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Physiological Evaluation of Serum Meteorin-Like Protein and Fibroblast Growth Factor-21 as Biomarkers of Renal Dysfunction in Chronic Kidney Disease

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Abstract
Chronic kidney disease (CKD) is a progressive disorder associated with the gradual deterioration of renal function and complex metabolic disturbances. This study aimed to evaluate circulating levels of Meteorin-Like protein (METRNL) and Fibroblast Growth Factor-21 (FGF-21) and to determine their diagnostic value and association with renal function parameters in CKD patients. A total of 90 subjects were enrolled, including 60 patients with CKD and 30 healthy controls. Patients were categorized into mild-to-moderate and advanced CKD stages. Serum METRNL and FGF-21 levels were measured using ELISA, while serum creatinine, blood urea, and estimated glomerular filtration rate (eGFR) were also assessed. The results demonstrated a significant reduction in serum METRNL levels in CKD patients compared with controls, with values of 245.7 ± 71.3 pg/mL and 182.6 ± 64.9 pg/mL in CKD groups versus 312.4 ± 85.6 pg/mL in controls. In contrast, serum FGF-21 levels were significantly elevated in CKD patients, reaching 214.9 ± 62.8 pg/mL and 356.2 ± 95.4 pg/mL compared with 108.5 ± 36.7 pg/mL in controls. FGF-21 showed a positive correlation with serum creatinine ($r = 0.56$) and blood urea ($r = 0.49$), and a negative correlation with eGFR ($r = -0.58$). Receiver operating characteristic (ROC) analysis demonstrated good diagnostic performance for both biomarkers, with FGF-21 exhibiting superior discriminative ability (AUC = 0.88). These findings indicate that METRNL decreases, whereas FGF-21 increases with CKD progression, and both biomarkers are significantly associated with renal dysfunction parameters. The combined assessment of METRNL and FGF-21 may provide a promising biomarker panel for the diagnosis and evaluation of renal dysfunction in patients with chronic kidney disease.

Keywords: Chronic kidney disease, Meteorin-Like protein, FGF-21, renal biomarkers, eGFR.

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Introduction

Chronic kidney disease (CKD) is considered a major health problem in the world, which is characterized by the development of abnormalities in the structure or function of the kidney that leads to the deterioration of the kidney's function in filtering the blood and the development of cardiovascular diseases and premature death. The epidemiological studies carried out on CKD have shown that the condition is prevalent among more than 10% of the global population and is considered among the top health conditions in the world in terms of prevalence [1,2]. According to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, CKD is considered a state where the glomerular filtration rate is reduced or where there is evidence of kidney damage for a period of at least three months [3]. Despite the progress made in the management of CKD, the condition continues to progress in most of the patients with the condition. Therefore, there is a need to develop further knowledge of the biological mechanisms involved in the development of the condition.

The pathophysiology of CKD is a complex process that involves a combination of several mechanisms, such as hemodynamic stress, oxidative stress, mitochondrial dysfunction, and activation of the inflammatory cascade. The process leads to tubular damage, endothelial dysfunction, and accumulation of extracellular matrix, which results in fibrosis and permanent loss of kidney cells [4]. What is also important is that CKD is not only considered a decrease in glomerular filtration capacity but also a systemic disorder with profound metabolic and inflammatory abnormalities.

Recently, the role of metabolic inflammation, also known as metaflammation, in the context of CKD pathophysiology has gained significant attention. In the context of chronic kidney disease, the presence of uremic toxins, oxidative stress, insulin resistance, and impaired lipid metabolism activates inflammatory pathways such as NF-κB, resulting in cytokine production and immune cell infiltration into the kidneys. These processes contribute to the progression of chronic kidney disease by activating renal tubular fibrosis, which is responsible for the loss of kidney function [1,5]. Thus, these biomarkers have significant implications for the assessment of chronic kidney disease, in relation to metabolic and inflammatory pathways . These tests, including creatinine level and eGFR, are more or less a measure of filtration capacity and may not totally encompass the biological process in question. Thus, there has been significant research interest in the identification of new circulating biomarkers that can more accurately reflect the spectrum of metabolic stress, as well as inflammatory and remodeling pathways in the context of RD. From a new class of biomarkers, there are several metabolically active cytokine-like proteins that have been researched for their potential in relating metabolic stress with RD functional impairment.

Meteorin-Like protein (METRNL), also called subfatin, is a newly recognized secreted protein involved in the regulation of immune metabolism. Experimental data indicate that METRNL is involved in the regulation of inflammation, energy metabolism, and tissue remodeling. It has been shown that circulating METRNL is associated with metabolic diseases, insulin resistance, and inflammation; thus, it may act as a biomarker of systemic metabolic stress [6,7]. Despite these data, the possible physiological role of METRNL in chronic kidney disease has not been sufficiently

explored in association with the progression of renal functional impairment.

