory and demographic factors were obtained from the analyses.

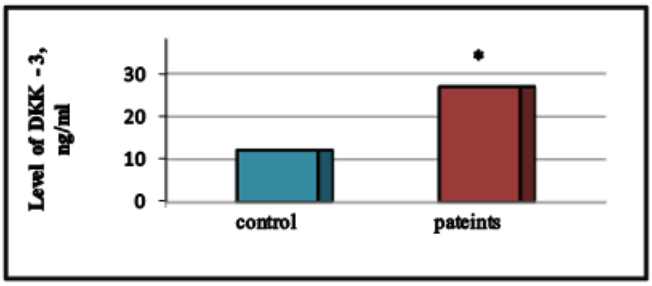
When compared to a control group, all participants who had chronic kidney disease showed that there where significant increase in age, blood pressure (BP), body mass index (BMI), and renal function, including GFR, urea, , Cystatin-C, creatinine, uric acid, total protein and albumin (Table 1).

Table 1: Demographical data and indicters of renal function for all participants.

Variable	Control group	Chronic renal patient group	*P* value
Age	38.28 ±8.7	43.65±10.4	0.016
Sex (Female / Male)	40/35	33/42	0.013
BMI (Kg/m^2)	28.42±6.25	33.14±5.62	0.01
Systolic blood pressure (mm Hg)	126.84 ±13.15	141.26 ±12.21	0.01
Diastolic blood pressure (mm Hg)	75.42 ±8.66	86.29 ±8.93	0.01
Smoking/ non-Smoking	45/30	48/27	0.014
GFR (ml/min/1.73 m^2)	114±12.67	45±9.87	0.001
Urea (mg/dl)	33.32±5.88	86.00±7.79	0.001
Creatinine (mg/dl)	0.68±0. 14	1.46±0.42	0.001
Uric Acid (mg/dl)	4.36±1.11	6.60±1.56	0.001
Cystanine C (mg/L)	1.22±1.03	4.62±1.12	0.001
Albumin (g/dl)	5.25±0.76	2.57±1.02	0.01
Total Protein (g/dl)	7.54±2.11	5.93±1.11	0.01

Level of DKK-3 in the serum for all participants

As seen in Figure (1), the overall mean levels of DKK-3 in the blood of the patients group were significantly higher than those of the control group (12.13 ± 1.67 ng/ml) at the probability level ($p < 0.001$).

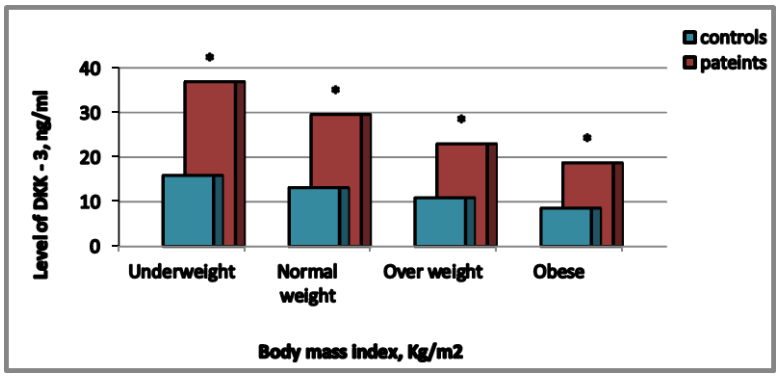


***Significant at the level p ≤ 0.001**

Figure 1: DKK-3 levels in the serum of control and patient groups.

Studying effecting of some factors on the level of DKK–3 in the serum of a patient and control group

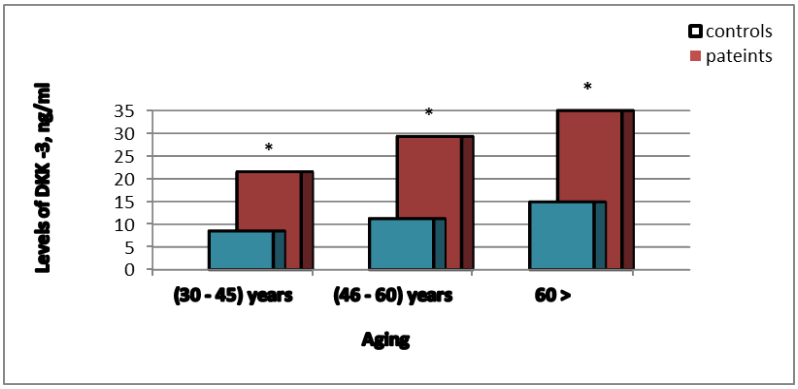
Figure (2) showed that there was a decrease in the level of DKK–3 with an increase in BMI for all participants, indicating an inverse relationship between DKK–3 and BMI. Also, Figure (2) showed that there was a significant increase in DKK-3 levels in patients' group serum compared to the control group at the probability level ($p \leq 0.001$) depending on BMI.



