

Plasma Kynurenine: A Promising Marker for the Assessment of Renal Functions

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ABSTRACT

BACKGROUND: Chronic kidney disease (CKD) is a worldwide issue due to the high prevalence and the serious complications, including death. Kidney functions are routinely evaluated by measuring creatinine levels, which are influenced by many factors (age, sex, diet, race, and body mass). Kynurenine is the first stable metabolite in the kynurenine pathway, which is activated in the course of CKD. Kynurenine levels in plasma can be correlated to kidney functions in CKD patients. We investigated the relationship between kynurenine levels and kidney functions indicators, and the influence of some variables (sex, age, and preexisting hypertension or diabetes) on its levels in CKD patients.

MATERIAL AND METHODS: The study included 66 CKD patients in stages 3 to 5 seen at Tishreen University Hospital, and 22 subjects served as control. Kynurenine levels were measured by using a kynurenine ELISA kit (IDK® immundiagnostik).

RESULTS: Kynurenine levels were significantly increased with the increase in CKD stage ($P < .001$), and were correlated with eGFR ($r = -.631$, $P < .001$), creatinine levels ($r = -.464$, $P < .001$), and urea levels ($r = .528$, $P < .001$). Kynurenine plasma levels were not influenced by age, sex, diabetes, and hypertension in CKD patients.

CONCLUSION: Kynurenine is a promising marker for estimating kidney functions, and its relation with kidney functions is not affected by age, sex, and presence of hypertension or diabetes in CKD patients.

KEYWORDS: Chronic kidney disease, estimated glomerular filtration rate, creatinine, kynurenine, tryptophan

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Introduction

Chronic kidney disease (CKD) has been recognized as a leading public health problem worldwide owing to the high global estimated prevalence (13.4%), and the serious complications, including increased all-cause and cardiovascular mortality, cognitive decline, anemia, bone disorders, and fractures.^{1,2} In the course of CKD, a change in many serum metabolites concentrations may occur, in addition to alteration in some metabolic pathways.^{3,4} Some of these metabolites may be related to CKD pathogenesis and complications. Therefore, assessment of the relation between these metabolites and kidney function indicators may reveal a new marker for evaluating kidney functions, and predicting prognosis in CKD patients. Despite that serum creatinine is the most widely used marker in the assessment of renal function, it has some limitations. Creatinine levels are influenced by sex, race, diet, and muscle mass.⁵

One of these metabolites is kynurenine (KYN). KYN is the main product of the essential amino acid, tryptophan (TRP), throughout the kynurenine pathway. The Kynurenine pathway is the most quantitatively significant metabolic way in TRP degradation (~95%). Indeed, KYN is produced by the action of, either tryptophan 2,3-dioxygenase (TDO) mainly in the liver, or indoleamine 2,3-dioxygenase (IDO) extrahepatically to

produce N-formylkynurenine. The latter is then converted to KYN via N-formylkynurinine formamidase. Subsequently, KYN metabolized throughout 3 main metabolic ways producing a variety of bioactive metabolites combined called kynurenines.⁶ Kynurenine and its metabolites contribute in many metabolic functions, including regulating immunity response, neurological functions, and cell development and division.^{7,8}

Accumulating evidence from both animal models and human studies have proved the increase of tryptophan metabolism throughout the kynurenine pathway in chronic renal insufficiency, basically via TDO or IDO activation. As a result, serum KYN levels were increased in the course of CKD.⁹⁻¹² Moreover, elevation in KYN levels is associated with regression of renal efficacy, and apoptosis induction in kidney epithelial cells.^{8,13} Elevation in KYN seems to be correlated with CKD complications, for example, bone disorders, anemia, atherosclerosis, and neurological disorders.¹⁴⁻¹⁶ In addition, KYN has shown predictive ability for CKD incidence.^{17,18} To conclude, measuring kynurenine levels can be a useful tool in the evaluation of kidney functions. In this study, we investigated if kynurenine elevation is proportional to kidney functions. We also evaluated if the increase in KYN levels significantly differ between CKD stages (3-5). In addition, we studied the relationship between KYN



levels and each of age, sex, diabetes, hypertension, and some inflammatory markers in CKD patients.