Fibroblast growth factor 21 (FGF-21) is a metabolic regulator of the endocrine glands, and its role in glucose metabolism, lipid oxidation, and adaptive responses to metabolic stress is well established. Recent studies indicate that the circulating levels of FGF-21 increase considerably in the blood of CKD patients. Moreover, the levels of FGF-21 correlate with the deterioration of renal function. High levels of FGF-21 have been related to oxidative stress, inflammation, and metabolic dysregulation. It is possible that the role of FGF-21 is compensatory in the context of metabolic processes under systemic stress conditions. Clinical studies have also demonstrated correlations between serum FGF-21 levels and various kidney function indicators, suggesting that FGF-21 may be a potential biomarker for impaired kidney function, as indicated by recent studies [8,9,10].

Despite the growing interest in metabolic biomarkers in chronic kidney disease, most previous studies have focused on evaluating these molecules individually rather than their physiological significance. In addition, although the role of FGF-21 in kidney diseases is increasingly being recognized, the role of METRNL in CKD is not clear. Since both molecules are involved in metabolic and inflammatory responses and adaptation mechanisms, it is logical to assess these molecules simultaneously to better understand the metabolic-inflammatory changes that accompany impaired kidney function.

Study Rationale

The rationale behind the current study is based on the hypothesis that the progression of CKD is closely related to metabolic inflammation and systemic metabolic stress. As such, the biomarkers related to the regulation of the metabolic and inflammatory processes might offer additional clues to the pathophysiological mechanisms related to impaired renal function.

Aim of the Study

To assess the circulating levels of Meteorin-Like protein (METRNL) and Fibroblast Growth Factor-21 (FGF-21), as well as ascertain the diagnostic value and correlation with the parameters of renal function in chronic kidney disease patients.

Materials and Methods

Study Design

This case-control physiological study was designed to evaluate the potential role of serum levels of Meteorin-Like protein (METRNL) and Fibroblast Growth Factor 21 (FGF-21) as integrated markers of renal function impairment in patients with chronic kidney disease.

Study Setting and Duration

The study was conducted in Al-Zahraa Teaching Hospital in Wasit city, Iraq, and the study extended from the beginning of January to the end of November 2025.

Study Population

The study population consisted of 90 participants for the current study. The study population was divided into three different groups based on the functional status of the kidneys.

• **Group I (Control group**): This group consisted of 30 apparently healthy individuals without any clinical and/or laboratory evidence of kidney disease. This group acted as a reference group for the study.

• **Group II (Mild-Moderate CKD):** This group consisted of 30 patients with a clinical diagnosis of chronic kidney disease stage 2-3.

• **Group III (Advanced CKD):** This group consisted of 30 patients with a clinical diagnosis of chronic kidney disease stage 4-5 not on dialysis therapy. The clinical diagnosis of chronic kidney disease is based on the clinical assessment and estimation of glomerular filtration rate by the Kidney Disease Improving Global Outcomes (KDIGO) guidelines.

Inclusion & Exclusion Criteria

Inclusion Criteria

Participants were included in the study based on the following criteria:

1. Adult patients diagnosed with chronic kidney disease for a duration exceeding three months.
2. Patients who have been diagnosed with impaired kidney function based on laboratory tests.
3. Participants willing to participate in the study.

Exclusion Criteria

Participants were excluded from the study based on the following criteria:

1. Patients who have been diagnosed with acute kidney injury.
2. Those with active infection and/or inflammatory diseases.
3. Those who have been diagnosed with chronic liver disease.
4. Cancer patients.
5. Those who have been diagnosed with metabolic disorders affecting circulating metabolic biomarkers.
6. Patients undergoing hemodialysis and/or peritoneal dialysis.

Blood Sample Collection

3 mL of venous blood was collected from each participant under aseptic conditions, then allowed for these blood samples to clot at room temperature, and then centrifuged at 3000 rpm for 10 minutes to separate the serum and stored at −20°C in a deep freezer for further biochemical analysis.

Measurement of the Serum Levels of Meteorin-Like protein (METRNL) and Fibroblast Growth Factor 21 (FGF-21)

Quantitation of the serum levels of Meteorin-Like protein (METRNL) and Fibroblast Growth Factor 21 (FGF-21) was done using commercial human enzyme-linked immunosorbent assay (ELISA) kits (MyBioSource, USA), which utilize the quantitative sandwich ELISA method.

