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Biochemistry Section

Adipokines and their Relation to Endothelial Dysfunction in Patients with Chronic Kidney Disease

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ABSTRACT

Introduction: Chronic Kidney Disease (CKD) patients are at high risk of cardiovascular diseases (CVDs). Reduced nitric oxide (NO) bioavailability is a key element in connecting kidney disease to endothelial dysfunction (ED) and cardiovascular (CV) complications. Further, inflammation is implicated in ED in CKD. Besides these, adipose tissue factors were thought to have a role in inflammation and ED in CKD.

Aim: It is proposed to evaluate the concentration changes of adipokines, inflammatory and ED markers in CKD patients compared to healthy controls. Further, to assess the associations between adipokines, inflammation and ED in CKD patients.

Materials and Methods: A total of 120 CKD patients were included and classified into 3 groups based on Glomerular filtration rate (GFR). Group I (n=40) patients had a GFR between 60-119 ml/min/1.73m^2 (stage I, II), group II (n=40) had 15-59 ml/min/1.73m^2 (stage III, IV) and group III (n=40) had <15 ml/min/1.73m^2 (stage V). Forty healthy subjects-served as controls. Adiponectin, Leptin, Interleukin-10 (IL-10), Interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α) were estimated by ELISA. High sensitivity C-reactive protein (hsCRP) was estimated by immunoturbidimetry and NO by Griess method.

Statistical Analysis: Mann-Whitney U test was used to compare the difference in variables between controls and CKD patients. One-way ANOVA Kruskalwallis test was used for comparison of variables between groups in CKD patients. Spearman's rank correlation was used to explore the associations between variables. Simple univariate linear regression analysis was used to predict the value of variable from another variable.

Results: A significant increase in leptin, IL-6, TNF-α, IL-6/IL-10 ratio, hsCRP and decrease in adiponectin, IL-10, NO was observed in CKD patients compared to controls (p<0.05). In CKD patients, adiponectin, leptin, IL-6, IL-6/IL-10 ratio, TNF-α were significantly increased and IL-10 levels were decreased from group I to group III (p<0.05). In group III CKD patients IL-6 showed a significant negative correlation with NO (r=-0.557; p=0.005). In linear regression analysis also, IL-6 showed a significant negative association with NO (B±SE=-0.038±0.11; p=0.002) in CKD patients.

Conclusion: The present study demonstrates that adipokine levels are altered from initial to final stages of CKD due to renal dysfunction which in association with an exaggerated inflammation may contribute to the ED and CV events.

Keywords: Adiponectin, Cardiovascular disease, Inflammation, Interleukin, Leptin, Tumour necrosis factor-α

INTRODUCTION

Chronic kidney disease (CKD) is a growing public health problem globally, with rising incidence and prevalence. It is increasingly apparent that; individuals with CKD are more likely to die of cardiovascular disease (CVD) than to develop kidney failure [1]. Much of the vascular disease seen in CKD is caused by atherosclerosis. The 'response to injury hypothesis' sets the endothelium as a key mechanism for the development of atherosclerosis. Reduced nitric oxide (NO) bioavailability plays an important role in associating kidney disease to endothelial dysfunction (ED) and cardiovascular (CV) events [2]. Besides this, inflammation is a ubiquitous feature and associated with endothelial injury in CKD [3]. Further, in CKD, this issue has added components because of the appearance of adipose tissue factors (adipokines such as adiponectin, leptin, interleukin-6 (IL-6), interleukin-10 (IL-10) and tumour necrosis factor-α (TNF-α) with the potential of contributing to ED through inflammation [4].

Recent evidence suggests that adiponectin, leptin, IL-6, IL-10 and TNF-α may play important roles in uremic cachexia [5]. The levels of these adipokines and cytokines may be altered in renal failure and these altered levels in CKD are involved in progression of inflammation and ED [6,7]. Further, these adipokines are involved directly or indirectly in ED by augmenting inflammation and reducing bioavailability of NO in CKD [8]. Thus, available findings suggest that adipokines may be a missing link between inflammation and ED in CKD [9]. However, there are sparse and conflicting data on the concentration changes of adipokines in CKD [10-13]. Available studies focussed on stage V (end stage renal disease {ESRD}) CKD patients, but not included all the stages especially, earlier stages of CKD [10,12]. Thus, studies on concentration changes of adipokines at earlier stages of CKD and their association with inflammation and ED are limited.

Hence, the present study is proposed to evaluate: (i) the concentration changes of adipokines, inflammatory and ED markers in CKD patients compared to healthy controls; (ii) the concentration changes of adipokines, inflammatory and ED markers at various stages of CKD (from stage I to V) patients; (iii) the associations between adipokines, inflammation and ED in CKD patients; and (iv) the contribution of adipokines and inflammation in the production of ED in CKD.

