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REVIEW ARTICLE

Sirtuin 1 and vitamin D3 as prognostic factors for chronic kidney diseases and nephrotic syndrome

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Abstract:

Background: The kidneys are essential organs that are both intricate and crucial for maintaining the normal functions of the body. Kidney disease encompasses any form of damage or illness that affects these organs. The most prevalent kidney illnesses are chronic kidney diseases and nephrotic syndrome, which frequently result in a decline in kidney function and, in severe cases, total kidney failure. Sirtuin-1 is an NAD+-dependent and class III histone deacetylase protein. Vitamin D3 is a fat-soluble steroid hormone. Recently, it was suggested that Sirtuin-1 and Vitamin D3 were involved in the pathogenesis of renal diseases. The exact protective mechanisms of Sirtuin-1 in renal diseases are still not completely understood.

Objectives: The aim of this study was to explore the potential involvement of Sirtuin-1 in modulating the inflammatory response in various kidney diseases. Additionally, the study aimed to investigate the levels of Sirtuin-1 and vitamin D3 in kidney diseases as prospective therapeutic agents for these conditions.

Materials and Methods: The research study was carried out between October 2022 and April 2023. A total of ninety subjects participated in the study, including thirty patients with chronic kidney disease (16 females, 14 males) with a mean age of 58.33 ± 18.33. Additionally, there were thirty patients with nephrotic syndrome (13 females, 17 males) with a mean age of 52.54 ± 14.02. A control group of thirty subjects was also included in the study, consisting of nineteen females and eleven males, with a mean age of 55.06 ± 8.03 years. Serum SIRT-1 and vitamin D3 were measured by Sandwich Enzyme Linked Immunosorbent Assay (ELISA). Blood urea nitrogen (BUN), serum creatinine, and serum albumin were measured by an automated Biorex diagnostics device.

Results: The results clearly demonstrated that all patient groups had lower Sirtuin-1 levels than the control group ($P \leq 0.05$). Serum Vitamin D3 levels were significantly lower in all patient groups as compared to the healthy group ($P \leq 0.05$).

Conclusions: Sirtuin-1 and Vitamin D3 play a critical role in inflammation and autophagy dysfunction in kidney tissue; thus, Sirtuin-1 activation and Vitamin D3 may alleviate inflammation in renal diseases and serve as potential therapeutic agents for the treatment of renal diseases.

Keywords: Kidney diseases, chronic kidney disease, nephrotic syndrome, sirtuin-1, vitamin D3

Introduction

The role of the kidneys in maintaining essential bodily functions is of utmost importance, as they regulate fluid balance and support the functioning of other organ systems (1). These vital organs consist of nephrons, which are the functional units of the kidney. Each nephron is composed of a glomerulus and renal tubules, working together to filter and process waste products, electrolytes, and water in order to maintain the body's internal balance (2). Kidney disease is any kind of damage or illness that affects the kidneys. This usually leads to a decrease in kidney function, and in very bad cases, the kidneys may stop working completely (3).

Chronic kidney disease (CKD) is a common health issue that affects a significant proportion of people around the world, with approximately 11% of individuals being affected. Furthermore, hypertension and diabetes are both independent factors that increase the risk of CKD (4). The synergetic effect of these two diseases is almost inevitable with their high prevalence (more than 50%) in individuals aged 65 years (5). Chronic kidney disease is characterized by a decrease in kidney function, as indicated by an estimated or measured glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m^2 (irrespective of kidney injury). It can also be diagnosed based on the presence of kidney damage markers, with or without a decreased GFR,

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persisting for a minimum of 3 months that is accompanied by albuminuria, hematuria, and proteinuria (6). Chronic kidney disease is regarded as a major health problem, affecting more than 11% of the global population and being strongly linked to morbidity and mortality (7).