Quantitation of the serum levels of METRNL had a range for detection of 15.6 to 1000 pg/mL with sensitivity to <7.3 pg/mL, while quantitation of the serum levels of FGF-21 had a range for detection of 7.8 to 500 pg/mL with sensitivity to < 3.0 pg/mL.

Intra-assay and inter-assay variation coefficients were within the acceptable limits.

All the assays were carried out following the manufacturer's instructions. The optical density values were recorded using the microplate reader.

The concentration values of the investigated biomarkers were derived using standard calibration curves generated for each plate.

Assessment of Renal Function

Renal function was assessed by estimating the levels of creatinine in the serum and blood urea by standard laboratory techniques.

The estimated glomerular filtration rate was also calculated for all the participants using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation to assess the severity of renal dysfunction and classify the patients according to the stages of CKD.

Ethical Considerations

The study received ethical approval from Wasit University and Al-Zahraa Teaching Hospital. Written informed consent was obtained from all participants before their inclusion in the study, in accordance with the ethical principles of medical research conducted on humans.

Statistical Analysis

SPSS version 26 was used to analyze the data. The continuous variables were described using mean and standard deviation values, while categorical variables were described using frequencies and percentage distribution. One-way analysis of variance (ANOVA) followed by post-hoc analysis using Tukey's method was used to compare the study groups. Pearson correlation analysis was used to evaluate the correlation of the circulating levels of the investigated biomarkers with the parameters of renal function. Moreover, partial correlation analysis was used after adjusting for potential confounders such as age, sex, and body mass index. Receiver operating characteristic curve analysis was used to evaluate the potential use of the investigated biomarkers in the diagnosis of the disease. The optimal cut-points were calculated using the Youden index. Multiple linear regression analysis was used to evaluate the independent predictive value of the investigated biomarkers on renal function using eGFR. A p-value less than 0.05 was considered statistically significant [11].

Results

Table 1 showed that there were no statistically significant differences found in the demographic characteristics of the studied groups, such as age, where $P = 0.28$, and the differences in age values were within the range of 44.2 ± 9.5, 46.8 ± 10.1, and 48.6 ± 11.3 years, respectively. Likewise, no statistically significant differences were found in terms of sex, where $P = 0.84$, and BMI, where $P = 0.31$. This indicates that the studied groups were well-matched.

Table (1): Baseline Characteristics of the Study Groups

Variables	Control Group (n=30)	Mild–Moderate CKD (n=30)	Advanced CKD (n=30)	P-value
Age (years)	44.2 ± 9.5	46.8 ± 10.1	48.6 ± 11.3	0.28
Male	17 (56.7%)	18 (60.0%)	19 (63.3%)	0.84
Female	13 (43.3%)	12 (40.0%)	11 (36.7%)	
BMI (kg/m²)	26.1 ± 3.2	27.3 ± 3.6	27.9 ± 4.1	0.31

*Values are expressed as Mean ± SD or number (%).
ANOVA test was used for continuous variables, while Chi-square test was used for categorical variables.
Statistically significant ($P < 0.05$).

Table 2 shows that highly significant differences were found in renal function tests, where serum creatinine increased progressively in CKD patients, from 0.89 ± 0.18 mg/dL in controls to 1.78 ± 0.42 mg/dL in mild to moderate CKD and to 4.12 ± 1.05 mg/dL in advanced CKD, where $P < 0.001$. Blood urea levels also increased progressively in CKD patients, from 28.6 ± 7.5 mg/dL in controls to 52.4 ± 13.2 mg/dL in mild to moderate CKD and to 96.7 ± 21.8 mg/dL in advanced CKD, where $P < 0.001$. Similarly, a marked decrease was noticed in eGFR, where $P < 0.001$.

Table (2): Renal Function Parameters Among Study Groups

Variables	Control Group (n=30)	Mild–Moderate CKD (n=30)	Advanced CKD (n=30)	P-value
Serum Creatinine (mg/dL)	0.89 ± 0.18^{a}	1.78 ± 0.42^{b}	4.12 ± 1.05^{c}	<0.001*
Blood Urea (mg/dL)	28.6 ± 7.5^{a}	52.4 ± 13.2^{b}	96.7 ± 21.8^{c}	<0.001*
eGFR (mL/min/1.73 m²)	96.4 ± 11.7^{a}	52.6 ± 8.9^{b}	21.3 ± 7.4^{c}	<0.001*

Values are expressed as Mean ± SD. Different superscript letters (^{a}, ^{b}, ^{c}) within the same row indicate statistically significant differences between the study groups ($P < 0.05$) based on One-way ANOVA followed by Tukey's post hoc analysis.