MATERIALS AND METHODS

The present study was conducted in the Department of Biochemistry, Sri Venkateswara Institute of Medical Sciences (SVIMS), Tirupati, Andhra Pradesh, India. All subjects were informed about the study and written informed consent was obtained from the patients enrolled. The study was approved by the Institutional ethical committee (IEC).

Subjects

Patients attending the Department of Nephrology, SVIMS hospital, with established diagnosis of CKD were subjects of the study. A total of (n=120) CKD patients were included in the study. Patients were classified into three groups based on glomerular filtration rate

(GFR) calculated from serum creatinine, using Cockcroft-Gault (CG) equation. Group I (n=40) consists of patients with mild kidney damage with a GFR between 60 and 119 ml/min/1.73m^2 (stage I, II CKD). Group II (n=40) consists of patients with moderate to severe kidney damage and GFR between 15 and 59 ml/min/1.73m^2 (stage III, IV CKD). Group III (n=40) consists of patients with ESRD (stage V CKD) patients with GFR <15 ml/min/1.73m^2. Forty healthy subjects served as controls. Adult patients with stage I-V CKD were included. Patients undergoing haemodialysis, peritoneal dialysis, patients with organ transplantation, with active or chronic infections, using anti-inflammatory or immunosuppressive drugs and of paediatric age group were excluded.

Sample Collection

Following an overnight fasting, 5ml of blood samples were drawn from the ante cubital vein of all the study subjects. Two (2) ml of blood drawn was transferred into a plain tube and 3ml was transferred into heparinized tubes. The plain tube samples were allowed to stand for 30 min, centrifuged at 3000 rpm for 15 minutes and the serum was separated. The heparinized tube samples were centrifuged immediately and the plasma was separated. The serum, plasma and haemolysate samples were aliquoted and stored in separate vials at -80^{0}C in deep freezer (Thermo Fischer Scientific) until analysis. Plasma was used for the estimations of adiponectin, leptin, IL-6, IL-10, TNF-α, high sensitivity C-reactive protein (hsCRP) and NO. Serum samples were used for estimations of urea and creatinine.

Laboratory Analysis

Demographic characteristics, metabolic factors and laboratory data were collected. Biochemical analysis which includes adipokines and cytokines such as adiponectin, leptin, IL-10, IL-6 and TNF-α was done by solid phase sandwich Enzyme Linked Immunosorbent Assay (ELISA) technique using ELISA commercial test kits purchased for human adiponectin, leptin, IL-10, from AviBion (Orgenium Laboratories Division, Vantaa, FINLAND), human Interleukin-6 (DIA Source, Belgium), human TNF-α (Assay Pro, Belgium) on Chemwell fully automated analyser. The level of hsCRP was estimated by Immunoturbidimetry method using commercial kit on Beckman Synchron DxC 600 fully automated analyser, USA. NO was estimated as nitrates on UV/VIS spectrophotometer, USA using Griess reaction [14].

STATISTICAL ANALYSIS

All the analysis was performed using statistical software, SPSS software for Windows 11.5 program (SPSS Inc, Chicago, IL, USA). Comparisons of means between controls and CKD patients were analysed using nonparametric Mann-Whitney test. Comparisons of means among CKD stages were analysed using nonparametric one-way analysis of variance (ANOVA), Kruskalwallis test. Correlation among the variables in CKD patients was performed using Spearman's rank correlation. Contribution of ED in CKD patients was performed using simple univariate linear regression analysis. A p-value of less than 0.05 was considered as statistically significant.

RESULTS

General Characteristics of Controls and CKD Patients

The base-line and biochemical characteristics of controls and CKD patients studied were shown in [Table/Fig-1]. Among the 120 patients, 86 (71.66%) were males and 34 (28.33%) were females. Co-morbidity conditions included 63 (52.5%) patients with diabetic nephropathy, 18 (15.0%) patients with chronic glomerulo nephritis, 27 (22.5%) patients with chronic interstitial nephritis, 09 (7.5%) patients with hypertensive nephropathy and 03 (2.5%) patients with other conditions. There was an increase in urea, creatinine and decrease in eGFR levels in CKD patients. No change in BMI was observed between controls and CKD patients.

Adipokines, Inflammatory and ED Markers in Controls and CKD Patients

The levels were assessed between controls and CKD patients and are presented in [Table/Fig-2]. Adiponectin and NO were significantly lower whereas, IL-6, IL-6/IL-10 ratio and hsCRP were higher in CKD patients when compared to control group. The changes observed among CKD patients from group I to group III are shown in [Table/Fig-3]. Adiponectin, leptin, IL-6, IL-6/IL-10 ratio and TNF-α were significantly increased whereas IL-10 levels were significantly decreased across the three groups of CKD. Although hsCRP was increased and NO was decreased, the difference was not statistically significant.