Nephrotic syndrome (NS) is a medical disorder characterized by extreme proteinuria (≥3 g/24 hours) and responsible for hypoalbuminemia (≤ 25 g/L), with hyperlipidemia, edema, and many different challenges (8). Patients may present with edema, typically periorbital, or with the implications of their nephrotic state, such as venous thromboembolism (9). NS has many different causes; the most common are primary kidney diseases that include minimal change disease (MCD), membranous glomerulonephritis (MGN), and focal segmental glomerulosclerosis (FSGS). NS can also be caused by systemic disorders that affect organs other than the kidneys, like diabetes, amyloidosis, and systemic lupus erythematosus (SLE) (10). NS occurs at any age but is more prevalent in children (primarily MCD), mostly between ages 1 and 4 years (11). The initial sign of NS in children is facial edema, which then circulates to other regions of the body (8).

Sirutin-1 is an NAD+-dependent histone deacetylase (class III) (12). The gene is made up of 747 amino acid residues, was first recognized in 1999, comprises (9) exons and (8) introns, and is approximately 33 kb long (13). Sirtuin-1 is localized mainly in the nucleus; however, it can also be found in the cytoplasm. This gene shows widespread expression in various adult and fetal tissues, including adipose tissue, muscle tissue, kidneys, liver, and brain (12). Sirtuin-1 regulates numerous physiological processes, including metabolism, immune response, oxidative stress, inflammatory response, and aging (14). During the deacetylation process, the acetyl group present on the protein substrate is transferred to the ADP-ribose (ADPR) molecule, which is produced from NAD+ (15). Sirtuin-1 coordinates a variety of processes at the cellular level, including autophagy, energetic homeostasis, mitochondrial biogenesis, and apoptosis (16). Sirtuin-1 is expressed in the kidney and plays beneficial roles in renal physiology and pathology (17). Sirtuin-1 can protect and maintain normal kidney cell function by mediating in various physiological processes (12). Studies conducted previously have provided evidence supporting the predominant expression of Sirtuin-1 in proximal tubule cells (PTCs) (18). Sirtuin-1 plays a crucial protective role in the kidney by mitigating inflammation, oxidative stress, blood pressure, diabetic albuminuria, and fibrogenesis, while also delaying renal aging (19).

Vitamin D3 is classified as a fat-soluble steroid. It is produced as a precursor molecule (7-dehydrocholesterol) in the skin when exposed to adequate Ultraviolet B (UVB) rays and undergoes two enzymatic hydroxylation steps to convert into the biologically active compound (1α,25(OH)2D3), or calcitriol (20). $1\alpha,25(OH)_2D_3$ is primarily inactivated in the intestine and kidneys by the enzyme 24-hydroxylase (21). A multitude of factors affect its synthesis, including skin pigmentation, time of day, season, latitude, altitude, and sunscreen use (22). Vitamin D3 deficiency is associated with inadequate exposure to the sun and is common in the winter, among the elderly, and in several disorders (23). The kidneys serve as the main regulators of the endocrine vitamin D system, playing a crucial role in controlling the levels of active vitamin D in the body. Specifically, it is the tubular epithelial cells within the kidneys that are responsible for the production of the biologically active form of vitamin D, known as 1,25-dihydroxyvitamin D3 (1,25(OH)2VD3) or calcitriol (23).

2. Materials and Methods

2.1 Subjects

This study enrolled 90 people between October 2022 and April 2023 at Imam Al-Sadiq Hospital and Marjan Medical City in Babil Province, specifically in Al-Hillah City, Iraq. Three groups of subjects were formed: 30 CKD patients (16 females and 14 males) with a mean age of 58.33 ± 8.33 years were studied, as were 30 patients with NS (13 females and 17 males) with a mean age of 52.54 ± 14.02 years. Nephrotic syndrome due to primary (MCD, MGN, and FSGS) and secondary (SLE) causes was included in this study and diagnosed according to the following criteria:

1. Significant Proteinuria: NS is characterized by significant proteinuria, which is the presence of excess protein in the urine. The criterion for significant proteinuria in NS is typically defined as a urinary protein excretion of 3.5 grams or more per day.
2. Hypoalbuminemia: NS is associated with low levels of serum albumin, a major protein in the blood; it is typically defined as serum albumin levels below 3.5 (g/dl).
3. Edema: NS often presents with edema, which is swelling caused by fluid retention. Edema is commonly observed in the lower extremities, face, and hands.
4. Hyperlipidemia: NS is frequently accompanied by dyslipidemia, characterized by elevated levels of blood lipids, particularly cholesterol and triglycerides.