Table 3 revealed that there is a highly significant difference between the study groups for the two biomarkers, as the P-value was less than 0.001. The serum concentration of the Meteorin-Like protein significantly reduced as the kidney diseases became more advanced, from the controls (312.4 ± 85.6 pg/mL) to the mild-moderate CKD patients (245.7 ± 71.3 pg/mL) and then to the

advanced CKD patients (182.6 ± 64.9 pg/mL). In contrast, the FGF-21 level significantly increased as the kidney diseases became more advanced, from the controls (108.5 ± 36.7 pg/mL) to the mild-moderate CKD patients (214.9 ± 62.8 pg/mL) and then to the advanced CKD patients (356.2 ± 95.4 pg/mL). The result was further confirmed by the post hoc analysis with the Tukey test, as the result showed that the differences between the study groups were statistically significant, as indicated by distinct superscript letters (a, b, c).

Table (3): Serum Meteorin-Like Protein and FGF-21 Levels in the Study Groups

Variables	Control Group (n=30)	Mild–Moderate CKD (n=30)	Advanced CKD (n=30)	P-value
Meteorin-Like Protein (pg/mL)	312.4 ± 85.6[a]	245.7 ± 71.3[b]	182.6 ± 64.9[c]	<0.001*
Fibroblast Growth Factor-21 (pg/mL)	108.5 ± 36.7[a]	214.9 ± 62.8[b]	356.2 ± 95.4[c]	<0.001*

Values are expressed as Mean ± SD. Different superscript letters ([a], [b], [c]) within the same row denote significant statistical differences (P < 0.05). This clarifies that while some numerical overlap may exist due to standard deviation, the mean differences between the Control, Mild–Moderate, and Advanced CKD groups remain statistically significant.

The results in Table 4 show that the METRNL had a significant moderate negative correlation with serum creatinine (r = -0.48; P value < 0.05) and blood urea (r = -0.42; P value < 0.05) and had a significant positive correlation with eGFR (r = 0.51; P value < 0.05). On the contrary, FGF-21 showed a significant moderate positive correlation with serum creatinine (r = 0.56; P value < 0.05) and blood urea (r = 0.49; P value < 0.05) and a significant negative correlation with eGFR (r = -0.58; P value < 0.05).

Table (4): Correlation Between METRNL, FGF-21, and Renal Function Parameters in CKD Patients

Variables	Serum Creatinine	Blood Urea	eGFR
Meteorin-Like Protein (pg/mL)	-0.48*	-0.42*	0.51*
Fibroblast Growth Factor-21 (pg/mL)	0.56*	0.49*	-0.58*

*r = Pearson correlation coefficient
n = 60 (CKD patients)
Significant at P < 0.05

Table 5 shows that both biomarkers (METRNL and FGF-21) were observed to possess significant diagnostic performance as inferred by a *P-value* < 0.001. The diagnostic performance of METRNL in diagnosing CKD was observed to possess a high level of diagnostic accuracy as inferred by a high AUC value of 0.82, 78% sensitivity, and 75% specificity at a cut-off value of ≤ 230 pg/mL. Conversely, the diagnostic performance of

FGF-21 in diagnosing CKD was observed to possess a high level of diagnostic accuracy as inferred by a high AUC value of 0.88%, 83% sensitivity, and 80% specificity at a cut-off value of ≥ 190 pg/mL, as shown in Figure 1.

Table (5): ROC Analysis of METRNL and FGF-21 for Detection of CKD

Biomarker	AUC	95% CI	Sensitivity	Specificity	Cut-off
METRNL	0.82	0.73–0.90	78%	75%	≤230 pg/mL
FGF-21	0.88	0.80–0.95	83%	80%	≥190 pg/mL