Materials and Methods

Subjects

The study included 88 subjects, after taking into consideration excluding criteria. All included subjects were clinically stable and free of active infections, autoimmune diseases, neuropsychiatric diseases, and cancer. The patients who received immunosuppressive treatment, steroid hormones (all types), biotin, or medications that interfere with L-tryptophan metabolism (eg, selective serotonin reuptake inhibitors) were excluded. After analysis, patients with C-reactive protein (CRP) > 10 mg/l, white blood cell (WBC) count $>10 \times 10^3 \mu\text{l}$, or triglyceride > 200 mg/dl were excluded. We included 66 CKD patients; 59.55 ± 16 (mean \pm SD) years of age; 36 male; from the department of Kidney disease at Tishreen University Hospital, Lattakia. These patients were classified into 3 groups according to eGFR; CKD stage 3 (30-59 ml/min/1.73 m², n=22), CKD stage 4 (15-29 ml/min/1.73 m², n=22), and CKD stage 5 (<15 ml/min/1.73 m² and on hemodialysis, n=22).¹ Twenty-two subjects; 45 ± 20 years of age; 10 male; without a medical history of renal disease, and with eGFR more than 60 ml/min/1.73 m² and serum creatinine less than 1.3 mg/dl for males and 1.1 mg/dl for females, served as control group. Estimation of glomerular filtration rate (eGFR) was calculated using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula ($\text{eGFR} = 141 \times \min(S_{\text{Cr}}/\kappa, 1)^\alpha \times (S_{\text{Cr}}/\kappa, 1)^{-1.209} \times 0.993^{\text{age}} \times 1.018$ [if female] $\times 1.159$ [if black]). The study was reviewed and approved by Tishreen University Council, and written consent was obtained from all participants.

Blood sampling

Peripheral venous blood was drawn from each individual in the morning between 8 and 11 a.m. Blood samples were collected on ethylenediamine tetraacetic acid (EDTA) tubes for complete blood count (CBC), and lithium heparin tubes for chemical analysis. After the CBC analysis, EDTA plasma were separated and stored at -40°C until the kynurenine assay. Blood was drawn before dialysis for CKD stage 5 patients.

Laboratory measurements

All laboratory measurements were performed in the central laboratory at Tishreen University Hospital. Heparinized plasma creatinine, urea, and CRP concentrations were measured using an automated biochemical analyzer (Mindray BS-380) with the commercially available kits. CBC analysis was done using a Sysmex XT-1800i analyzer.

Kynurenine levels were measured in the immunology department at the central laboratory using L-kynurenine

ELISA kit (IDK® L-Kynurenine Eliza from Immundiagnostik AG, K7728-200525) according to the manufacturers' instructions. About 20 μl of EDTA plasma were used from each sample stored at -40°C in the 96-well plate competition ELISA assay. The absorbance of each plate was measured at 450 nm with the reference wavelength of 620 nm using the Eliza Plate Analyzer (NS TOUCH). Optical density measurements were converted into concentrations according to a standard curve.

Statistical analysis

Statistical analyses were performed using SPSS statistical software (version 20), and Microsoft Excel 2010. All results are expressed as mean \pm SD and percentages as appropriate. For checking the normal distribution of the data, the Kolmogorov-Smirnov test was used. We used a one-way analysis of variance (ANOVA) to examine the differences in variables of interest. Correlations were assessed using the person test for continuous data and Spearman rank test for bivariate data. Multiple linear regression models were carried out to estimate the effects of other variables.

Results

Subject characteristics

The demographic and laboratory characteristics of the participants are presented in Table 1. Among CKD subjects, 34 (39%) patients had diabetic mellitus and 35 (40%) patients had hypertension, without significant difference in percentages of those patients among the 3 stages of CKD ($P > .05$) for both variables. The mean creatinine concentration was 3.56 ± 3.7 mg/dl, and the mean eGFR of the study participants was 46.34 ± 41 ml/min/1.73 m². The mean urea and CRP levels were 82.1 ± 59.4 mg/dl and 3.48 ± 2.3 mg/l, respectively, with a significant difference among groups (for urea $P < .001$, for CRP $P = .011$). While there were no significant differences in WBC and platelet count among groups ($P > .05$), RBC counts declined gradually with the increase of CKD stage ($P < .001$).