The control group consists of 30 apparently healthy subjects (19 females and 11 males) with an average age of 55.06 ± 8.03 years. All these cases were diagnosed by expert physicians in Imam Al-Sadiq and Marjan Medical City following specific criteria. The control group visited the hospital for routine check-ups and had no history of cardiovascular disease (CVD), DM, hypertension, or renal diseases. They also did not have any other endocrine problems, metabolic disorders, infections, or acute or chronic illnesses. The Clinical Biochemistry Research Lab, College of Medicine, University of Al-Qadisiyah, is where the laboratory tests were carried out. The traditional formula of dividing weight in kilograms by the square of height in meters was used to determine body mass index (BMI). Each participant's specific details, such as age, gender, and medical background, were written down. Written informed consent was obtained from each participant prior to the study, and the research protocols were authorized by the Ministry of Health and the Ethical Committee of the College of Medicine, University of Al-Qadisiyah, ensuring accordance with ethical standards.

2.2 Blood sample collection

A 5 ml blood sample was collected from each participant and allowed to coagulate for 30 minutes. Following coagulation, the serum was separated by centrifugation at 4000 rpm for 15-20 minutes at room temperature (37°C). The serum is then aliquoted into parts using Eppendorf tubes (0.3 ml) and stored at -20°C for biochemical analysis. SIRT-1 and Vit. D3 were quantified using Sandwich ELISA assay following the manufacturer's recommendations (Elabscience and Bioassay BT, respectively, China). Blood urea nitrogen (BUN), serum creatinine, and serum albumin were measured by the automated Monarch 240 device.

2.3 Inclusion criteria

Adult patients with chronic kidney disease and nephrotic syndrome

2.4 Exclusion criteria

Patients with a previous history of infection, chronic respiratory diseases, liver diseases, a chronic systemic autoimmune disease, or a history of malignancy should be excluded.

2.5 Statistical analysis

The information was provided as the mean ± standard deviation of the mean (SD). SPSS version 23, a statistical software package typically used in the social sciences, was used for the statistical study. The chi-square test was used to analyze differences between groups, and quantitative measurements were reported as numbers and percentages. The Andersen-Darling test was used to determine the data's normality. The Student's t-test was used to determine whether there were significant differences between the control and experimental groups. To compare significant differences among several groups, a one-way analysis of variance (ANOVA) was performed, followed by a post hoc analysis using Tukey's test. A level of $P \leq 0.05$ was considered statistically significant for all analyses.

3. Results

The study included a total of 90 subjects, with 30 patients diagnosed with CKD (16 females, 14 males) and a mean age of 58.33 ± 8.33. There were also 30 patients with NS (13 females, 17 males) and a mean age of 52.54 ± 14.02. Additionally, a healthy control group consisting of 30 subjects (19 females, 11 males) with an average age of 55.06 ± 8.03 was included. Table 1 provides a summary of all clinical and hemodynamic variables. The mean age of individuals with kidney diseases (CKD and NS) and the healthy control group is presented in table (1). There were no significant differences observed in the mean age between all patient groups and the control group ($P = 0.451$). Similarly, there were no significant differences in BMI between the patient groups and the control group ($P = 0.321$, Table 1).

3.1 Results of renal function tests

The blood urea, serum creatinine, eGFR, and albumin levels between individuals with CKD, NS, and the control subject were measured. The mean blood urea was significantly increased in CKD patients in comparison to the control ($P < 0.01$), while its levels did not change significantly in NS patients ($P > 0.05$, Table 2). Also, serum creatinine showed significant changes in their levels in CKD patients as opposed to the NS and control subjects ($P < 0.01$). eGFR decreased significantly in CKD patients compared to the control ($P < 0.001$). However, NS patients kept their eGFR as nearest to control eGFR values ($P > 0.05$). Albumin concentrations were decreased but non-significant in both patient groups in comparison to the control ($P=0.56$).