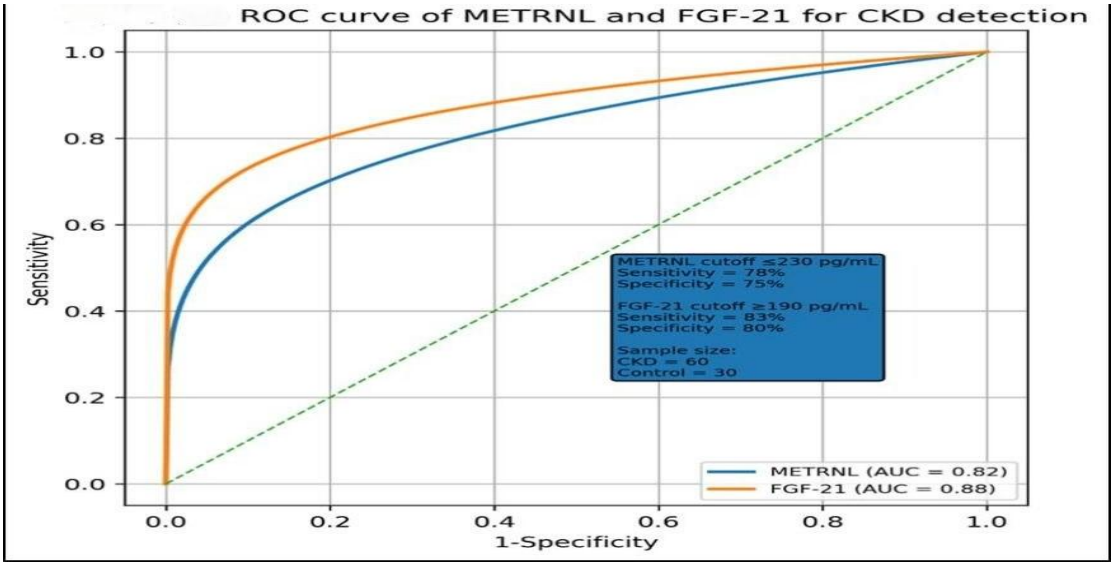

Figure 1: Receiver operating characteristic (ROC) curve analysis for the detection of chronic kidney disease using serum METRNL and FGF-21. The area under the curve (AUC) was 0.82 for METRNL and 0.88 for FGF-21, indicating that the diagnostic test performed well. The diagonal line represents the reference line for random classification.

Table 6 shows the results of the partial correlation analysis between the studied biomarkers and the parameters of kidney function after adjusting for age, sex, and BMI. It is evident from the results that the levels of METRNL had a significant negative relationship with serum creatinine levels ($r = -0.44$, $P < 0.05$), blood urea levels ($r = -0.38$, $P < 0.05$), while it had a significant positive relationship with eGFR ($r = 0.47$, $P < 0.05$).

In contrast, the levels of FGF-21 had a significant positive relationship with serum creatinine levels ($r = 0.52$, $P < 0.05$), blood urea levels ($r = 0.46$, $P < 0.05$), while it had a significant negative relationship with eGFR ($r = -0.54$, $P < 0.05$).

Table (6): Partial Correlation Between Serum Biomarkers and Renal Function Parameters in CKD Patients.

Variables	Serum Creatinine (r)	Blood Urea (r)	eGFR (r)
METRNL (pg/mL)	-0.44*	-0.38*	0.47*
FGF-21 (pg/mL)	0.52*	0.46*	-0.54*

Values represent partial correlation coefficients (r) after adjustment for age, sex, and BMI.
n = 60 CKD patients.
*Correlation significant at $P < 0.05$.

Table 7 shows the results of the multiple linear regression analysis conducted in order to identify independent predictors of renal function as determined by eGFR in patients with CKD. It is evident from the results obtained in the analysis that circulating levels of FGF-21 were a significant negative predictor of renal function as determined by eGFR in patients with CKD ($\beta = -0.37$, $B = -0.052$, $P < 0.001$). This suggests that patients with CKD experiencing high circulating levels of FGF-21 had a significant decrease in their eGFR values.

On the contrary, circulating levels of METRNL were a significant positive predictor of renal function as determined by eGFR in patients with CKD ($\beta = 0.32$, $B = 0.041$, $P = 0.001$). This implies that patients with CKD experiencing high circulating levels of METRNL were associated with better values of eGFR.

However, age demonstrated a trend toward statistical significance ($P = 0.052$), whereas BMI ($P = 0.202$) and sex ($P = 0.292$) were not significant predictors in the regression analysis. The regression analysis was significant ($F = 10.6$, $P < 0.001$) and managed to explain 48% of the variance in eGFR values ($R^2 = 0.48$).

Table (7): Multiple Linear Regression Analysis for Predictors of Renal Function (eGFR) in CKD Patients.

Variables	B	Standardized β	t-value	P-value
METRNL (pg/mL)	0.041	0.32	3.38	0.001*
FGF-21 (pg/mL)	-0.052	-0.37	-3.71	<0.001*
Age (years)	-0.18	-0.15	-1.98	0.052
BMI (kg/m²)	-0.22	-0.10	-1.29	0.202
Sex (Male = 1)	-1.83	-0.08	-1.06	0.292
Model Statistics				
$R^2 = 0.48$				
Adjusted $R^2 = 0.45$				
$F = 10.6$				
$P < 0.001$				

Dependent variable: Estimated Glomerular Filtration Rate (eGFR).
Independent variables: METRNL, FGF-21, age, BMI, and sex.

