RESEARCH ARTICLE

Hyperuricaemia and Inflammatory Markers in Patients with Chronic Kidney Disease

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ABSTRACT

Background: Increased serum uric acid (SUA) level is associated with joint damage and has been positively correlated with various diseases such as chronic kidney diseases (CKD) due to inflammation. This study aimed to investigate the relationship between hyperuricemia (increased SUA) and inflammatory status in Iraqi people with different stages of CKD.

Methods: A cross-sectional study recruited 128 participants with CKD (45 stage I, 42 stages II and, 41 stage III CKD patients) and 88 age-and sex-matched healthy controls. SUA, tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), interleukin-10 (IL-10), blood urea, serum creatinine, cholesterol, triglyceride (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and very-low-density lipoprotein (VLDL) levels were determined and compared between the groups.

Results: The stage III disease group had significantly higher values of SUA, TNF-α, IL-6, creatinine, triglyceride, and blood urea levels ($p < 0.0001$), as well as HDL ($p < 0.001$), and VLDL ($p < 0.05$) in comparison to the controls. No significant differences in serum cholesterol, LDL, and IL-10 were found between the stages I, II and III CKD patients and controls.

Conclusion: This study found CKD (stage III) patients had higher SUA. Hyperuricemia is a potential risk factor for CKD progression. These findings propose that SUA may play a critical role in inflammatory status in stage III CKD patients.

Keywords: Chronic kidney disease, Hyperuricaemia, Inflammatory marker, Uric acid

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INTRODUCTION

Chronic kidney disease (CKD) is one of the most common progressive renal disorders worldwide. It is defined either as an indication of renal damage or by a decrease in glomerular filtration rate (GFR) and can further be delineated as CKD stage 1-5 depending on GFR.[1,2] CKD may progress to renal failure and hence compromises dialysis and renal transplant; which is commonly associated with considerable increases in morbidity and mortality. Several risk factors are associated with the progress of CKD, in particular hyperuricemia: an increase in the serum uric acid (SUA), diabetes mellitus, hypertension, dyslipidemia, proteinuria, hypoalbuminemia and smoking.[3,4]

Researchers have observed a close relationship between systemic inflammation and CKD. Tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6) are components of the Th-1 pro-inflammatory cytokine response that may play an important function in CKD.[5] Interleukin-10 (IL-10) is a cytokine with anti-inflammatory and immune-regulatory functions, part of the Th-2 response, which is part of the self-regulating balance of the immune system.[6]

Dyslipidemia is commonly associated with CKD.[3] Abnormal lipoprotein metabolism has been identified as having a strong association with CKD and is associated with declining GFR and increasing proteinuria.[7] Early detection and treatment of lipid disorders will reduce the risk factor to accelerate CKD progression.[8]

Hyperuricemia is a strong predictor of gout, inflammatory arthritis resulting from urate crystal deposition within synovial joints. Uric acid is actively secreted by renal tubular cells and renal impairment is a strong risk factor for both hyperuricaemia and gout. Hyperuricemia is identified as an independent harmful cause for morbidity and premature mortality due to CKD. While a decrease influences reduced renal clearance of SUA in GFR, it has also been proposed that hyperuricaemia itself may influence inflammation, a risk factor for the development and progression of CKD.[4] Blood urea and serum creatinine, are both excreted by kidney. Blood urea, is the main nitrogenous end product of protein and amino acids catabolism while creatinine is produced in muscle by breakdown of creatine. They are affected by paranchymal damage and reflect kidney function; being remarkably considered as markers of progression of kidney damage.[9]

In few studies, there are positive associations between SUA and TNF-α in CKD patients, although SUA has been proposed

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as a CKD biomarker. Previous researches have reported that SUA stimulates the synthesis of TNF-α. SUA levels correlate with serum levels of TNF-α, and it has been proposed that SUA may be directly involved in endothelial damage.[3,10]

The current study hypothesis is that SUA is implicated in the systemic inflammatory response in CKD. Therefore, the present study aimed to investigate whether SUA is associated with increased circulating pro-inflammatory and anti-inflammatory cytokines in patients with I, II and III stages of CKD.