The relationships between kynurenine and CKD markers

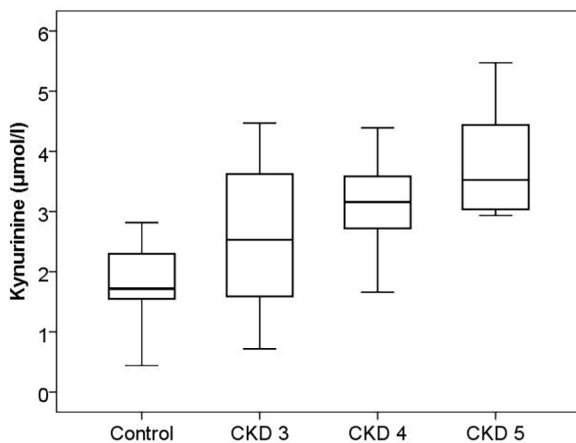
In this study, plasma KYN levels were between 0.43 and 5.45 $\mu\text{mol/l}$; thus they were compatible with linearity limits determined by the kit manufacturer (0-10 $\mu\text{mol/l}$). KYN levels were assessed for correlation with CKD stages (3-5) and parameters of kidney functions (eGFR, creatinine, and urea). The mean of KYN levels increased among study groups with the increase of CKD stage (Table 1; Figure 1). The Kolmogorov-Smirnov test indicated that KYN levels in each group followed the normal distribution. In analyses of variation, the ANOVA test showed a statistically significant difference in means of KYN levels among groups ($P < .0001$). By applying post hoc

Table 1. Characteristics of the study population.

PARAMETERS	CONTROL (N=22)	CKD 3 (N=22)	CKD 4 (N=22)	CKD 5 (N=22)	P-VALUE
Male, n (%)	10 (45)	16 (73)	6 (27)	14 (64)	.013
Age (years)	45 ± 20	59.5 ± 16.5	66.6 ± 12.8	52.5 ± 16.2	<.001
Hypertension (n [%])	0	14 (64)	12 (55)	9 (41)	.315
Diabetes (n [%])	0	13 (59)	11 (50)	10 (45)	.654
KYN (μmol/l)	1.84 ± 0.65	2.61 ± 1.1	3.17 ± 0.65	3.72 ± 0.74	<.001
S _{Cr} (mg/dl)	0.87 ± 0.12	1.77 ± 0.3	2.6 ± 0.46	8.9 ± 3.5	<.001
eGFR-EPI (ml/min/1.73 m ²)	111 ± 21	42 ± 7.2	25 ± 4.1	7 ± 3.3	<.001
Urea (mg/dl)	22 ± 6.6	57 ± 18.7	94 ± 38	156 ± 48	<.001
CRP (mg/l)	2.3 ± 1.8	3.2 ± 2.2	4.2 ± 2.7	4.2 ± 3.3	.011
WBC (×10 ⁹ /l)	6.7 ± 1.4	7.8 ± 1.8	7.2 ± 2.8	7 ± 2	.424
RBC (×10 ¹² /l)	4.6 ± 0.8	4.2 ± 0.7	3.3 ± 1.0	3.2 ± 0.8	<.001
PLT (×10 ⁹ /l)	265 ± 78	269 ± 93	232 ± 114	200 ± 81	.059

Abbreviations: CKD, chronic kidney disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; KYN, kynurenine; PLT, platelets; RBC, red blood cell; S_{Cr}, serum creatinine; WBC, white blood cell.

Values are presented as mean ± standard deviation or n (%). The ANOVA was used for continuous variables; the X²-test was used for categorical variables.

**Figure 1.** Kynurenine level by stages of chronic kidney disease (3-5) and control.

Least significant difference test (LSD), we found a statistically significant difference between all groups ($P < .05$) (Table 2). Eventually, each time the CKD stage progressed, there was a statistically significant increase in plasma KYN levels.

Additionally, we assessed the correlation between KYN and the parameters of the kidney using a person coefficient. We found a negative strong correlation with eGFR calculated with CKD-EPI equation ($r = -.631, P < .001$) (Figure 2a) and with MDRD equation ($r = -.639, P < .001$) (Figure 2b). A positive correlation was also found with creatinine ($r = .464, P < .001$) (Figure 2c), and with urea concentrations ($r = .528, P < .001$) (Figure 2d).

Table 2. Post hoc analysis (LSD) for kynurenine means between study groups.

	CONTROL	CKD 3	CKD 4	CKD 5
Control	0			
CKD 3	0.775**	0		
CKD 4	1.333**	0.557*	0	
CKD 5	1.888**	1.11**	0.555*	0

* $P < .05$. ** $P < .01$.

