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Evaluation of YKL-40 as a Biomarker of Inflammation and Atherosclerosis in Chronic Kidney Disease Patients

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

Background: Chronic kidney disease (CKD) has been recognized as a leading public health problem worldwide. In Egypt, CKD approximately affects 13% of the adult population, resulting in significant morbidity, mortality, and health care costs. Patients with advanced CKD (stage 3 or more) experience a high rate of cardiovascular complications compared to earlier stages of CKD.
Objective: To evaluate serum YKL-40 levels in patients with CKD to assess its value as a biomarker of inflammation and its correlation with carotid intima-media thickness (CIMT) as a predictor for early atherosclerosis.
Patients and Methods: The present study was conducted on fifty subjects divided into 2 groups: group I includes 25 patients with CKD (from stage 1 to stage 5 "pre-dialysis") and group II (control group) includes 25 healthy volunteers. The patients were recruited from Internal Medicine Department and Nephrology Unit, Tanta university hospitals in the period between," August 2020 to September 2021 ".
Results: In our study, YKL-40 levels were significantly high in CKD patients(P=0.001). As regards CIMT measurements for the studied cases its median value was 0.90 and1 mm for the right and left carotid respectively. On the other hand, CIMT measurements for the studied volunteers were within the normal range with statistically significant differences between both groups (p=0.001).

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There is a positive significant correlation between the serum YKL-40 level from the studied cases with each of triglycerides, serum urea, serum creatinine, CRP, ESR, R CIMT, and L CIMT. Systolic blood pressure, triglyceride, cholesterol, LDL, serum urea, serum creatine, e-GFR, ESR, CRP, and YKL-40 were found to be independent predictors for CIMT ($P<0.05$). Serum YKL-40 is a highly sensitive predictor of atherosclerosis in CKD and its specificity is 74% in CKD cases.

Conclusion: Serum YKL-40 was significantly high in CKD patients. YKL-40 could be used as a biomarker for inflammation and early detection of atherosclerosis in patients with CKD, but further studies are needed. YKL-40 is an independent predictor of increased CIMT and early atherosclerosis. YKL-40 is highly sensitive to increased CIMT.

Keywords: Chronic kidney disease; atherosclerosis; YKL-40; inflammation.

1. INTRODUCTION

"Chronic Kidney Disease (CKD) has been recognized as a leading public health problem worldwide, the global estimated prevalence of CKD is 13.4% (11.7–15.1%)" [1].

"The Kidney Disease Improving Global Outcomes (KDIGO) initiative classifies an individual as having CKD if abnormalities of kidney structure or function persist for >3 months" [2].

"The primary cause of CKD varies by setting, with hypertension and diabetes being the most common causes, whereas factors such as human immunodeficiency virus (HIV) and exposure to toxins or heavy metals have an additional role in developing countries. In some regions of the world with especially high burdens of CKD, the cause remains unknown" [3].

CKD is associated with a spectrum of complications involving several important organ systems [4].

"These complications contribute to high morbidity and mortality and poor quality of life. Some of these complications can be readily defined and quantified (cardiovascular disease, hypertension, anemia, mineral bone disorder, volume overload, electrolytes, and acid-base abnormalities). Other less well-defined complications with less distinct pathogenesis, such as anorexia, fatigue, cachexia, pruritus, nausea, and sexual dysfunction, may manifest as complex symptoms often associated with advanced CKD" [5].

The most common cause of death for those with CKD is cardiovascular disease [6].

Inflammation is now considered one of the main mechanisms of atherosclerosis [7]. "Early detection of atherosclerosis in apparently healthy people has mainly focused on peripheral arteries and carotid arteries. Using ultrasonography, carotid intima-media thickness (CIMT) can be assessed non-invasively" [8].

"Chronic kidney disease (CKD) is characterized by systemic inflammation. Increased inflammatory markers in CKD are associated with adverse clinical outcomes including all-cause mortality, cardiovascular events, and kidney disease progression" [9].

"C-reactive protein (CRP), an acute-phase protein first described by Tillet and Francis, is synthesized by the liver in response to interleukin-6 (IL- 6) and is a widely available biomarker of inflammation. Elevated CRP concentrations are associated with cardiovascular disease and kidney disease" [10].

"YKL-40, also known as chitinase-3-like-protein1 and human cartilage glycoprotein 39, is a glycoprotein primarily secreted by macrophages, neutrophils, and certain types of local epithelial cells. YKL-40 belongs to the chitinase family of evolutionarily conserved hydrolases that are characterized by their ability to cleave the polysaccharide chitin. The precise physiological function of YKL-40 remains unclear; however, previous reports have implicated YKL-40 in inflammation, cell proliferation, and tissue remodeling" [11].

"Since atherosclerosis has an inflammatory component, it is unsurprising that YKL-40 could be used as a biomarker for identifying the early stages of this disease. Additionally, increased YKL-40 levels have been suggested to serve as a marker of renal function and composite renal outcome" [12].

1.1 Aim of the Work

This work was carried out to evaluate serum YKL-40 levels in patients with CKD to assess its value as a biomarker of inflammation and its

correlation with carotid intima-media thickness (CIMT) as a predictor for early atherosclerosis.

2. PATIENTS AND METHODS

Study Design: Cross-sectional study.

Study population: This cross-sectional study includes fifty subjects divided into 2 groups: Group I included 25 patients with CKD (from stage 1 to stage 5 “pre-dialysis”), our patients were 52%females, 48%males whose ages ranged between 29 and 75 years. Group II includes 25 healthy volunteers. The patients were recruited from Nephrology Unit, Internal Medicine Department, Tanta university hospitals in the period between," August 2020 to September 2021".