MATERIALS AND METHODS

Study Design: A cross-sectional study of a total of 128 CKD patients (45 stage I, 42 stage II and 41 stage III), defined according to the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines,[11] were recruited from the Al-Kadhmiya Teaching Hospital. A 88 healthy control participants were recruited from the recruited patients' family. Participants' demographic data, including height and weight, was recorded. The study was approved by the Ethics Committee of the Al-Kharkh District Health Committee. All participants were fully informed about the study procedures and provided written consent for study participation.

Inclusion Criteria

Patients were adults age 18 years or older, not using lipid-lowering and SUA lowering medications.

Exclusion Criteria

Patients with malignancies or autoimmune diseases.

Sample Collection and Processing

Blood samples were obtained in the morning, after the subjects had fasted for 10 hours, and then isolated by centrifugation at 3000 rpm for 10 minutes to collect serum (Sorvall® 4K15 centrifuge, Thermo Scientific, UK); lipid profile, urea and creatinine were estimated immediately after the collection and rest of the serum was stored at -70°C for the estimation of IL-10, IL-6 and TNF-α.

To determine TNF-α, IL-10, and IL-6 enzyme-linked immunosorbent assay (ELISA) technique and (American Bioscience, USA) and (Bender Med System, Austria) kits were used. The concentration of serum levels of triglycerides, cholesterol, HDL, LDL, and VLDL were determined using commercial kits (Olympus AU-600, Tokyo, Japan). Serum creatinine (Enzymatic method, Arbor Assays, KB02-H kit Michigan, United States), SUA and blood urea (Berthelot-urease method enzymatic colorimetric method, Cambridge, UK).

Statistical Analysis

Descriptive statistics were used to demonstrate the mean ± SD of variables. t-tests were used for comparisons between patients and controls. Statistical analysis was carried out via one-way analysis of variance (ANOVA), followed by Pearson's correlation analysis to find out the linear association between clinical parameters. Graphical/statistics were generated by Prism Version 7 (Graph Pad Software, San Diego, CA) for all assays. $p < 0.05$ was considered to indicate statistical significant.

RESULTS

Participants' demographics are presented in Table 1. Patients (stage I, stage II and III CKD) and control groups were similar concerning age, BMI, and education. GFR was significantly different ($p < 0.05$) between the stage III CKD patients and the control group.

Biochemical parameters were examined in patient and control groups and are presented in Table 2.

As shown in Table 2, TNF-α concentration from patients with stages I, II and III of CKD were higher than those for the control group ($p < 0.05$, $p < 0.001$, and $p << 0.0001$, respectively). The SUA and IL-6 levels were statistically higher in CKD stage III patients ($p < 0.0001$) than in the control group, whereas the difference between stage I, II and control groups was not significant. Blood urea and serum creatinine values were different among stage I, II ($p < 0.05$), and stage III ($p < 0.0001$) CKD patients, compared with controls as shown in Figure1. The stages III CKD patient group had significantly higher levels of serum triglyceride ($p<0.0001$) and serum VLDL ($p < 0.05$) and significantly lower levels of HDL ($p < 0.001$), compared to controls. IL-10, cholesterol, and LDL levels were higher in the patient groups compared to controls; differences were not significant.