3.2 Results of serum SIRT-1 levels.

SIRIT-1 has a critical role in inflammation and autophagy dysfunction in kidney tissue; therefore, its serum concentration was measured using ELISA. The results showed low SIRT-1 levels in patient groups with CKD and NS in comparison to the control ($P < 0.05$). Furthermore, non-significant differences were observed between the patient groups ($P > 0.05$, Figure 1).

3.3 Results of serum vitamin D3 levels.

Vitamin D3 deficiency was indicated in all stages of CKD; therefore, when renal function reduces, its prevalence is enhanced. Serum Vit. D3 levels were decreased significantly in both patient groups in comparison to the healthy group ($P < 0.05$, Figure 2). Non-significant modifications were observed in serum vitamin D3 levels in patient groups with CKD and NS ($P < 0.05$).

3.4 Correlation between SIRT-1 and Vitamin D3 in patients with kidney diseases.

A- In the CKD patients group: A moderate positive correlation but non-significant was found between SIRT-1 and Vit. D3 ($r=0.420$, $P=0.989$) (Table 3).

B- In the NS patients group: The correlation between all factors was shown in table (4). Non-significant correlation was observed between all factors ($P>0.05$).

3.5 Receive operating characteristic (ROC) analysis for parameters

The ROC curve is created by plotting the true positive rate (sensitivity) against the false positive rate at various threshold settings (1-specificity). The optimal cut-off assessment of serum SIRT-1 and vitamin D3 that can expect a positive diagnosis of kidney diseases in terms of sensitivity and specificity was determined by ROC analysis.

In CKD patients, the SIRT-1 and vitamin D3 cutoffs were 24.3215 and 22.2663, respectively. The degree of significance was likewise high, as shown in table (5). This cutoff value had a good sensitivity in vitamin D3 (93.5) and a high specificity in SIRT-1 (100). This means that the diagnostic tests for SIRT-1 have a high accuracy in correctly identifying individuals without CKD, and vitamin D3 has an excellent ability to correctly identify individuals with CKD (Figure 3).

In NS patients, the SIRT-1 and Vit. D3 cutoffs were 24.3215 and 60.8593. The degree of significance was likewise high, as shown in table (6). The specificity in SIRT-1 and Vit. D3 was 100 and 87.1, respectively, and the sensitivity was 46.6 and 19.4, respectively. This means that the diagnostic tests for SIRT-1 and vitamin D3 had a high accuracy in correctly identifying individuals without NS but have a low ability to correctly identify individuals with NS.

4. Discussion

Kidney diseases refer to any damage affecting the kidneys, which often leads to a loss of kidney function and, in severe cases, complete kidney failure (3).

In the study, the participants ranged from 24 to 76 years old. The mean age and body mass index between the groups didn't differ statistically, which is consistent with other findings in research on renal illness. However, as compared to the healthy group, family history showed statistical significance in each patient group ($P \leq 0.05$). Due to the hereditary component connected to many kidney disorders, family history represents a substantial risk factor for renal disease. Genes passed down from parents can raise the risk of kidney illnesses such as PKD, IgA nephropathy, and Alport syndrome developing (24). Specific gene mutations can cause kidney disease and damage under these circumstances. In addition, there are common environmental and lifestyle variables that cause kidney disease, such as DM and hypertension, which are acknowledged as known risk factors (25).