***Significant at the level p ≤ 0.001**

Figure 2: DKK-3 levels in the serum of control and patient groups, depending on BMI.

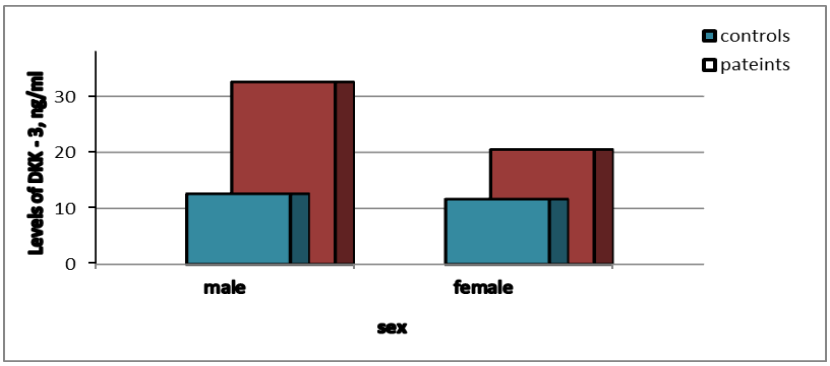
Figure (3) shows an increase in the level of DKK–3 with age, also indicating an inverse relationship with age. Also, DKK-3 levels are constantly higher in patients with chronic renal failure (CKD) than in controls, suggesting a sustained increase of DKK-3. The 30- to 45-year-old group has substantially higher DKK-3 levels than controls. There is a discernible rise in DKK-3 levels in the 46–60 age range, indicating that aging may worsen the elevation linked to chronic kidney disease. The greatest DKK-3 levels are seen in the 60+ age range.



***Significant at the level p ≤ 0.001**

Figure 3: DKK-3 levels in the serum of control and patient groups, depending on age.

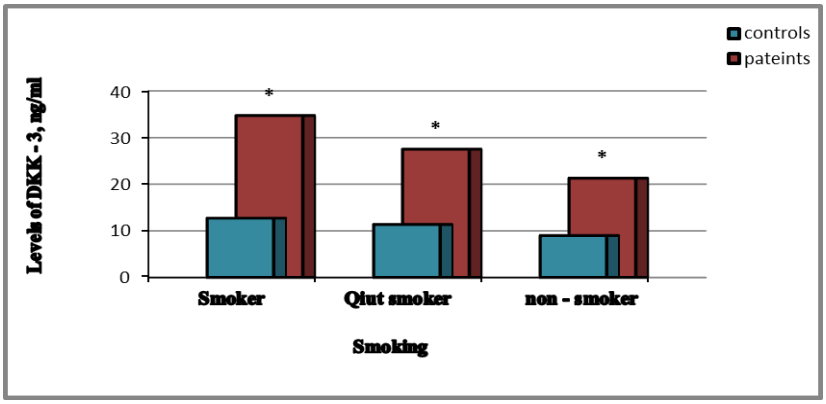
According to Figure (4), There is no difference between males and females in the level of DKK-3 in the control group and patients. Also, the DKK-3 levels of the male and female patients were considerably greater than those of the male and female control group indicating that DKK-3 expression is affected by CKD in a gender-neutral manner.



***Significant at the level p ≤ 0.001**

Figure (4): DKK-3 levels in the serum of control and patient groups, depending on sex.

Figure (5), shows an increase in DKK–3 in smokers compared to non-smokers for all participants. In smokers, patients show the highest levels of DKK-3, and its levels in smokers who quit smoking elevated in patients compared to controls, which may indicate continued effects of smoking on DKK-3 levels even after smoking cessation. In the non-smokers group, patients again show higher levels of DKK-3 than controls, although the gap is narrower compared to smokers.