We used multiple regression models to examine the relationship between KYN levels and kidney functions. The best model that explained this relationship was the linear regression between KYN and eGFR. KYN concentrations were significantly associated with eGFR ($P < 0.0001$), and the model explained 39% of the results. According to this model, KYN concentration increased 0.16 μmol/l for each 10 ml/min/1.73 m² decrease in eGFR. Adjusting the model for age did not enhance the relation ($R^2 = .39$). In multi regression analysis; sex ($P = .07$), diabetes ($P = .64$), and hypertension ($P = .85$) were insignificant variables in the model. The evaluation of the relation between KYN with creatinine and urea revealed that urea model explained 27% from the result ($P < .0001$), and were superior to the creatinine model, which explained 20% of the result ($P < .0001$). Using both parameters in 1 model resulted in insignificance of creatinine as a predictor. Like in the relationship

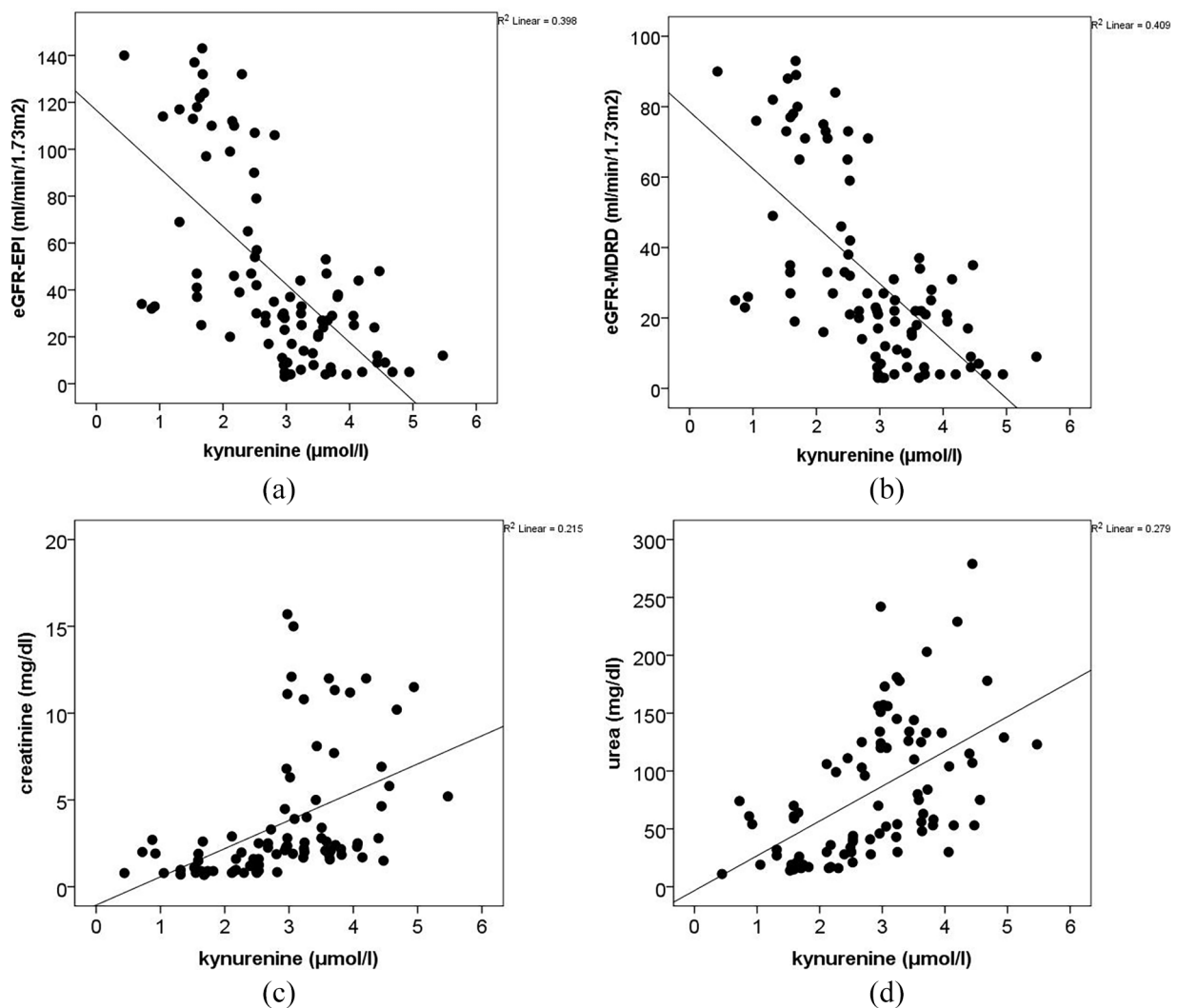


Figure 2. Correlation between kynurenine and kidney functions indicators: (a) kynurenine with eGFR calculated with CKD-EPI equation, (b) kynurenine with eGFR calculated with MDRD equation, (c) kynurenine with creatinine, and (d) kynurenine with urea.

with eGFR; adjusting the model for age and other demographic variables were insignificant.