The kidneys are progressively damaged and lose their ability to filter and excrete waste products; as a result, urea and serum creatinine levels in the blood increase significantly in patients with renal disease, while eGFR decreases as the kidneys become damaged and lose their ability to filter blood

effectively. In line with the present study, the blood urea, serum creatinine, and eGFR were significantly changed in the CKD patient group compared to the control ($P < 0.01$, Table 2). In CKD, the increase in urea and serum creatinine blood levels is due to a combination of several factors. One of the main factors is a decrease in GFR, which leads to impaired clearance of urea and serum creatinine from the blood. Another factor that can contribute to this elevation is a decrease in urine production, because the damaged kidneys may not be able to produce enough urine to effectively remove these waste products from the body (26).

Regarding the Sirtuin-1 level, SIRT-1 can protect and maintain kidney function. It has less of an impact in healthy conditions. Strong renal protection from ischemic or toxic chemical harm can be achieved by SIRT-1 (12). Through its control of fibrosis, cell death, senility, oxidative stress, and inflammatory processes, SIRT-1 has considerable kidney protective effects. The present study showed decreased serum levels of SIRT-1 in patients with CKD, which was higher than the control group (27). Kidney scarring is a common characteristic of advanced CKDs. SIRT-1 deficiency in endothelial cells causes peritubular capillary rarefaction and worsens nephron sclerosis by down-regulating matrix metalloproteinase 14, indicating a role for SIRT-1 in kidney fibrosis (28). SIRT-1 also regulates renal fibrosis in kidney tubular epithelial cells by activating Smad-4 deacetylation and decreasing TGF-mediated matrix metalloproteinase-7 production (29). While SIRT-1 has been studied in relation to kidney diseases and other conditions, the specific measurements of SIRT-1 levels in nephrotic syndrome are not well-documented in the scientific literature up to that point. However, there was a study that demonstrated the effects of SIRT1 activation on podocyte injury, which is a key feature of NS. The researchers demonstrated that activating SIRT1 protected against podocyte injury and reduced proteinuria in a mouse model (30) (31) (32).

The kidneys produce and regulate the preponderance of 1α-hydroxylase CYP27B1 and other hydroxylases involved in Vit. D3 metabolism, as well as 1,25(OH)2D and vitamin D-dependent proteins (33). Serum vitamin D3 levels in this study were significantly decreased in patient groups compared to controls ($P < 0.05$). In CKD, phosphate is retained and accumulated due to the failure to eliminate it as a result of the progressive loss of renal function. Phosphate functions as a negative regulator of 1-hydroxylase and thus negatively impacts the metabolism of Vit. D3. In addition, because the final hydroxylation occurs in the kidney's active unit, the gradual depletion of active nephrons reduces the body's capacity to synthesize vitamin D3 (34). Fibroblast growth factor-23 (FGF-23), which is common, primarily in CKD, has also been found in AKI due to a rise in secretion by bone and decreased elimination, acting on the FGF receptor, suppressing the kidneys' 1-hydroxylase, and inducing 24-hydroxylase, which catalyzes the initial step of vitamin D catabolism, resulting in a decreased amount of active vitamin D3 Recent findings suggest that kidney disease has been linked with a high incidence of vitamin D3 insufficiency or deficiency, particularly in the secondary hyperparathyroidism that develops in the course of CKD, which is associated with 25-hydroxyvitamin D levels. Extremely proteinuric patients have the lowest levels (36).

Patients with NS have low blood levels of the metabolite 25-hydroxyvitamin D3 and also lose this nutrient in their urine or secondary to corticosteroid therapy, especially in long-term therapeutic courses (37). Insufficiency of 25(OH)D is caused by the active phase of NS, when VDBP is lost in the urine. It's possible that this anomaly is causing the hypocalcemia. Due to a lack of 1,25-dihydroxyvitamin D ($1,25\text{-}(OH)_2D$) and ($24,25\text{-}(OH)D_3$), which may be caused by a 25(OH)D deficiency, intestinal calcium (α) absorption defects and resistance to PTH's calcemic action may occur, leading to hypocalcemia (38).