A positive correlation was shown using Pearson's correlation analysis in stage IIICKD patients between SUA and TNF-α ($r = 0.903$, $p=0.0001$; Figure 1A), IL-6 ($r = 0.865$, $p= 0.0001$; Figure 1B), IL-10 ($r = 0.745$, $p=0.0001$; Figure 1C), triglyceride ($r = 0.651$, $p=0.0002$; Figure 1D), and VLDL

Table 1: Participants' demographic data

Demographic variable	*Stage I CKD (n=42)*	*Stage II CKD (n= 45)*	*Stage III CKD (n=41)*	*Control (n= 88)*
Age (years)mean	56.5 ± 11.3	56.9 ± 6.7	58 ± 8.2	51.2 ± 9.5
BMI (kg/m2) mean	23.9 ± 2.6	22.4 ± 1.7	21.6 ± 2.3	25.6 ± 6.1
Male/Female	27/18	26/16	22/19	55/33
GFR (mL/min) mean	85 ± 4	71.5 ± 6	57 ± 7*	94 ± 3
Education:	19	19	13	10
Illiterate Secondary	15	10	16	14
Tertiary	11	13	12	14

BMI: body mass index,GFR: glomerular filtration rate.
Data are presented as mean ± standard deviation. The differences is statistically significant, *$p < 0.05$.

Table 2: One-way ANOVA comparison of the biochemical parameters between CKD patients and controls

Parameters	*Stage I CKD (n = 45)*	*Stage II CKD (n = 42)*	*Stage III CKD (n = 41)*	*Control (n = 88)*
IL-10 (pg/mL)	0.09 ± 0.03	0.10 ± 0.01	0.11 ± 0.02	0.09 ± 0.02
IL-6 (pg/mL)	2.9 ± 2.3	3.2 ± 1.9	3.5 ± 1.3***	2.1 ± 1.1
TNF-α (pg/mL)	2.9 ± 2.05*	4.7 ± 1.5**	5.4 ± 1.06***	2.2 ± 1.40
Blood urea (mg/dL)	61.71 ± 7.5*	98.12 ± 5.1*	116.91 ± 8.3***	23.39 ± 5.5
Serum creatinine (mg/dL)	2.36 ± 1.8*	3.6 ± 2.6*	5.82 ± 2.3***	0.70 ± 0.1
Serum uric acid (mg/dL)	5.16 ± 1.2	6.9 ± 1.6	7.66 ± 0.7***	5.01 ± 0.8
Serum cholesterol (mg/dL)	185.94 ± 29.2	196.61 ± 8.3	204.6 ± 9.8	134.8 ± 40.9
Serum triglyceride (mg/dL)	124.56 ± 13.7	149.21 ± 15.1	162.14 ± 18.4***	60.6 ± 11.2
Serum HDL (mg/dL)	32.03 ± 6.4	24.2 ± 4.1	17.6 ± 6.8**	46.90 ± 8.7
Serum LDL (mg/dL)	73.86 ± 20.8	78.3 ± 11.5	79.48 ± 18.1	74.10 ± 12.3
Serum VLDL (mg/dL)	22.55 ± 7.4	25.21 ± 5.1	33.16 ± 10.1*	20.15 ± 3.3

CKD: chronic kidney diseases, SUA: serum uric acid, TNF- α: tumor necrosis factor-α, IL-6: interleukin-6, IL-10: interleukin-10, HDL: High density lipoprotein, LDL: Low density lipoprotein, VLDL: Very low density lipoprotein.
Values of the parameters are Mean ± Standard deviation.
The differences are statistically significant *p<0.05, **p<0.001, ***p<0.0001