Data collection: adult CKD patients were categorized into five stages, according to estimated glomerular filtration rate (eGFR) using modification of diet in renal disease formula : GFR in mL/min per 1.73 m^2 = 175 x $SerumCr^{-1.154}$ x $age^{-0.203}$ x 1.212 (if patient is black) x 0.742 (if female).CKD stages include stage 1 (GFR 90 mL/min/1.73 m2), stage 2 (GFR 60-89 mL/min/1.73 m2), stage 3a (45-59 mL/min/1.73 m2), stage 3b (30-44 mL/min/1.73 m2), stage 4 (15-29 mL/min/1.73 m2) and stage 5 (<15 mL/min/1.73 m2). Patients from stage 1 to stage 5 pre-dialysis were included in the current study. Data were obtained from patients’ medical records including age, gender, onset, and cause of the disease, Complete clinical examination, and Laboratory evaluation. YKL-40 was measured by using double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) kits to assay the level of YKL- 40 in samples with a normal assay range (3 up to 290 ng/ml). All included patients were referred to the radiology department for CIMT measurement. It was determined ultrasonically by an experienced radiologist. It was done by using B-mode ultrasound with a high-definition L12-5 linear wideband probe (Philips HDI 5000, Bothell, Washington, USA).

Provision of privacy*:* Privacy of all data was guaranteed as the following: There was a code number for each patient, so the data of patients were strictly confidential.

Inclusion criteria: Adult patients (more than 18 years) with CKD from stage 1 to stage 5 "pre-dialysis".

Exclusion criteria: Acute or chronic infection or inflammation. Type I and II diabetes mellitus. Chronic liver diseases. Autoimmune diseases. ischemic heart disease or atherosclerotic vascular diseases (established coronary artery disease, cerebrovascular disease, or peripheral vascular disease). history or existence of malignancy. The patient is under steroid treatment.

Possible Hazards during the research: Slight risks of bleeding or infection during blood sampling for investigations, it was avoided by good compressing or by using sterile techniques. No other hazards are expected during the period of research. There was safe disposal of waste products e.g., needles…etc. Any unexpected risks that appeared during the research were cleared to participants and the ethical committee on time.

2.1 Methods

All patients included in this study were subjected to History taking, age, gender, onset, and cause of the disease. Complete clinical examination: Assessment of vital signs of the patient including blood pressure, pulse, temp, chest auscultation and abdominal examination for lymph node, ascites, hepatomegaly, and splenomegaly.

Laboratory evaluation: Kidney function test (urea, creatinine, and e-GFR). Serum albumin. Lipid profile (triglycerides, cholesterol, LDL, HDL). CBC. CRP. ESR. Serum ferritin. Serum YKL-40 (using ELISA technique).

CIMT of carotid artery measurement: All included patients were referred to the radiology department for CIMT measurement. It was determined ultrasonically by an experienced radiologist. It was done by using B-mode ultrasound with a high-definition L12-5 linear wideband probe (Philips HDI 5000, Bothell, Washington, USA). CIMT measurements of the proximal and distal common carotid artery posterior wall were done manually by the provided distance measurement system of the sonography device after magnification of the images.

Blood sampling and processing: Under quality control and safety procedure for sample collection, 8 ml venous blood sample was collected in plain vacutainer tubes. 2 ml were added to EDTA for CBC assay. Serum was separated from the other 6 ml blood for all

specimens using centrifugation at 3000 rpm for 15 min. serum sample for assayed for urea, creatinine, ferritin, YKL-40, lipid profile, CRP.

Renal function test: Ureaand creatinine automated by (Au 480-Beckman coulter). Estimated glomerular filtration rate (eGFR) using a modification of diet in renal disease formula: GFR in mL/min per 1.73 m^2 = 175 x $SerumCr^{-1.154}$ x $age^{-0.203}$ x 1.212 (if patient is black) x 0.742 (if female).

Serum albumin: using Modified bromocresol green colorimetric method.

The lipid profile was carried out by colorimetric techniques.

CBC automated by ERMA PCE-210N cell counter.

CRP using a Rapid latex agglutination test for the qualitative screening and semi-quantitative determination of C-reactive protein (CRP) in serum.

ESR: expresses in mm per hour the rate at which red blood cells settle when anti-coagulated blood is allowed to stand in a narrow tube. It is measured by the height of the column of clear plasma at the end of one hour.

Serum ferritin with I-CHROMA ™ Reader is a fluorescence immunoassay that quantifies human ferritin in serum/plasma.

Serum YKL-40: Test principle: The kit uses a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) to assay the level of Human Chitinase-3-like Protein 1(YKL-40/CHI3L1) in samples with a normal assay range (3-290 ng/ml). Add Chitinase-3-like Protein 1(YKL-40/CHI3L1) to monoclonal antibody Enzyme well which is pre-coated with Human Chitinase-3-like Protein 1(YKL-40/CHI3L1) monoclonal antibody, incubation; then, add (YKL-40/CHI3L1) antibodies labeled with biotin, and combined with Streptavidin-HRP to form an immune complex; then carry out incubation and washing again to remove the uncombined enzyme. Then add Chromogen Solution A, and B, the color of the liquid changes into blue, and at the effect of acid, the color finally becomes yellow. The chroma of color and the concentration of the Human Substance Chitinase-3-like Protein 1(YKL-40/CHI3L1) of the sample were positively correlated.