The relationship between kynurenine and other variables in CKD patients

We examined the correlation between plasma KYN and the variables presented in Table 3 in CKD patients. Plasma KYN was not influenced by changes in sex or age. Using an independent *t*-student test there was no significant difference in KYN means between males (3 ± 1.07) and females (3.36 ± 0.76) ($t[64] = -1.534$, $P = .130$), and within each group (all $P > .05$). Similarly, KYN levels did not correlate with age ($r = -.127$, $P = .31$). In addition, there were no statistically significant differences in the means of KYN levels between diabetic (3.17 ± 1.1) and nondiabetic (3.18 ± 0.78) CKD patients ($t[64] = 0.021$, $P = .983$), and between hypertensive (3.14 ± 1.05) and nonhypertensive (3.21 ± 0.85) CKD patients ($t[64] = 0.2775$, $P = .784$), and within each group (all $P > .05$). Red blood cell indicators (RBC count, hemoglobin, hematocrit) correlated significantly with KYN levels, however, the correlations were weak. For

inflammatory markers, white blood cell and lymphocytes count also had a weak statistically significant correlation, whereas CRP and neutrophils count didn't correlate with kynurenine levels.

Discussion

In the present study, we investigated the correlation between KYN levels and kidney indicators (eGFR, creatinine, and urea), and its association with CKD stages. We found that KYN levels had a statistically significant negative correlation with eGFR independent from age, sex, diabetes, and hypertension, and a significant positive correlation with creatinine and urea levels. In addition, the mean of KYN levels increased with the increase of CKD stages (3-5).

Although it has been reported previously that some of the KYN pathway metabolites/metabolites' ratios (ie, kynurenic acid/TRP;¹² KYN/TRP,¹⁹ TRP²⁰) correlate with kidney functions, our study revealed that KYN, on its own, can be a sensitive, reliable, and more affordable marker for kidney functions. Indeed, the significant correlation between KYN and kidney indicators (eGFR, creatinine, and urea), and the increase in

Table 3. Correlations between kynurenine and some variables in CKD patients (N=66).

VARIABLE	CORRELATION WITH L-KYNURENINE	P-VALUE
Age	-.127	.31
Sex	.158	.20
Diabetes	.005	.97
Hypertension	.023	.85
CRP	.085	.50
WBC	-.272	.031
Neutrophils	-.146	.246
Lymphocytes	-.374	.002
RBC	.386	.001
Hematocrit	-.316	.01
Hemoglobin	-.311	.011
PLT	-.308	.013

Continuous data analyzed using person correlation, bivariate data analyzed using spearman correlation.

means of KYN levels among CKD stages, besides the independency of KYN levels on age, sex, and presence of hypertension and/or diabetes, suggests applying KYN as marker for kidney function in clinical practice. KYN as a marker is superior to serum creatinine, because it is independent of age and sex, elevates earlier¹⁷ and is more related to metabolic complications in CKD patients.^{8,14,21}

In general, the reports included measuring KYN in CKD patients agree in KYN elevation, and in the significant correlation with eGFR.^{12,20,22} Despite Debnath et al²⁰ finding that KYN levels in CKD stage 3 to 5 patients were significantly elevated, the elevation didn't correlate with the CKD stage (mean KYN levels in stage 3 > stage 4 patients). This may be explained by the relatively small sample size in stage 3 and 4 groups in their study. Although Schefold et al¹¹ found a statistically significant difference in KYN levels in CKD stages 3 to 5 compared to control, they didn't find a direct correlation with kidney functions. However, they did not mention neuropsychiatric diseases and consuming corticosteroid hormones within excluding criteria, and with a relatively small sample size, these factors may influence the correlation significantly. In addition, the WBC counts for the CKD stage 4 group was slightly elevated (exceeded the normal range), which may indicate inflammation. In general, the mean KYN concentrations in CKD stages 3 and 4 patients seen in previous studies were similar to those in our study, while KYN levels in CKD stage 5 patients were slightly higher compared to ours.^{20,22}

Since the activation of the KYN pathway has been reported frequently in the course of CKD, we may conclude that this mechanism would explain KYN elevation in CKD patients. Both Saito et al¹⁰ and Pawlak et al¹³ have found an elevation in