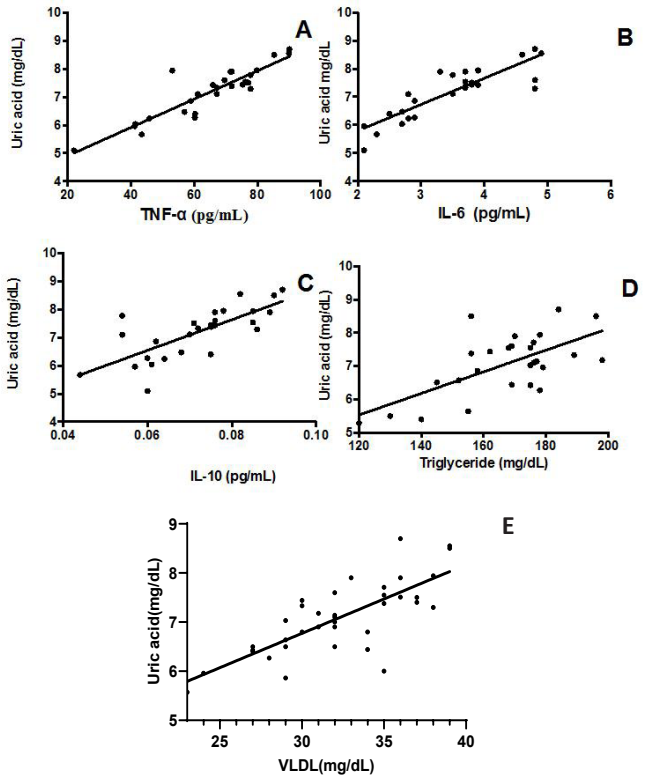

Figure 1: Correlation of SUA with TNF-α (A), IL-6 (B), IL-10 (C), Triglyceride (D) and VLDL (E) in patients of stage III CKD;(r=0.903, p=0.0001); (r=0.865, p=0.0001); (r=0.745, p=0.0001); (r=0.651, p=0.0002) and (r=0.7606, p=0.0001), respectively.

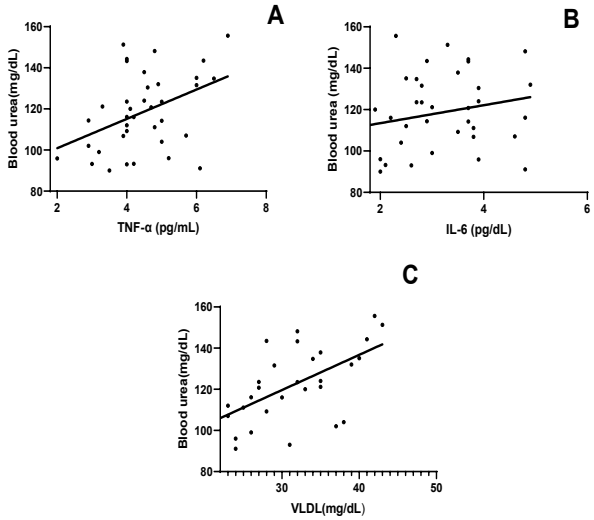

Figure 2: Correlation of blood urea with TNF-α (A), IL-6 (B) and VLDL (C) in patients of stage III CKD;(r=0.4181, p=0.01); (r=0.2127, p=0206); (r=0.6369, p=0001), respectively

(r= 0.7606, p=0.0001; Figure 1E). Likewise, there was correlation between blood urea and TNF-α, IL-6 and VLDL; (r=0.4181, p=0.01; Figure 2A), (r=0.2127, p= 0206; Figure 2B), (r=0.6369, p= 0.0001; Figure 2C) respectively and between serum creatinine and TNF-α (A), IL-6 (B) and VLDL (C); (r=0.4603, p=0.001; Figure 3A), (r=0.1153, p=0.5298; Figure 3B), (r=0.2678, p=0.1383; Figure 3C), respectively. While SUA showed a negative correlation in stage III CKD patients with HDL and GFR (r=-0.459, p=0.0159; Figure 4A) and (r=-0.4229, p=0.0066; Figure 4B) respectively. In addition, serum creatinine and Blood urea revealed negative correlation with HDL in stage III CKD patients (r=-0.5220, p=0.0009; Figure 5A) and (r=-0.2991, p=0.0721; Figure 5B), respectively. While no correlation in stage I CKD patients and controls was found.

DISCUSSION

The important result of the current study was the significant association between levels of SUA, TNF-α, and IL-6 in Iraqi patients of stage III CKD. These findings verify the hypothesis that SUA is involved in inflammation by activating the release of inflammatory cytokines.