2.2 Statistical Analysis of the Data

The collected data were organized, tabulated, and statistically analyzed using the IBM® SPSS statistical software, version 21 (Statistical Package for Social Studies) created by IBM, Illinois, Chicago, USA. We used the one-sample Kolmogorov-Smirnov test to check the normality of the data. For numerical values, the mean range and standard deviations were calculated. The differences between the two mean values were used using the student's t-test. For categorical variables, the number and percentage were calculated and differences between subcategories were tested by the chi-square test. We used Pearson's correlation coefficient (r) to calculate the correlation between

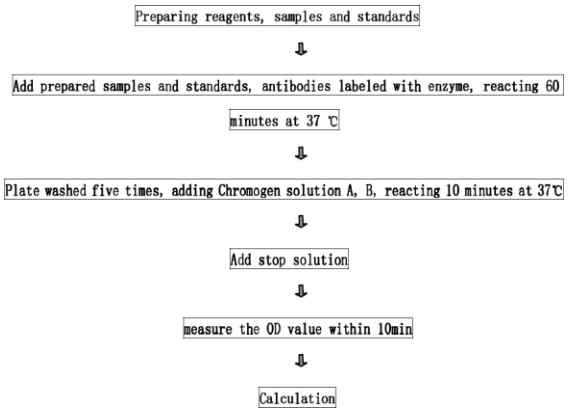

Fig. 1. Summary of procedure of YKL-40 measurement

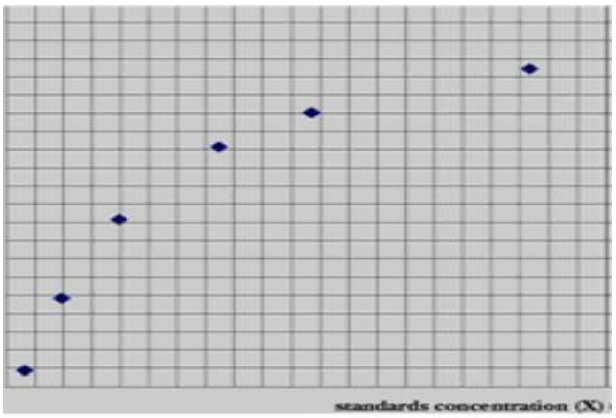

Fig. 2. Shows the standard concentration curve for calculation of the YKL-40 level

variables. For the risk estimated, Linear regression was used to detect the predictor variables. The level of significance was adopted at p<0.05. The ROC (receiver operating characteristic) curve: The ROC curve is a graphical representation of the interaction between sensitivity and specificity for a diagnostic test at various cutoff points. The left upper corner of the curve is a good diagnostic test. Sensitivity and specificity are both 100% at this point. The point of the curve closest to the upper left corner provides the highest test potential and minimizes the sum of incorrect diagnoses. The area below a curve is the overall accuracy of the test; the bigger the zone, the better the results. The curve nearest to the upper left corner is more sensitive and specific, which means that both curves are more accurate.

3. RESULTS

In this study, the socio-demographic data of the studied groups including age and gender were comparable in the studied groups with no significant difference (P >0.05) (Table 1). Furthermore, (Table 2) shows that the duration of CKD in the studied patients ranged from one to 15 years with a median of 3 years. Additionally, this study's results demonstrate that hypertension was the most frequently detected cause of CKD in the studied cases followed by idiopathic etiology. Obstructive Uropathy accounted for two patients and finally one patient with Membranous GN (Table 3). Most of the patients included in the study had normal blood pressure with no significant difference between both groups (Table 4). Regarding laboratory investigations, anemia was found in many of the studied cases, the white blood cells count and platelet count was normal in all patients with no significant differences between the studied groups. The study results revealed that renal function tests were impaired in the studies cases with significant differences between the studied groups. Regarding lipid profile, triglyceride and cholesterol were at borderline high levels in the studied cases with a significant difference between the two groups. On the other hand, HDL and LDL were comparable between both groups with no significant difference (Table 5). Regarding inflammatory markers, serum albumin was comparable between both groups with no significant difference. On other hand, CKD patients presented with high results of ferritin, ESR, and CRP with significant differences between both groups (Table 6). The serum YKL-40 concentrations drawn from the studied cases were variable with a median of 299.3 ng/ml. Additionally, the median serum YKL-40 concentration was 69.10 ng/ml in the control group with a significant difference between both groups (Table 7). As regards CIMT measurements for the studied cases its median was 0.9 mm for the right carotid while it was 1 mm for the left carotid. On the other hand, CIMT measurements for the studied volunteers were within the normal range with significant differences between the studied groups (Table 8). As shown in Table 9, Pearson's rank correlation revealed a positive correlation between the obtained serum YKL-40 level from the studied cases with each of triglycerides, serum urea, serum creatinine, CRP, ESR ($1^{st}$and 2^{nd} hour), R CIMT, and L CIMT. The linear regression analyses in this study showed that systolic blood pressure, triglyceride, cholesterol, LDL, serum urea, serum creatine, eGFR, ESR 2^{nd} hour, CRP, and YKL-40 can be considered as independent predictor factors of CIMT (P<0.05) (Table 10). Additionally, our results showed that the area under the ROC curve was 0.71. at a cut-off value of more than 107.34 which indicates that serum YKL-40 can predict cases with increased CIMT with a sensitivity of 99% and specificity of 74% (Table 11).

Table 1. Baseline demographic characteristics of the studied groups

	Cases (n = 25)		**Control (n = 25)**		**Test of sig.**	**P. value**
	No.	**%**	**No.**	**%**		
Gender					X^2 = 0.08	0.77
Male	12	48	11	44		
Female	13	52	14	56		
Age (Years)					t-test =3.13	
Min.–Max	29 – 75		27 – 62			0.75
Mean ± SD.	58.48 ± 11.95		43.64 ± 9.89			
Median	52		42			

χ2: Chi-square test; t: independent sample Student's t-test

Table 2. The duration of disease in the studied patients

The duration of the disease (year)	Cases (n = 25)
Min.–Max	1 – 15
Mean ± SD.	3.68 ± 1.4
Median	3.0

Table 3. Causes of Chronic Kidney Diseases (CKD) among Studied Cases

Causes of CKD	Cases (n = 25)	
	No.	%
Idiopathic	9	36%
Hypertension	13	52%
Obstructive Uropathy	2	8%
Membranous GN	1	4%

Table 4. Blood pressure among patients with chronic kidney diseases (CKD) and the control group