Multicollinearity was assessed using the variance inflation factor (VIF), and no significant multicollinearity was seen among independent variables.

Table 8 clearly shows that the METRNL test alone demonstrated good diagnostic accuracy, with an AUC of 0.82, 78% sensitivity, and 75% specificity ($P < 0.001$). On the other hand, FGF-21 exhibited a higher diagnostic accuracy with an AUC of 0.88, 83% sensitivity, and 80% specificity with a P value of < 0.001.

Most importantly, when these two biomarkers were used in a combined diagnostic model (METRNL + FGF-21), there was a significant improvement in discriminative power, as shown by the AUC of 0.91, along with 86% sensitivity and 84% specificity at a $P < 0.001$ level. These results indicate that the combined biomarker diagnostic model is better suited for diagnosing CKD than when each biomarker is used as a separate entity.

Table (8): Combined ROC Analysis of METRNL and FGF-21 for Detection of CKD

Model	AUC	95% CI	Sensitivity	Specificity	P-value
METRNL	0.82	0.73–0.90	78	75	<0.001
FGF-21	0.88	0.80–0.95	83	80	<0.001
Combined biomarkers	0.91	0.84–0.97	86	84	<0.001

The combined diagnostic model was developed using a binary logistic regression analysis, and both METRNL and FGF-21 were used as predictors, and ROC curve analysis was carried out using the predicted probabilities from the model.

4. Discussion

The main objective of the present study was to assess the possible physiological importance of Serum Meteorin-Like Protein (METRNL) and Fibroblast Growth Factor-21 (FGF-21), which are biomarkers for impaired kidney function in patients with chronic kidney disease (CKD). The results showed that there were significant variations in the levels of these biomarkers in patients with CKD, and there was a gradual decrease in the levels of METRNL and a significant increase in the levels of FGF-21 in patients with CKD. In addition, these biomarkers were significantly related to conventional indices of kidney function, and their diagnostic value was confirmed by ROC analysis.

The baseline characteristics indicated that the stratification of the study groups was appropriate, as evidenced by the significant increase in the levels of serum creatinine and blood urea in patients with CKD stages, while there was a gradual decrease in the levels of eGFR with the progression of CKD stages.

This is in line with the known pathogenesis of chronic kidney disease (CKD), which is associated with a series of biochemical changes, including the progressive destruction of functioning renal units, glomerulosclerosis, renal tubular dysfunction, and interstitial fibrosis, which eventually results in the impairment of the kidney's ability to filter the blood. These biochemical changes in CKD have been demonstrated by various studies examining other metabolic and inflammatory biomarkers in patients with chronic kidney disease [4,12].

One of the important findings from the present study is the significant reduction in the serum concentration of METRNL in CKD patients compared to healthy controls, with the lowest concentrations found in the more advanced stages of CKD. METRNL is an adipomyokine that was discovered to play important roles in the regulation of inflammation and metabolic pathways, including insulin sensitivity, browning of adipose tissues, and the suppression of inflammatory pathways. Previous studies have indicated that the reduced concentration of circulating METRNL is associated with increased inflammatory burdens as well as metabolic dysregulation [7,13]. The continuous decline in the concentration of METRNL in the present study is an indication of the inflammatory and metabolic disorders associated with CKD.

This is further evidenced by various studies that have shown inverse correlations between the circulating levels of METRNL and inflammatory cytokines/endpoints of endothelial dysfunction. For example, a study that was recently done by El-Ashmawy *et al.*[14] showed that reduced circulating levels of METRNL were associated with endothelial dysfunction and the risk of atherosclerosis. CKD is known to be a pro-inflammatory condition associated with oxidative stress, endothelial dysfunction, and pro-fibrotic pathways; hence, reduced circulating levels of METRNL in CKD patients may be an indicator of the lack of protective anti-inflammatory pathways.

The protective role of METRNL in the maintenance of normal renal physiology is further evidenced by experimental studies. Various experimental studies done on animal models of renal damage have demonstrated that upregulation of METRNL is associated with reduced renal fibrosis and inflammation through modulation of the TGF-β/Smad pathway, an important pathway in CKD pathogenesis. Thus, reduced circulating levels of METRNL in CKD patients may be a reflection of a loss of protective mechanisms against renal fibrosis, thereby leading to a higher risk of structural damage to the kidneys.