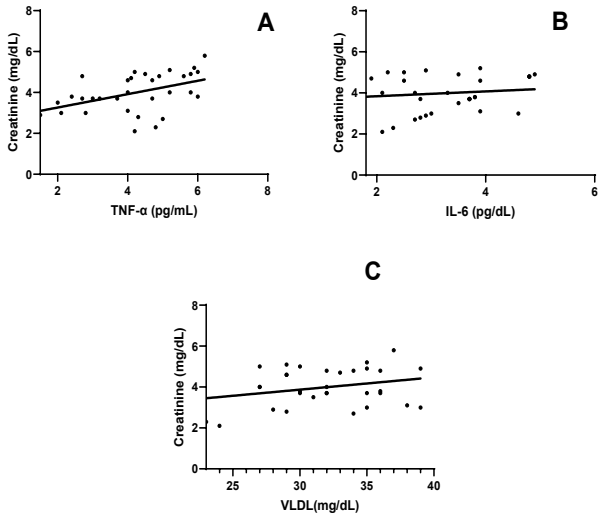

Figure 3: Correlation of serum creatinine with TNF-α (A), IL-6 (B) and VLDL (C) in patients of stage III CKD; (r=0.4603, p=0.001); (r=0.1153, p=0.5298) and (r=0.2678, p=0.1383), respectively

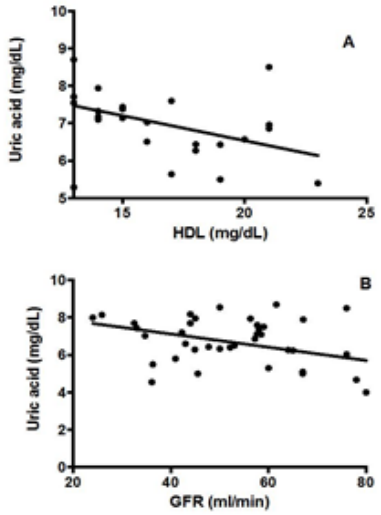

Figure 4: Correlation between HDL (A); GFR (B) and SUA in patients of stage III CKD; (r= -0.459, p=0.0159) and (r=-0.4229, p=0.0066), respectively

The role of hyperuricemia in CKD progression is still under debate. Hyperuricaemia is associated with deteriorating renal function in CKD, but one of these associations is linked to reducing renal urate clearance in the renal tubules. However, high urate blood levels themselves may also lead to an inflammatory reaction, hence a deterioration in renal function, through several mechanisms: losing cell-to-cell contact in renal tubular cells by decreasing the expression of the epithelial cell. Another mechanism is attributed to oxidative changes through nicotinamide adenine dinucleotide phosphate oxidases (NADPH) which promote apoptosis.[12] The incidence and prevalence of CKD may be increased in hyperuricemia and one condition could accentuate the other.[13,14]

CKD is associated with a systemic inflammatory process, most commonly in advanced stage CKD. Several studies have

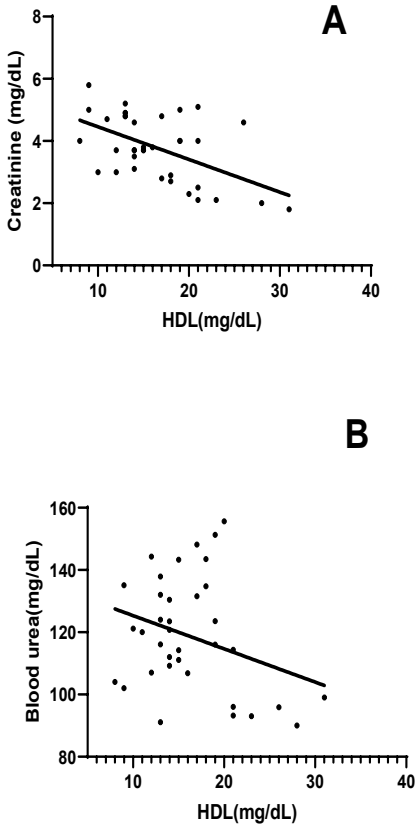

Figure 5: Correlation of HDL with serum creatinine (A) and blood urea (B) in patients of stage III CKD; (r=-0.5220, p=0.0009) and (r=-0.2991, p=0.0721), respectively

reported that raised SUA level has been linked with oxidative stress and inflammatory condition in some pathological status. Complex pathways that can stimulate oxidative stress and disorder of endothelial cells are involved in the mechanisms by which SUA induces inflammation.[10]