Vital signs		Cases (n = 25)	Control (n = 25)	t test (p value)
SBP	Min.–Max	90 – 170	90 – 140	3.88(0.51)
	Mean ± SD.	130 ±10.36	112.6 ±9.25	
	Median	130	110	
DBP	Min.–Max	60 – 100	60 – 90	3.05 (0.97)
	Mean ± SD.	80.95±11.25	72.25 ±10.11	
	Median	80	70	

*t: independent sample Student's t-test. *: Statistically significant at P ≤ 0.05*

Table 5. Laboratory investigations among Chronic Kidney Diseases (CKD) and the control group

Laboratory investigation		Cases (n = 25)	Control (n = 25)	t test (p value)
Hb	Min.–Max	7.3 – 14.8	10.2 - 13.8	5.2 (0.01)*
	Mean ± SD.	9.8 ± 2.3	12.26 ± 1.0	
	Median	8.40	12.4	
WBCs	Min.–Max	4.5 – 13.3	4.3 – 14.5	8.3 (0.17)
	Mean ± SD.	8.07 ± 2.7	8.00 ±2.6	
	Median	8.10	7.60	
Platelets	Min.–Max	89.0 – 284.0	119.0 – 419.0	0.67 (0.520)
	Mean ± SD.	217.7 ± 80.3	214.8 ± 78.9	
	Median	188.0	191.0	
Urea	Min.–Max	54.0 – 180.0	15.0 – 40.0	9.70 (0.001)*
	Mean ± SD.	110.35+ 45.25	24.40 + 6.12	
	Median	120.0	25.0	
Creatinine	Min.–Max	1.4 – 7.0	0.3 – 1.10	7.3 (0.001)*
	Mean ± SD.	2.8 + 1.02	0.71 + 0.18	
	Median	2.40	0.70	
e-GRF	Min.–Max	7.0 – 47.0	65.0 – 233.0	10.3 (0.001)*
	Mean ± SD.	25.6 + 12.1	106.50 + 34.2	
	Median	22.0	97.0	
Triglycerides	Min.–Max	43.2 – 409.0	31.1 – 130.0	4.31 (0.05)*
	Mean ± SD.	163.4 + 89.2	88.8 + 23.3	
	Median	150.0	90.0	
Cholesterol	Min.–Max	123.2 – 550	90 - 224.7	2.81 (0.001)*
	Mean ± SD.	195.27 + 88.8	141.66 + 34.2	
	Median	180	129	

Laboratory investigation		Cases (n = 25)	Control (n = 25)	t test (p value)
HDL	Min.–Max	39.6 – 48	44.3 – 58.5	11.2 (0.21)
	Mean ± SD.	37.5 + 1.9	51.5 +4.9	
	Median	37.4	51.0	
LDL	Min.–Max	90 -155.02	29.40 – 85.0	11.51(0.28)
	Mean ± SD.	111.02 +16.85	64.08+12.2	
	Median	106.0	67.0	

*t: independent sample Student's t-test. *: Statistically significant at P ≤ 0.05*
e-GRF": estimated glomerular filtration rate; HB: hemoglobin WBCs: white blood cells

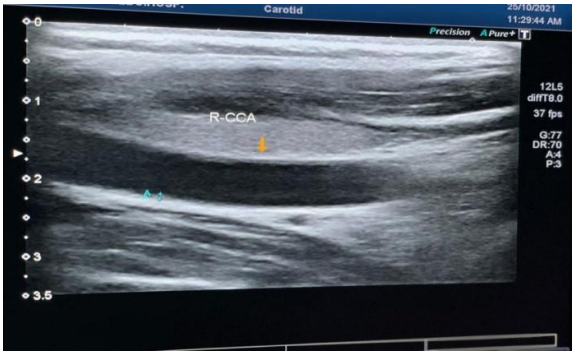

Fig. 3. U/S image of CIMT for a 52-year-old healthy female volunteer in the control group showing normal CIMT (0.6mm on both sides)

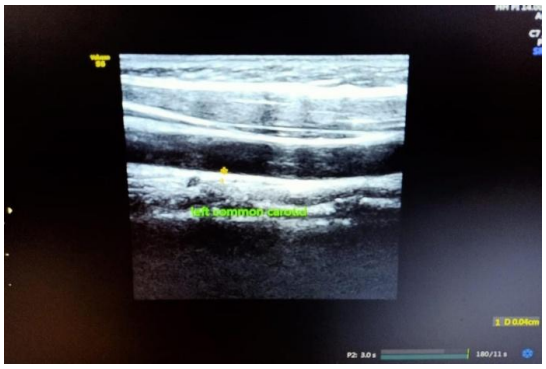

Fig. 4. U/S image of Left common carotid for a 39-year-old healthy male volunteer in the control group showing normal CIMT(0.4mm)

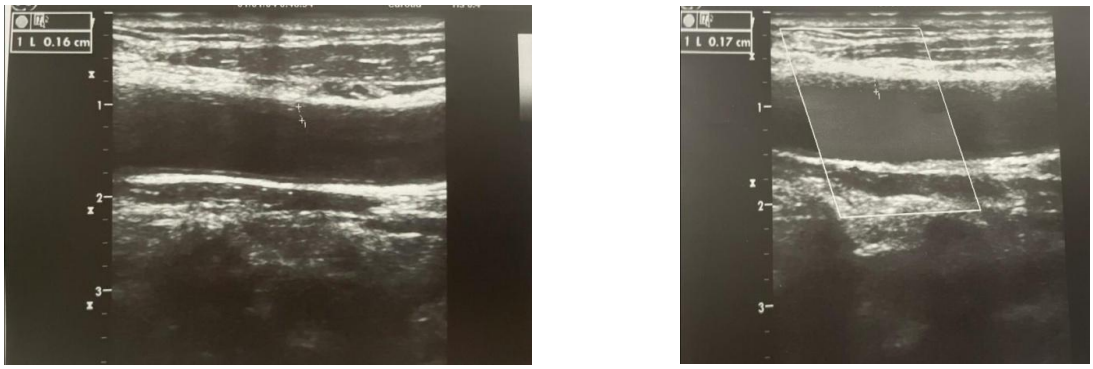

Fig. 5. U/S image of Rt and LT CIMT from 64 years old male patient with CKD and HTN shows increased CIMT. (CIMT = 1.6 mm, 1.7mm respectively)