Regarding METRNL, this study revealed a significant and progressive increase in FGF-21 levels in the serum of patients with CKD stages. This is in line with the results obtained from most clinical studies, which indicate an elevation in the levels of FGF-21 in patients with impaired renal function. Research has indicated that the levels of FGF-21 are elevated in proportion to the severity of impaired renal function, particularly in the case of chronic kidney disease, including end-stage renal failure [10,15,16]. The mechanisms by which these increased levels of FGF-21 in CKD patients might occur can probably be multifactorial in nature. The decreased renal clearance rate of peptides in CKD patients might cause increased levels of various metabolic hormones in these patients. Conversely, elevated FGF-21 levels in chronic kidney disease (CKD) patients due to metabolic stress may also play a significant role.

It was also established that FGF-21 is a stress hormone, and its roles include physiological activities such as glucose metabolism, lipid metabolism, mitochondria, and oxidative stress [9].

However, the gradual increase in the concentration of FGF-21, as noted, could be a mechanism of compensating for the stress encountered in the body. In the case of CKD, the stress would comprise the dysfunction of the mitochondria, oxidative stress, and lipid metabolism, which would result in the production of FGF-21, which is regarded as a systemic adaptation [17]. The production of FGF-21 could also be a result of the low rate of clearance of the hormone in the advanced stages of kidney dysfunction [18].

The results obtained from the correlation analysis conducted in the study further support the physiological significance of the biomarkers in the bodies of CKD patients. In the current study, it has been observed that the levels of the biomarkers, i.e., METRNL, show negative correlations with the levels of creatinine, blood urea, and a positive correlation with eGFR, which clearly indicate the increased levels of the biomarkers in the body of the CKD patients due to the improvement in the condition of the patients. On the other hand, the levels of the biomarkers, i.e., FGF-21, show positive correlations with the levels of creatinine, blood urea, and negative correlations with eGFR in the body of the CKD patients, which clearly indicate the increased levels of the biomarkers in the body of the CKD patients.

The correlation trends of the biomarker FGF-21 with the biomarkers of renal dysfunction in the body of the CKD patients were observed in the previous study, which clearly indicates the potential of the biomarker in the body of the CKD patients. Analysis of the ROC curve provided further evidence regarding the diagnostic potential of these biomarkers. Both METRNL and FGF-21 were observed to have good discriminatory power in differentiating between patients with chronic kidney disease and healthy individuals, with AUC values of 0.82 and 0.88, respectively. This proves that these biomarkers have good diagnostic potential. However, FGF-21 was found to have higher diagnostic potential than METRNL. This may be due to the fact that FGF-21 levels are more closely associated with renal metabolic stress and reduced renal clearance. The dysfunction of the kidney has a direct impact on the levels of FGF-21, and the hormone might be more sensitive to variations in the physiology of the kidney than METRNL. The second rationale for the better diagnostic ability of FGF-21 lies in the fact that this marker reflects systemic metabolic stress [19]. High levels of FGF-21 indicate mitochondrial stress, oxidative damage, and abnormalities in lipid and glucose metabolism. The last three conditions are major contributors to the progression of CKD [18].

METRNL, on the other hand, is a marker of general anti-inflammatory and metabolic protection and may not be so sensitive to disorders of kidney filtration. When these two factors are considered together, the combined effect of decreased levels of METRNL and elevated levels of FGF-21 may offer important clues to the metabolic and inflammatory status related to the progression of CKD. While the decreased level of METRNL may indicate protective metabolic signals that decrease with the severity of the disease, the elevated level of FGF-21 may indicate compensatory stress responses to the dysfunction[20].

The current research has a number of strengths, which include, firstly, this study is the simultaneous assessment of two metabolically related biomarkers and their integration into a common diagnostic model; secondly, there were clear CKD groups, which were classified according to the severity of CKD, thus enabling the

assessment of biomarker levels in different stages of CKD. Thirdly, this research employed multiple analysis techniques, which include comparing groups, correlation analysis, and evaluation of ROC curves, thus enabling a clearer understanding of the results obtained in this research. Lastly, this research focused on pre-dialysis CKD patients, thus eliminating any confounding effects of dialysis-induced metabolic changes.

This research, however, is subject to several limitations, which include the following: First, the number of participants in this research was small. This makes the results of the current study limited. Secondly, this research did not measure the inflammatory markers, oxidative stress, and albuminuria, which would have given a clearer picture of the mechanisms behind the change in the biomarkers in CKD patients. Finally, this was a case-control study, which cannot be used to establish causality between the biomarkers under investigation and renal dysfunction. It would be recommended that more longitudinal studies be carried out with a large sample size.