Shahbazian *et al.*[14] reported that the prevalence of SUA level may rise 40 to 60% in stages I, II and III CKD patients, which may lead to an inflammatory response and it showed that plasma uric acid levels in CKD patients are higher than normal. A study by Mutluary *et al.*[15] observed that SUA is a factor that contributes to identifying premature vascular lesions in CKD patients.

This study found a positive correlation between SUA and TNF-α, and IL-6 in stage III ($p<0.0001$) CKD groups compared to controls. Our result agreed with the finding of Lobo, *et al.*[10] who observed a positive correlation between SUA and both TNF-α and IL-6. Our findings may suggest that SUA levels may serve as a predictive marker for CKD progress in Iraqi patients.

A considerable number of studies has known the role of traditional and nontraditional risk factors, e.g., elevated LDL, cholesterol, and HDL.[16,17] Tbahriti, *et al.*[18] observed that elevated inflammatory markers are associated with CKD due to raised pro-inflammatory cytokines, although significantly increased levels of SUA, TNF-α, and IL-6 in

stage III CKD patients ($p<0.0001$). Therefore, it is uncertain whether it is renal insufficiency, CKD, causing chronic inflammation in stage I CKD, which indicates patients' health outcome.[19]

Lipoprotein metabolism is altered in most patients with renal insufficiency, resulting in atherosclerosis and lipoprotein accumulation in glomerular structures.[15,20,21] In CKD patients' dyslipidaemia is characterized by increased levels of TG, LDL, and reduced HDL. Nevertheless, total cholesterol might be normal or decreased particularly in malnutrition cases. Different studies have reported that it is still unclear if TG, total cholesterol, and LDL impact CKD progression.[22] The current study revealed that the serum level of total cholesterol was insignificant in CKD patients compared to the controls. In addition, triglyceride levels showed higher significant difference ($p=0.0001$) between stage III CKD patients and controls. This result was in agreement with the finding of Yang, *et al.*[23] whereby the triglyceride values were higher in CKD patients than the control group ($p<0.01$).

In the current study, HDL level was significantly lower for stage III CKD patients than controls, and inversely correlated to SUA level. Peng observed a similar finding, *et al.* [24] however opposing results were obtained by Basok, *et al.* [25] Following our results, Singh, *et al.*[26] observed that the serum LDL level was higher in patients with CKD. Atherogenesis is stimulated by LDL cytotoxicity and leukocyte recruitment that alters the vascular endothelium, hence increasing risk. Many studies have shown the increased LDL levels in patients with CVD and CKD,[26,27] suggesting that in CKD patients, the increased level of LDL could be contributed to the improvement of the atherogenic process. In addition, the level of VLDL in the current study was higher in stage III CKD patients than controls which support previous study.[26]

In our study, a significant difference was found in the level of creatinine in stage I, II ($p=0.01$) and III ($p=0.0001$) CKD groups, consistent with a previous study of hemodialysis and pre-dialysis patients.[28] Serum creatinine is used as an index to estimate kidney function and indicates many factors besides GFR, such as malnutrition. It is considered as a marker for nutritional status and its low levels are associated with increased mortality.[29] Elevated serum creatinine has been found in 20–40% of hospitalized individuals.[28] The present study also found a high statistically significant difference in blood urea level in stage I, II ($p<0.01$) and III ($p<0.0001$) CKD groups in comparison to controls, compatible with Pandya, *et al.*[30] Renal hypoperfusion can be predicted if the blood urea is elevated, which could be due causing renal failure, cardiac congestion or a low output.[29]

CONCLUSIONS

The data support the argument that hyperuricemia is a potential risk factor for CKD patients, through enhanced inflammatory processes. The increased level of inflammatory markers coexisting with abnormally elevated uric acid suggests that it might contribute to the pro-inflammatory state that characterizes the chronicity of the diseases, particularly in old age. This hypothesis would have to be tested in future clinical studies

The study verifies previous studies that higher SUA levels were significantly associated with decreased renal function and a higher risk of kidney failure in patients. However, further studies, including intervention trials, are needed to determine causality relationships between SUA and inflammatory markers and their relationship with the progression of CKD stages.