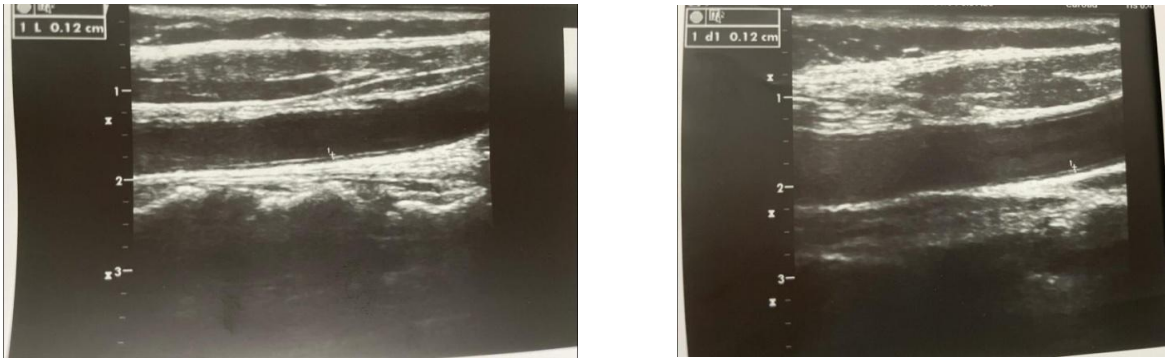

Fig. 6. U/S image of Rt and LT CIMT from 60 years old female patient with CKD shows increased CIMT. (CIMT = 1.2 mm on both sides)

Table 6. Inflammatory markers among patients with CKD and the control group

Inflammatory markers		Cases (n = 25)	Control (n = 25)	t test (p value)
Serum albumin	Min.-Max.	2.1 – 4.2	3.5 – 4.7	4.31 (0.06)
	Mean ± SD	3.35 + 0.51	4.03 + 0.33	
	Median	3.6	4.0	
Serum ferritin	Min.-Max.	58.0 – 766.0	105.0 - 360.0	1.5 (0.001)*
	Mean ± SD	285.19 +180.3	208.2 ± 68.3	
	Median	280.0	210.0	
ESR 1st hour	Min.-Max.	7.0 -100.0	3.0- 15.0	5.6 (0.001)*
	Mean ± SD	38.3 + 25.3	7.8 + 3.02	
	Median	30.0	7.0	
ESR 2nd hour	Min.-Max.	12.0 – 120.0	10.0-35.0	7.2 (0.001)*
	Mean ± SD	85.52 + 30.86	18.90 +7.6	
	Median	70.0	16.0	
CRP	Min.-Max.	2 – 43.0	0 – 37.1	1.92 (0.05*)
	Mean ± SD	12.46 + 10.2	7.56 + 6.4	
	Median	8.0	4.0	

*t: independent sample Student's t-test. *: Statistically significant at P ≤ 0.05*

Table 7. Serum YKL-40 among patients with CKD and the control group

Serum YKL-40	Cases (n = 25)	Control (n = 25)	t test (p value)
Min.-Max.	57.09 – 368.4	30.9 – 112.4	**10.38 (0.001)***
Mean ± SD	253.12 ± 97.06	65.69 ± 17.9	
Median	299.3	69.10	

*t: independent sample Student's t-test. *: Statistically significant at P ≤ 0.05*

Table 8. CIMT of carotid artery measurement among patients with Chronic Kidney Diseases (CKD) and the control group

CIMT		Cases (n = 25)	Control (n = 25)	t test (p-value)
R CIMT	Min.–Max	0.6 – 1.6	0.2 - 0.7	9.14 (0.001) *
	Mean ± SD.	1.0 ± 0.26	0.47 ± 0.14	
	Median	0.9	0.5	
L CIMT	Min.–Max	0.7 – 1.7	0.2 -0.8	8.34 (0.001) *
	Mean ± SD.	1.04 ± 0.3	0.51 ± 0.16	
	Median	1.0	0.5	

*t: independent sample Student's t-test. *: Statistically significant at P ≤ 0.05 CIMT: carotid intimal media thickness*

Table 9. Pearson correlation between YKL-40 level and some studied parameters of Case

Cases	YKL-40 level	
	r	P-value
Age	0.23	0.26
Triglycerides	0.77	0.001*
Cholesterol	0.12	0.54
HDL	-0.24	0.24
LDL	0.36	0.07
Serum urea	0.44	0.02*
Serum creatinine	0.78	0.001*
e-GFR	-0.71	0.001*
Hb	0.36	0.07
WBCs	0.17	0.41
Platelets	0.08	0.63
serum albumin	-0.09	0.63
Serum ferritin	0.19	0.35

Cases	YKL-40 level	
	r	P-value
CRP	0.56	0.005*
ESR 1st hour	0.47	0.001*
ESR 2nd hour	0.41	0.002*
R CIMT	0.48	0.001*
L CIMT	0.58	0.001*

*r: Pearson correlation test; *: Statistically significant at P ≤ 0.05*

Table 10. Linear regression of the predictor variables affecting CIMT of carotid artery measurement among patients with Chronic Kidney Diseases (CKD)

Predictor variables	Standardized coefficients	T	P-value
	Beta		
Age	0.112	1.122	0.278
Systolic blood pressure	0.293	3.509	0.003*
Triglycerides	-0.039	2.432	0.002*
Cholesterol	-0.019	3.212	0.005*
HDL	0.001	0.009	0.253
LDL	-0.089	1.990	0.002*
Serum urea	0.034	2.397	0.04*
Serum creatinine	0.106	1.311	0.004*
e-GFR	-0.145	1.868	0.050*
Hb	0.041	0.443	0.664
WBCs	0.068	0.757	0.460
Platelets	-0.060	0.712	0.487
serum albumin	0.040	0.465	0.649
CRP	-0.035	2.741	0.002*
Serum ferritin	-0.108	1.106	0.285
ESR 1st hour	0.124	1.214	0.245
ESR 2nd hour	0.471	2.956	0.005*
YKL-40	-0.148	1.321	0.050*