5. Conclusion

Sirtuin-1 is critical in slowing the development of renal disease. It has been shown that Sirtuin-1 inhibits apoptosis triggered by kidney cell injuries, alleviates renal inflammation, enhances mitochondrial function, and reduces oxidative stress, and could be a targeted therapy for renal diseases. Vitamin D3 supplementation may improve the anti-inflammatory role of SIRT-1. Both markers are not useful as diagnostic tests for CKD and NS, as explained by ROC.

6. Acknowledgements

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1.Tables

Table (1): The demographic characteristics of renal disease .patients and control participants

Characteristic	CKD Number = 30	NS Number = 30	Control Number=30	p-value
Old (in years)				
Mean ± SD	58.33 ± 18.33	52.54 ± 14.02	55.06 ± 8.03	0.451 NS
Range	32-73	24-76	25-58	
BMI (kg/m^2)				
Mean ± SD	24.5 ± 3.8	25.79 ± 4.05	24.79 ± 3.34	0.321 NS
Range	14.24 - 30.21	31.74 ± 17.95	17.95-28.74	
Sex				
Male N (%)	14 (46.6 %)	17 (56.67 %)	11 (36.67 %)	0.23 NS
Female N (%)	16 (53.3 %)	13 (20.43 %)	19 (63.33 %)	
Family history with kidney diseases				
Yes N (%)	5 (16.67 %)**	2 (6.67 %)**	0	P < 0.01
No N (%)	25 (83.34 %)	28 (93.33 %)	30 (100 %)	0.41 NS

N: numeral of subjects ; NS: not significant

Table (2): Renal function test in individuals with kidney diseases and control subjects.

Parameter	CKD N = 30	NS N=30	Control N=30	P-value
Blood urea (mmol/l)				
Mean ±SD	26.72±8.85**	5.7±1.56	4.58±0.86	<0.01 #
Range	13.7-43	9 – 3.1	17 -45	
S. creatinine (µmol/l)				
Mean ±SD	568.6±161.45**	80.93± 9.67	80.86±10.12	< 0.01#
Range	273-855	62-94	63-95	
eGFR				
Mean ±SD	12.83±5.43***	115.78±17.77	112.4±14.35	< 0.01#
Range	5-24	81-144	78-138	
Albumin (g/l)				
Mean ±SD	31.71±4.82	32.52±4.44	42.96±3.54	0.56 NS
Range	24-39	26.9-40	39-50	

N: numeral of subjects; NS: Not Significant

Table (3): Correlation among SIRT-1 and Vit.D_3 in patients with CKD group.

Characteristic		Vit.D_3	SITR-1
SIRT-1	Pearson r	0.420	
	P value	0.989	
Vitamin D_3	Pearson r		0.420
	P value		0.989

Table (4): Correlation among SIRT-1 and Vit.D_3 in patients with NS group.

Characteristic		Vit.D_3	SITR-1
SIRT-1	Pearson r	0.200	
	P value	0.856	
Vitamin D_3	Pearson r		0.203
	P value		0.860

Table (5): ROC for SIRT-1and Vit.D_3 to check sensitivity, specificity and accuracy in CKD patients group.

Parameter	CKD				
	Sensitivity	Specificity	Cut off	AUC	95% CI
SIRT-1	50.5	100	24.3215	0.033	0 to 0.071
Vitamin D_3	93.5	16.1	22.2663	0.434	0.287 to 0.581

AUC: area under curve; CI: confidence interval

Table (6): ROC for SIRT-1 and Vit.D_3 to check sensitivity, specificity and accuracy in NS patients group.