The clinical implications of the research findings are significant. From the research findings, it is evident that the two biomarkers, FGF-21 and METRNL, which were identified in the research, may be useful in the early diagnosis of CKD. Moreover, it is evident that the two biomarkers may be involved in the early diagnosis of CKD through different pathways. Furthermore, it is evident that the biomarker FGF-21 is highly diagnostic and may be useful in the early diagnosis of CKD through a non-invasive method for the investigation of the impairment of the functioning of the kidney.

Further studies are needed to determine the potential role of these biomarkers in the early diagnosis of CKD. Further studies should be carried out to determine the relationship between the two biomarkers, FGF-21 and METRNL, with inflammatory mediators, oxidative stress markers, and the pathways of renal fibrosis. Further studies should be carried out to determine if the combination of the two biomarkers, which include both FGF-21 and METRNL, can be useful in the early diagnosis and treatment of CKD patients compared to the normal methods used to determine the level of functioning of the kidney[21].

Conclusion: The current study concluded that the levels of METRNL were reduced, while FGF-21 levels were increased progressively with worsening renal function in patients with chronic kidney disease. The two biomarkers were found to have significant correlation with conventional renal function parameters and were found to have good predictive value in ROC analysis. The use of the two biomarkers also showed better accuracy in diagnosis.

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no conflict of interest

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التقييم الفسيولوجي لبروتين الميتيورين الشبيه المصلي (Meteorin-Like Protein) وعامل نمو الأرومة الليفية-21 (FGF-21)كمؤشرات حيوية للخلل الوظيفي الكلوي في مرض الكلى المزمن(CKD)

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يُعد مرض الكلى المزمن (CKD) اضطرابًا تدريجيًا يرتبط بالتدهور المستمر في وظائف الكلى وحدوث اضطرابات أيضية معقدة. هدفت هذه الدراسة إلى تقييم مستويات بروتين الميتيورين الشبيه (METRNL) وعامل نمو الأرومة الليفية-21 (FGF-21) في الدم، وتحديد قيمتهما التشخيصية وعلاقتهما بمؤشرات وظائف الكلى لدى مرضى CKD. شملت الدراسة 90 مشاركًا، منهم 60 مريضًا مصابًا بمرض الكلى المزمن و30 شخصًا سليمًا كمجموعة سيطرة. وتم تصنيف المرضى إلى مراحل خفيفة إلى متوسطة ومراحل متقدمة من المرض. جرى قياس مستويات METRNL و-FGF 21في المصل باستخدام تقنيةELISA ، بالإضافة إلى قياس الكرياتينين في المصل، ويوريا الدم، ومعدل الترشيح الكبيبي المقدر (eGFR). أظهرت النتائج انخفاضًا معنويًا في مستويات METRNL لدى مرضى CKD مقارنةً بالأصحاء، حيث بلغت القيم 245.7 ± 71.3 و182.6 ± 64.9 بيكوغرام/مل في مجموعات المرضى مقابل 312.4 ± 85.6 بيكوغرام/مل لدى مجموعة السيطرة. في المقابل، ارتفعت مستويات FGF-21 بشكل معنوي لدى مرضىCKD ، إذ بلغت 214.9 ± 62.8 و356.2 ± 95.4 بيكوغرام/مل مقارنةً بـ 108.5 ± 36.7 بيكوغرام/مل لدى الأصحاء. كما أظهر FGF-21ارتباطًا إيجابيًا مع الكرياتينين في المصل (r = 0.56) ويوريا الدم(r = 0.49) ، وارتباطًا سلبيًا مع معدل الترشيح الكبيبي المقدر (r = 0.58–)وأوضح تحليل منحنى ROC وجود قدرة تشخيصية جيدة لكلا المؤشرين الحيويين، إلا أن FGF-21 أظهر قدرة تمييزية أعلى (AUC = 0.88)وتشير هذه النتائج إلى أن مستويات METRNL تنخفض بينما ترتفع مستويات FGF-21 مع تقدم مرض الكلى المزمن، وأن كلا المؤشرين يرتبطان بصورة معنوية بمؤشرات اختلال وظائف الكلى. كما يبدو أن التقييم المشترك لـ METRNL و FGF-21قد يوفر مجموعة واعدة من المؤشرات الحيوية لتشخيص وتقييم الخلل الكلوي لدى مرضى مرض الكلى المزمن..

الكلمات المفتاحية : المرض الكلوي المزمن، بروتين ميتيورين-لايك (الشبيه بالميتيورين)، عامل نمو الأرومة الليفية 21(FGF-21) ، المؤشرات الحيوية الكلوية، معدل الترشيح الكبيبي التقديري.(eGFR)