Table 11. Sensitivity and specificity of YKL40 as a predictor of increased CIMT among CKD patients

The area under the curve	p	Cut off point	Sensitivity	Specificity
0.71	0.07	> 107.34 ng/ml	99%	74%

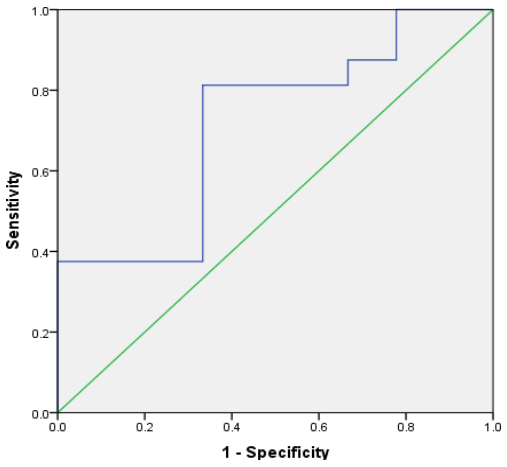

Fig. 7. ROC curve

4. DISCUSSION

"Chronic kidney disease (CKD) is one of the leading public health problems, with increasing frequency and prevalence" [13].

"Patients with CKD have a marked increased risk of accelerated atherosclerosis which led to the development of cardiovascular diseases (CVD) resulting in exceptionally elevated morbidity and mortality rates" [14]. "In this population, the high prevalence of CVD diseases could not be exclusively explained by traditional risk factors such as diabetes, hypertension (HTN), smoking, and dyslipidemia" [15]. "Additionally, chronic inflammation has become a non-traditional risk factor contributing to accelerated atherosclerosis in CKD patients" [16].

"YKL-40 is a 40kDa heparin and chitin-binding glycoprotein which is highly expressed in a variety of inflammatory diseases and is also recognized as a non-invasive prognostic biomarker for inflammation" [17].

The present study was conducted on fifty subjects divided into 2 groups: group I includes 25 patients with CKD (from stage 1 to stage 5 "pre-dialysis") and group II (control group) includes 25 healthy volunteers.

The patients were recruited from Nephrology Unit, Internal Medicine Department, Tanta university hospitals in the period between," August 2020 to September 2021 ".

"Cardiovascular disease is a leading cause of death worldwide, especially in patients with risk factors such as CKD and diabetes" [18]. "As the underlying pathophysiologic mechanism is mainly atherosclerosis" [19].

Therefore, the aim of this study was to evaluate serum YKL-40 levels in patients with CKD to assess its value as a biomarker of inflammation and its correlation with carotid intima-media thickness (CIMT) as a predictor for early atherosclerosis.

Regarding demographic data, the results of this study showed a mild predominance of female patients. (52% of cases). This is in agreement with the result of Hamed, et al. who performed "a hospital-based study in Upper Egypt to study restless leg syndrome in patients with chronic kidney disease and they found that 61.54% of the recruited patient from the Nephrology Unit of Internal Medicine of Assiut University hospital were females" [20].

On other hand, El-Ballat, et al. found that CKD is more common in males than females explained by cigarette smoking being more common in males [21].

"This gender disparity was explained by many factors, including gender differences in the prevalence of risk factors for CKD development and progression, attention to personal health care, access to medical care, availability of medications, and access to renal replacement therapy" [22].

"Additionally, a prospective community-based study of over 10,000 subjects to evaluate the increased risk of rapid progression of chronic kidney disease after non-steroidal anti-inflammatory drugs (NSAID) exposure. Females were more likely than males to use any NSAID" [23].

In this study, most of the recruited cases were elderly as the median age of cases was 52 years. This was in agreement with a study done on 222 patients at different CKD stages. The median of patients' age was 65 [24]. Similarly, this was in agreement with Coresh et al. who found that after "the age of 30 years, e-GFR progressively declines at an average rate of 8 mL/min/1.73 m^2 per decade" [25]. In the same line, a large prospective study reported that (e-GFR) declined with increasing age, and that age is an important risk factor for renal impairment [26].

Concerning the etiology of CKD in the studied patients, hypertension was found to be the most common cause of CKD as it represents about half of cases. This result agrees with Romagnani et al. who studied "CKD and stated that the most common underlying etiology associated with CKD are diabetes mellitus and hypertension" [2]. "As regards diabetic patients, were excluded from our study. The finding results can be explained by different mechanisms including progressive intimal thickening of small arterioles, which in turn cause glomerular damage as narrowing of afferent arteriole in hypertension causes partial ischemia of the glomerular tuft that becomes smaller and gradually reduces the filtration, podocyte loss, tubulointerstitial damage and epithelial to mesenchymal transition" [27].

Furthermore, in the current study idiopathic nephropathy was found to be the second contributing etiology. This coincides with the findings of Kalantar-Zadeh et al. who reported that CKD of unknown etiology and for which there is no known treatment is found in many regions [28].

Clinical examination of the studied patients revealed that most of the patients presented with grade I hypertension.

These findings could be attributed to the favorable effect of antihypertensive drugs received by hypertensive cases.

Regarding the laboratory investigations, the most common CBC disturbance observed in this study was anemia. This finding is in line with a systematic review obtained by Spinowitz et al. who reported that "anemia is a serious complication of CKD, associated with increased cardiovascular comorbidity among other deleterious outcomes, and stated that more than half of patients with end-stage renal disease (ESRD) were anemic" [29].