Parameter	NS				
	Sensitivity	Specificity	Cut off	AUC	95% CI
SIRT-1	45.6	100	24.3215	0.002	0.000 to 0.008
Vitamin D_3	19.4	87.1	60.8593	0.379	0.236 to 0.521

AUC: area under curve; CI: confidence interval

1. Figures

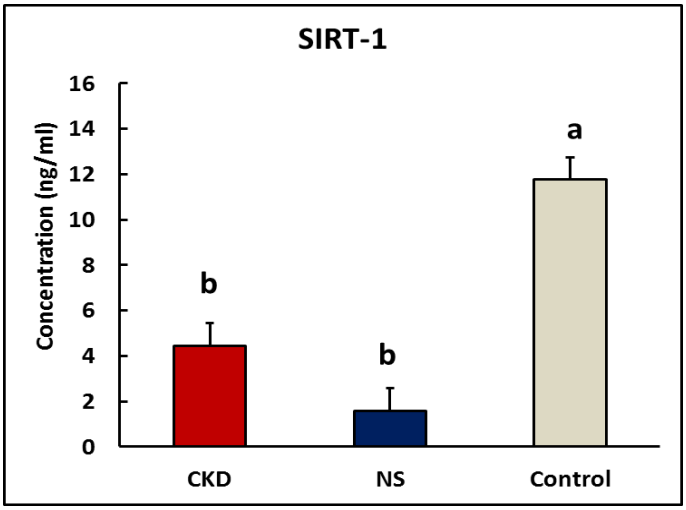

Figure (1): Serum SIRT-1 levels were evaluated in patients with CKD, NS, and the control individuals. The findings were presented as mean ± SD. Different letters denoted significant variations between the patients and the control groups (P ≤ 0.05).

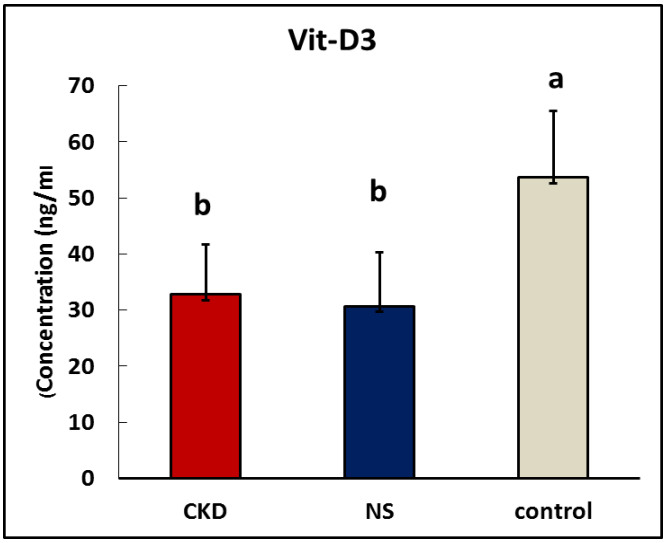

Figure (2): Serum levels of vitamin D3 were evaluated in the CKD, NS, and control groups. The data shown includes mean ± SD values. Significant variations between the patient and control groups were designated by different letters (P ≤ 0.05).

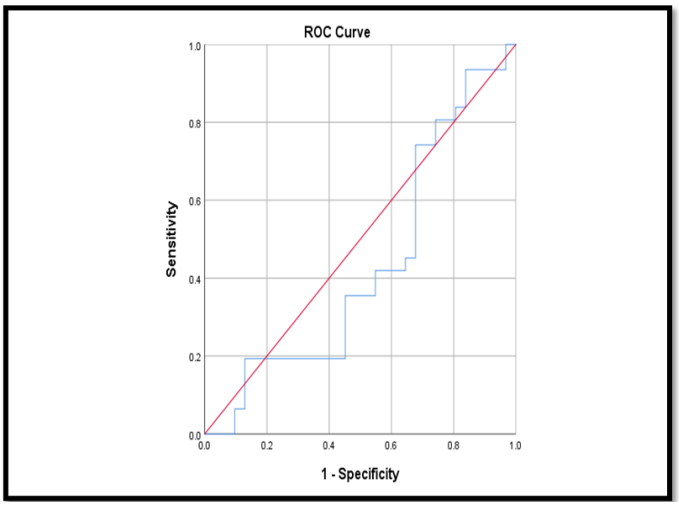

Figure (3): ROC arch examination to find the best cutoff assessment of Vit.D_3 that can forecast a positive diagnosis of CKD in terms of sensitivity and specificity.

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