***Significant at the level p ≤ 0.001**

Figure (5): DKK-3 levels in the serum of control and patient groups, depending on smoking

DISSCUSION

It was noted from the results of this study that the patient group was older and had higher body mass index (BMIs) compared to the control group, which may be due to the fact that obesity is an independent risk factor for CKD patients (Stasi et al., 2022). The patient group also

showed higher diastolic and systolic blood pressure (DBP and SBP), indicating that blood pressure may be an independent risk factor for CKD patients (Korogiannou et al., 2022).

As noted from the results, the glomerular filtration rate decreased in all chronic renal failure patients due to kidney damage (Sharki, 2017; Jamshidi and Najafi, 2020). The results of the biochemical variables of kidney function showed high levels of urea and creatinine in the serum of the patient group. This may be due to the fact that urea and creatinine are metabolic wastes that can be naturally excreted from the body through urine, but in the case of renal failure, a malfunction and deficiency in kidney function occurs, which leads to the lack of excretion of these wastes from the body, so their concentration accumulates in the blood serum. These results are consistent with the researchers (Mahmoud et al., 2021; Efros et al., 2023). The patient group also showed that they had high levels of uric acid compared to the control group due to the lack of kidney excretion of uric acid from the body due to the low glomerular filtration rate (Isaka et al., 2016). t was also found that the levels of cystatin C in the patient group appeared much higher than the levels of cystatin C in the control group, This conclusion is consistent with what the researchers mentioned (Di Somma et al., 2019), as the kidneys suffer from a dysfunction such that they are unable to filter the blood normally. Under normal conditions, cystatin C is easily filtered by the glomeruli and metabolized after tubular reabsorption, but as a result of a defect in the glomeruli, it accumulates in the blood.

A decrease in albumin levels was found in the patient group compared to the control group, due to the deterioration of the kidneys and their function in purifying the body from waste, as when the selectivity of the glomeruli deteriorates, this leads to an increase in the urine loss of large molecules such as albumin, immunoglobulin, and alpha beta macroglobulin (Abdullah et al, 2011). A significant decrease in total protein levels was also observed in the patient group, and this was due to a decrease in albumin in the blood, increased protein metabolism, or nutritional deficiency, which leads to a decrease in the concentration of total protein in the blood, and this is consistent with what the researchers found (Yin et al, 2023).

The results of this study also indicated an increase in DKK3 levels in the group of chronic kidney disease patients compared to the control group. These results are consistent with the researchers (Kamal & Alluwsh, 2024), as DKK3 is considered a biomarker for early detection of kidney damage as a result of an increase in stressed renal tubular epithelial cells due to stress on the kidneys. The effect of obesity on DKK3 levels was observed at high levels in individuals with a BMI of less than 18 kg/m2 in both patient and control groups, while its levels were low in obese individuals with a BMI of more than (30 kg/m^2) , which may be attributed to its potential role in protecting the body from obesity and insulin resistance (Baetta et al., 2019; Wang et al., 2021).

As for the effect of age, the results showed that DKK3 levels were high in older people and in both patient and control groups, which may be due to the effect of oxidative stress and the loss of nephrons that occurs with age, which plays a role in the deterioration of renal function (Fang et al., 2020; Shank et al., 2021), but for the effect of gender, there was no significant effect between males and females in DKK3 levels, and this is consistent with the researcher (Caffo et al., 2024).

While the effect of smoking was clearly evident on DKK3 levels, high levels of DKK3 were observed in smokers and in both patient and control groups due to the inhalation of cadmium present in cigarettes and its accumulation in the blood. Studies have indicated that cadmium is the cause of the development and occurrence of chronic kidney disease because it causes changes in the dynamics of the kidney structure and increases albuminuria (Hafez et al., 2020; Rezonzio et al., 2012; Wang et al., 2020), but people who quit smoking have lower levels of DKK3 as a result of the kidneys regaining part of their function and reducing albuminuria.

DKK3 can stimulate the factor responsible for renal fibrosis and increase its expression (TGF-β), and its increased expression causes a decrease in the efficiency of the formation of renal blood vessels and also increases renal fibrosis (Al Shareef et al., 2022 Khttab et al., 2023).

CONCLUSION

DKK3 exerts an adverse impact in chronic kidney disease, although its capacity to regulate Wnt signaling. The DKK-3 may correlate with many clinical characteristics of chronic kidney disease (CKD). The gradual deterioration of the kidneys and the reduction in renal filtration capacity may primarily account for the elevated levels of DKK-3 and its heightened expression in the bloodstream of CKD patients. The latter may significantly contribute to the rise and worsening of CKD. This may signify a therapeutic target for pharmacological intervention in chronic kidney disease (CKD).

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