"According to the KDIGO Anemia Work Group, anemia in CKD is the hemoglobin (Hb) level of <13 g/dL for men and <12 g/dL for women. It is caused by multiple pathophysiological mechanisms which include erythropoietin deficiency, nutritional deficiencies (iron, folate, and B12), pro-inflammatory conditions, and poor response to erythropoietin that results in erythropoiesis suppression" [30].

"Additionally, inflammation can also induce a functional iron deficiency, as cytokines can inhibit the delivery of iron from reticuloendothelial cells to hematopoietic cells. So, patients with high CRP levels showed poor response to erythropoietin therapy meaning that the patients had a low rise in Hb for the same dose of erythropoietin" [31].

"This result agrees with a recent cross-sectional study using data from the Japan Chronic Kidney Disease Database to assess the prevalence of anemia in Japanese patients with CKD. The prevalence of anemia according to that study was 40.1% in patients with CKD stage 4 and 60.3% in patients with CKD stage 5" [32].

"Similarly, in a multicenter study in Canada, the prevalence of anemia was found to be approximately 25% in patients with creatinine clearance greater than 50 mL/min/1.73 m^2. By the time a patient reaches a GFR of 15 to 29 mL/min/1.73 m^2, approximately 44% of patients are anemic, and by stage 5 CKD about 90% of patients are anemic" [33].

Concerning the renal function tests, they were high in all the studied CKD cases with mean values of 110.35± 45.25, 2.8 ± 1.02 for urea and creatinine respectively. While the mean value of e GFR was 25.6 + 12.1 for CKD cases.

Regarding the lipid profile measures in the studied CKD cases, the results of this study showed that they were normal to borderline high in CKD cases with a significant difference between the two groups regarding triglycerides and total cholesterol. On the other hand, HDL level was low in CKD cases. HDL and LDL were comparable between both groups with no significant difference.

This result agrees with Mikolasevic et al. who stated that "patients with non-dialysis-dependent CKD and without nephrotic syndrome have low HDL and high triglycerides and normal cholesterol and LDL" [13].

"Elevated serum triglycerides represent the most frequent abnormality in the lipid profile of CKD patients due to an increased concentration of triglyceride-rich lipoproteins (VLDL, chylomicrons, and their remnants). Hypertriglyceridemia occurs because of both the delayed catabolism and the increased hepatic production of triglyceride-rich lipoproteins. It is also possible that secondary hyperparathyroidism plays an additional role in triglyceride-rich lipoprotein catabolism impairment, resulting in raised plasma triglyceride concentrations associated with CKD" [34].

HDL is diminished because of several mechanisms. First, patients who have impaired kidney function often have decreased levels of apolipoproteins AI and AII, the main components of HDL.

"Furthermore, in CKD patients, the activity of lecithin–cholesterol acyltransferase, the enzyme important for the esterification of free cholesterol in HDL, is impaired. On the other hand, the activity of cholesterol ester transfer protein (CETP), which supports the transfer of cholesterol esters from HDL to triglyceride-rich lipoproteins, is increased. All these processes

are responsible for the decreased serum level of HDL" [13].

On other hand, Bermúdez-López et al. mentioned that "LDL levels depend on the stage of CKD. Whereas in the early stages patients show high LDL levels, in ESRD and particularly in hemodialysis they show normal or reduced concentrations. Usually, renal patients show a reduced LDL particle catabolism and a decreased production of LDL, resulting in nearly normal or reduced amounts. However, nephrotic syndrome is commonly associated with elevated LDL due to an overproduction of these particles" [35].

The present study revealed that serum albumin level among CKD patients was within normal level with a median value of 3.6. This coincides with Zuo et al. who measured albumin in Chinese patients with CKD and reported that albumin level was 4.1 + 0.6 g/dL in the studied patients [36].

On the other hand, Zhang et al. reported that Hypoalbuminemia is well known to be an important problem in patients with end-stage renal disease (ESRD). They explained this finding by malnutrition in ESRD with accompanying anorexia and resultant reduced oral intake [37].

Concerning serum ferritin levels among CKD cases in the current study, our result revealed a high level of ferritin with a median value of 280.

Similarly, Ford et al. stated that Ferritin is an acute-phase reactant that is elevated independently of iron stores in infection, inflammation, malignancy, and chronic disease. This can limit the utility of serum ferritin for the assessment of iron deficiency or overload in disease states such as CKD [38].

Patients with CKD in the current study had elevated erythrocytes sedimentation rate (ESR). This result is in accordance with a recent retrospective study by Buckenmayer et al. who reported that ESR may be helpful as a screening tool for estimating systemic inflammation in patients with renal insufficiency and is significantly increased in ESRD patients. Furthermore, it does not differentiate between various stages of renal insufficiency [39].

In the present study, regarding CRP, there is a variable range of CRP levels in CKD cases with a median value of 8 with statistically significant differences between both groups.

CRP is a pentameric protein synthesized by the liver, it is an acute-phase reactant protein produced in response to many inflammatory conditions [40].

However, serum CRP elevation is not specific but may change due to several inflammatory or noninflammatory responses. It appears that elevated serum CRP may be more associated with CVS risk in CKD patients [41].

This is in agreement with Okyay et al. who reported that neutrophil/lymphocyte ratio, IL-6, and CRP concentrations, were significantly higher in all CKD groups compared to the healthy subjects [42]. Furthermore, Noor et al. concluded that leptin and CRP levels increased significantly with the progression of CKD and they explained their results by the reactive oxygen species being activated and causing an inflammatory condition in CKD patients [43].

Similarly, Elmenyawi, et al. stated that there is a significant increase in CRP in hemodialysis patients compared with healthy controls. This could be attributed to the risk of inflammatory and infection processes during dialysis. However, patients with RRT were excluded from the current study [44].

On the other hand, Menon et al. reported that CRP levels in patients with renal failure were approximate to those in the general population. GFR level does not appear to be related to CRP level in their randomized cohort study [45].