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REFERENCES

1. Gai Z, Wang T, Visentin M, Kullak-Ublick GA, Fu, X, Wang Z. Lipid Accumulation and Chronic Kidney Disease. Nutrients. 2019;11(4):722. https://doi.org/10.3390/nu11040722
2. Aziz MA, Majeed GH, Diab AK, Tamimi RJ. The association of oxidant-antioxidant status in patients with chronic renal failure. Ren Fail. 2016; 38(1):20-26 DOI: 10.3109/0886022X.2015.1103654
3. Mikolasevic I, Žutelija M, Mavrinac V, Orlic L. Dyslipidemia in patients with chronic kidney disease: etiology and management. Int J Nephrol Renovasc Dis. 2017;10:35-45.
4. Liu X, Zhai T, Ma R, Luo C, Wang H, Liu L. Effects of uric acid-lowering therapy on the progression of chronic kidney disease: a systematic review and meta-analysis. Renal failure. 2018;40(1):289-297.
5. Yilmaz MI, Solak Y, Saglam M, Cayci T, Acikel C, Unal HU, Eyileten T, Oguz Y, Sari S, Carrero JJ, Stenvinkel P. The relationship between IL-10 levels and cardiovascular events in patients with CKD. Clin J Am Soc Nephrol. 2014;9(7):1207-1216.
6. Ezekiel UN, Joshua O, Ross SR, Phillip TB, Eunice OI. Prevalence and correlations of hepatorenal functions in diabetes and cardiovascular disease among stratified adults. Acta Bio Medica: Atenei Parmensis. 2019;90(1):97-103.
7. Tsuruya K, Yoshida H, Nagata M, Kitazono T, Hirakata H, Iseki K, Moriyama T, Yamagata K, Yoshida H, Fujimoto S, Asahi K. Association of the triglycerides to high-density lipoprotein cholesterol ratio with the risk of chronic kidney disease: analysis in a large Japanese population. Atherosclerosis. 2014;233(1):260-267.
8. Adejumo OA, Okaka EI, Ojogwu LI. Lipid profile in pre-dialysis chronic kidney disease patients in southern Nigeria. Ghana medical journal. 2016;50(1):44-49.
9. Damiati S. A pilot study to assess Kidney functions and toxic dimethyl-arginines as risk biomarkers in women with low vitamin D levels. Journal of medical biochemistry. 2019;38(2):145-152.
10. Lobo JC, Stockler-Pinto MB, da Nóbrega AC, Carraro-Eduardo JC, Mafra D. Is there association between uric acid and inflammation in hemodialysis patients?. Renal failure. 2013;35(3):361-366.
11. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney inter. 2012;3:1-150.
12. Giordano C, Karasik O, King-Morris K, Asmar A. Uric Acid as a Marker of Kidney Disease: Review of the Current Literature. Dis Markers. 2015; 2015:1-6| https://doi.org/10.1155/2015/382918