TDO activity in the liver of rats with experimental renal insufficiency compared to the control group. TDO activation in CKD may be explained by the elevation in glucagon, which metabolized in the kidney.¹⁰ IDO, on the other hand, will be induced as a consequence of the chronic inflammation process due to the secretion of pro-inflammatory factors, essentially INF- γ .^{8,11,12,19} In their research, they have assumed that KYN/TRP ratio as an IDO activity. However, Badawy et al²³ have pointed out that this ratio may not reflect only IDO activity in vivo, and it may be influenced by other factors. Probably, both enzymes contribute to KYN elevation in the course of CKD. We suggest measuring neoptren as a complementary marker because it elevates in response to INF- γ production²⁴ (along with IDO activation) in order to differentiate between IDO and IDO-induced elevation of KYN in future study. Since KYN is metabolized and excreted in urine, it is expected that regression in kidney functions would contribute to KYN elevation in plasma. However, Saito et al¹⁰ have suggested that this may not be a significant mechanism in KYN elevation, because the total urinary excretion of kynurenine increased. Another indirect mechanism that contribute to kynurenine levels elevation, is the impairment of vitamin B6 absorption in the course of CKD. Since vitamin B6 acts as a coenzyme for both kynurenine hydroxylase and kynureninase (both catabolize KYN), the activity of these enzymes will be reduced significantly, leading to the increase in KYN concentration.¹⁰

In our study, there were no significant differences in KYN levels between males and females, hypertensive and nonhypertensive, and diabetic and nondiabetic CKD patients. In addition, KYN levels weren't correlated with age. KYN independent of age and sex makes it superior to creatinine and urea as a marker. Regarding the relation between KYN levels and hypertension, reports are still insufficient.⁸ However, in the Hordaland Health study, KYN levels in hypertensive patients were slightly elevated.²⁵ We can conclude that KYN levels alteration in hypertensive patients is of little significance in the presence of CKD. On the other hand, KYN pathway activation in diabetic mellitus has been reported previously, through IDO activation and chronic long-grade inflammation.^{8,26-28} However, the significant increase in KYN levels in diabetic patients compared to the control is contradictory in these studies.^{25,27,28} As in the case of Hypertension, KYN levels elevation in diabetic patients may be of little significance in the presence of CKD. We recommend studying KYN levels on a larger number of CKD hypertensive and diabetic patients to obtain better insight in using KYN as marker for kidney function in these patients.

Since chronic inflammation is a well-known feature in CKD, and it may contribute to KYN elevation throughout IDO activation, it is useful to assess the relationship between some inflammatory markers in CKD patients and KYN levels.²⁹ The elevation of many inflammatory markers in correlation with TRP metabolites in CKD patients has been reported previously.^{11,17,20} In our study, KYN levels weren't correlated with CRP, similar to the Subrata et al²⁰ findings. However, there was a weak correlation in

other studies.^{11,17} Also, KYN had a weak negative correlation with WBC counts ($r=-.272$), and slightly higher with lymphocytes ($r=-.374$) and platelets counts ($r=-.308$). Scheffold et al¹¹ found a weak positive correlation with platelet counts and no correlation with WBC counts. Despite the association of KYN with CRP, WBC, and lymphocytes counts in CKD patients, the correlation was weak, and these parameters may be influenced by many factors other than KYN alteration.

It is acknowledged our study had several limitations. First, we didn't include measuring KYN levels in CKD patients with eGFR > 60 ml/min/1.73 m², because stage 1 and 2 CKD patients had kidney damage markers, other than creatinine, that we didn't investigate in our study (their creatinine level nearly normal).³⁰ Second, we didn't measure KYN levels in fasting blood samples. In addition, although we excluded the subjects who consumed L-tryptophan containing supplements, we didn't consider the effect of consuming protein and tryptophan-rich diet on KYN levels.³¹ Even though, our results are consistent with other research with regard to the significant correlation between KYN and eGFR reported in similar populations.^{10,11,20,22}

In conclusion, the study findings have demonstrated that the increase in CKD stages and the regression in kidney functions are associated with the significant increase in KYN level in CKD patients. Furthermore, KYN correlation with eGFR was independent of age, sex, diabetes, and hypertension in CKD patients. Based on these data and the data from other studies, plasma kynurenine may be a promising marker for kidney functions evaluation. It gives insight into the kynurenine pathway alteration in CKD patients due to its association with metabolic complications in the course of CKD.

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Author Contributions

All authors designed the study. FB collected the samples, run the analysis, analyzed the data, and wrote the paper. All authors contributed to manuscript revisions and approved the final version of the manuscript.

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