In the current study, there is a significant elevation of serum level of YKL-40 in all patients with CKD compared with the control group.

This result coincides with the findings of Keskin et al. who studied the relationship between plasma YKL-40 level and endothelial dysfunction in CKD patients and reported that YKL-40 is a new inflammatory marker that is elevated in CKD patients with various stages of kidney disease [46].

Decreased clearance, uremia, and dialysis procedure per se are suggested as potential contributors that are responsible for increased acute-phase proteins and proinflammatory cytokines in CKD patients [47].

As a pro-inflammatory cytokine, IL-6 favors mononuclear cell accumulation at the site of injury during chronic inflammation. Increased concentrations of YKL-40 in response to elevated IL-6 concentrations have also been reported by Nielsen et al. [48].

Moreover, Okyay et al. mentioned that decreased plasma YKL-40 concentrations have been reported in the renal vein compared to the femoral artery which was an important finding supporting the renal clearance of YKL-40. Therefore, it is reasonable to speculate that patients receiving dialysis might have increased levels of YKL-40 due to decreased renal clearance and/or dialysis procedure per se.

However, in this study, the lack of hemodialysis patients with renal failure prevented us from getting a clear interpretation of this point.

Furthermore, they reported that YKL-40 could be used as a significant marker to assess cardiovascular risk and inflammatory processes in CKD cases including both hemodialysis and pre-dialysis patients [49].

Recently, Laucyte-Cibulskiene et al. stated that YKL-40 could serve as a marker of renal function and renal outcome. Moreover, it is used as a biomarker for identifying the early stages of atherosclerosis [12]. The results of the current study revealed a positive correlation between serum YKL-40 levels obtained from the studied cases with each triglyceride, CRP, ESR, and CIMT in addition to kidney function.

This result coincides with Malyszko et al. who mentioned that YKL-40 was significantly higher in patients with coronary artery disease, hypertension, increased CIMT, and diabetes compared with their counterparts without these diseases. Similarly, it was related to mean corpuscular volume and CRP [50].

Moreover, an Egyptian study by El Senosy et al. (2018) evaluate YKL-40 levels in patients with CKD to assess its correlation with CRP and CIMT. They noted that there was a highly significant positive correlation between YKL-40 with chronic renal failure. Also, a positive correlation between YKL-40 level with each of CIMT and CRP was found in all patients with CKD [51].

Additionally, our study result was in accordance with a large prospective study of subjects from the general population, Kjaergaard et al. found that elevated YKL-40 levels were strongly associated with elevated triglyceride levels and with a 2-fold increased risk of ischemic stroke [52].

Furthermore, Chen et al. mentioned that the circulating YKL- 40 is significantly correlated with indicators for systemic inflammation such as ESR, CRP, and IgG [53].

Concerning CIMT measurements for the studied cases in our study, its median value was 0.90 mm for the right carotid and 1 mm for the left carotid with a statistically significant difference between both groups.

A study by Lahoti et al. (2017) reported that mean CIMT was increased in all stages of CKD and there was no significant difference in CIMT in different stages of CKD [54]. Patients having hypertension were having higher mean CIMT in comparison to patients having normal blood pressure [55].

CIMT is considered a predictor of early atherosclerotic changes in CKD and has significantly increased CVD risk in any age group. This is stated by Rizikalo et al. who concluded that CIMT is a strong and independent predictor of cardiovascular mortality in the CKD population while exhibiting a significant negative correlation with eGFR [56].

Regarding the linear regression of the predictor variables affecting CIMT of carotid artery measurement, the current study result revealed that each of systolic blood pressure, triglyceride, cholesterol, LDL, serum urea, serum creatine, eGFR, ESR, CRP, and YKL-40 can be considered as an independent contributing factor to CIMT.

This result agrees with Urbina et al. who stated that CIMT is associated with the traditional cardiovascular risk factors such as blood pressure, obesity, or diabetes mellitus which contributed independently to carotid structure and function [60].

Moreover, Zahran et al. reported that creatinine, urea, e-GFR, and inflammatory markers as CRP were predictors for CIMT [61].

In the same line, Ammirati, et al. stated that inflammation is a basic pathogenic element in the development of atherosclerotic disease [62]. This

is supported by the result of a study done by Lawal et al. (2019) who concluded that ESR is the positive predictor of CIMT in CKD patients [63].

Laucyte-Cibulskiene et al. reported that elevated YKL-40 levels were predictors of atherosclerosis by measuring CIMT [12]. Furthermore, a study of 200 patients undergoing coronary angiography by Kucur et al. revealed that elevated serum YKL-40 levels were independently associated with the presence and extent of coronary artery disease and CVD mortality [64].

This result was explained by Massy et al. who mentioned that YKL-40 is expressed in macrophages in the earliest atherosclerosis lesions [65].

Concerning the sensitivity and specificity of YKL40 as a predictor of atherosclerosis among CKD patients, our result shows that serum YKL-40 is a highly sensitive predictor of atherosclerosis in CKD patients with a cut-off value of more than 107.34 ng/ml.

This coincides with Jin et al. who reported that serum YKL- 40 level could predict atherosclerosis with a sensitivity of 75.9% and a Cut- off value: 127.7 ng/ml, indicating its potential value of being a useful tool in discriminating atherosclerotic events such as coronary artery disease “CAD” [66].

5. CONCLUSION

Serum YKL-40 was significantly high in CKD patients. YKL-40 could be used as a biomarker for inflammation and early detection of atherosclerosis in patients with CKD, but further studies are needed. YKL-40 is an independent predictor of increased CIMT and early atherosclerosis. YKL-40 is highly sensitive to increased CIMT.

ETHICAL APPROVAL AND CONSENT

Permission was obtained from Research Ethics Committee as a part of the Quality Assurance Unit in the Faculty of Medicine at Tanta University to conduct this study and to use the facilities in the hospital. Informed written consent was obtained from all patients after a full explanation of the benefits and risks.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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