13. Sah OS, Qing YX. Associations between hyperuricemia and chronic kidney disease: a review. Nephro-urology monthly. 2015;7(3):5
14. Shahbazian H, Rezaii I. Diabetic kidney disease; review of the current knowledge. J Renal Inj Prev. 2013;2(2):73-80.
15. Mutluay R, Konca C, Erten Y, Paşaoğlu H, Değer SM, Ağirgün C, et al. Predictive markers of asymptomic atherosclerosis in end-stage renal disease patients. Ren Fail. 2010;32:448-454.
16. Locatelli F, Canaud B, Eckardt KU, Stenvinkel P, Wanner C, Zoccali C. Oxidative stress in end-stage renal disease: an emerging threat to patient outcome. Nephrol Dial Transplant. 2003;18(7):1272-1280.
17. Oberg BP, McMenamin E, Lucas F. L. E. E., McMonagle, E., Morrow, J.,Ikizler, et al. Increased prevalence of oxidant stress and inflammation in patients with moderate to severe chronic kidney disease. Kidney Int. 2004; 65:1009-1016.
18. Tbahriti HF, Meknassi D, Moussaoui R, Messaoudi, A., Zemour, L., Kaddous, A, et al. Inflammatory status in chronic renal failure: The role of homocysteinemia and pro-inflammatory cytokines. World J Nephrol. 2013; 2(2):31-37.
19. Dungey M, Hull KL, Smith AC, Burton JO, Bishop NC. Inflammatory factors and exercise in chronic kidney disease. Int J Endocrinol. 2013;2013:1-13.
20. Olexa P, Olexovà M, Gonsorcîk J, Tkàc I, Kiseľovà J, Oleinîkovà M. Uric acid-a marker for systemic inflammatory response in patients with congestive heart failure? Wien. Klin. Wochenschr. 2002;114(5-6):211-215.
21. Lin YH, Huang JC, Wu PY, Chen SC, Chiu YW, Chang JM. Greater low density lipoprotein cholesterol variability is associated with increased progression to dialysis in patients with chronic kidney disease stage 3. Oncotarget. 2018;9(3):3242-3253.
22. Liang X, Ye M, Tao M, Zheng D, Cai1 R, Zhu Y. The association between dyslipidemia and the incidence of chronic kidney disease in the general Zhejiang population: a retrospective study. BMC Nephrology. 2020;21:2-9
23. Yang GY, Chen HH, Huang, MT, Raya JL, Yang JH, Chen CH. Pro-apoptoic low density lipoprotein subfractions in type II diabetes. Atherosclerosis. 2007;193:283-291.
24. Peng TC, Wang CC, Kao TW, Chan JYH, Yang YH, Chang YW. Relationship between hyperuricemia and lipid profile in US adults. BioMed Res Int. 2015;2015: 1-7.
25. Basok EK, Atsu N, Rifaioglu MM, Kantarci G, Yildirim A, Tokuc R. Assessment of female sexual function and quality of life in predialysis, peritoneal dialysis, hemodialysis, and renal transplant patients. Int Urol Nephrol. 2009;41(3):473-481. DOI: 10.1007/s11255-008-9475-z
26. Singh RB, Mengi SA, Xu YJ, Ameja AS, Dhalla NS. (2002)
27. Pathogenesis of atherosclerosis: A multifactorial process. Exp Clin Cardiol. 2002; 7(1):40-53.
28. Cadamuro J, Mrazek C, Leichtle A B, Kipman U, Felder TK, Wiedemann H. Influence of centrifugation conditions on the results of 77 routines clinical chemistry analytes using standard vacuum blood collection tubes and the new BD-Barricor tubes. Biochemia medica. 2018;28(1):010704.
29. Seethalakshmi C, Koteeswaran D, Chiranjeevi V. Correlation of serum and salivary biochemical parameters in end stage renal disease patients undergoing hemodislysis in pre and post dialysis state. J Clin Diagn Res. 2014; 8(12):CC12-CC14.
30. Oliveira RB, Kirsztajn GM, Alcantara FP. Kidney disease and calibration of creatinine determination: where are we in Brazil? J Bras Nefrol. 2015;37(4):431-432.
31. Pandya D, Nagrajappa AK, Ravi KS. Assessment and correlation of urea and creatinine levels in saliva and serum of patients with chronic kidney disease, diabetes and hypertension-Aresearchstudy. J Clin Diagn Res. 2016;10(10):ZC58-ZC62.