S. No.	Parameter	Controls	Group I	Group II	Group III
1.	Number of Patients (n) 40	40	40	40	40
2.	Gender (M/F)	21/19	26/14	31/09	29/11
3.	Age (Years)	42.25±10.10	52.90±14.61	56.15±8.91	53.73±13.76*
4.	BMI (kg/m^2)	23.44±3.64	25.75±9.02	23.63±4.70	21.97±4.44**
5.	Urea (mg/dL)	18.80±3.86	29.67±12.09	54.93±16.66	114.50±39.24*
6.	Creatinine (mg/dL)	0.67±0.16	0.94±0.37	2.34±1.03	6.75±3.79*
7.	eGFR (ml/min)	119.86±39.25	98.12±38.55	31.81±13.67	11.35±6.36*

[Table/Fig-1]: Baseline characteristics of healthy controls and CKD patients.
Data was expressed as Mean ± SD (standard deviation); BMI: body mass index; eGFR: estimated glomerular filtration rate; CKD group I (stage I, II), group II (stage III, IV); group III (stage V).
*significant, p<0.05; **p>0.05 not significant (NS)

S. No.	Parameter	Controls (n=40)	CKD Patients (n=120)	p-value
1.	Adiponectin (ng/mL)	27425.00±1922.60	19477.00±1407.00	0.037*
2.	Leptin (pg/mL)	9044.60±1679.80	17219.00±1864.90	0.056
3.	IL-6 (pg/mL)	20.19±4.13	80.46±10.00	<0.001*
4.	IL-10 (pg/mL)	2.27±0.23	2.41±0.19	0.440
5.	TNF-α (pg/mL)	0.33±0.02	0.36±0.02	0.921
6.	IL-6/ IL-10	12.11±2.31	119.70±22.75	0.002*
7.	hsCRP (mg/dL)	0.09±0.01	0.60±0.09	<0.001*
8.	NO (µmol/L)	36.79±1.09	27.37±0.69	<0.001*

[Table/Fig-2]: Comparison of adipokines inflammatory and endothelial dysfunction markers in healthy controls and CKD patients.
Data was expressed as Mean±SEM (standard error of mean); CKD group I (stage I, II), group II (stage III, IV); group III (stage V). Comparison was made using the Mann-Whitney Test; *statistically significant,
IL-6: Interleukin-6, IL-10: Interleukin-10, TNF-α: Tumour necrosis factor-α, hsCRP: high sensitive C reactive protein, NO: nitric oxide.

Parameter	Group I (n=40)	Group II (n=40)	Group III (n=40)	p-value
Adiponectin (ng/mL)	4128.20±671.08	19876.00±2412.60	33660.00±627.93	<0.001*
Leptin (pg/mL)	8370.00±987.80	12033.00±2459.90	30146.00±3962.40	0.004*
IL-6 (pg/mL)	23.58±3.81	26.84±3.77	186.50±19.85	<0.001*
IL-10 (pg/mL)	3.19±0.26	2.86±0.37	1.32±0.27	<0.001*
TNF-α (pg/mL)	0.30±0.03	0.27±0.02	0.50±0.04	<0.001*
IL-6/ IL-10	8.95±1.85	24.46±5.91	99.86±51.07	<0.001*
hs CRP (mg/dL)	0.41±0.05	0.97±0.25	0.42±0.08	0.226
NO (µmol/L)	28.51±0.56	26.05±1.04	27.62±1.57	0.192

[Table/Fig-3]: Comparison of adipokines inflammatory and endothelial dysfunction markers between CKD groups.
Data was expressed as Mean ± SEM (standard error of mean); CKD group I (stage I, II), group II (stage III, IV), group III (stage V). Comparison was made using the one-way ANOVA Kruskalwallis's test; *statistically significant.
IL-6: Interleukin-6, IL-10: Interleukin-10, TNF-α: Tumour necrosis factor-α, hsCRP: high sensitive C reactive protein, NO: nitric oxide.

Associations Among Adipokines, Inflammatory and ED Markers in CKD

The associations observed among the parameters studied are presented in [Tables/Fig-4,5]. In CKD patients, adiponectin showed a significant positive correlation with leptin (r=+0.207; p=0.027, IL-6 (r=+0.449; p<0.001), IL-6/IL-10 ratio (r=+0.612; p<0.001) and a significant negative correlation with IL-10 (r=-0.480; p<0.001). Leptin showed a significant positive correlation with IL-6 (r=+0.357; p<0.001), and IL-6/IL-10 ratio (r=+0.329; p=0.001). IL-6 showed a significant positive correlation with TNF-α (r=+0.374; p<0.001), IL-6/IL-10 ratio (r=+0.872; p<0.001) and a significant negative correlation with IL-10 (r=-0.327; p=0.001) and NO (r=-0.557; p=0.005). TNF-α showed a significant positive correlation with IL-6/IL-10 ratio (r=+0.368; p<0.001). Creatinine had a significant positive correlation with adiponectin (r=+0.649; p<0.001), leptin (r=+0.222; p=0.017), IL-6 (r=+0.553; p<0.001), TNF-α (r=+0.262; p=0.006), IL-6/IL-10 ratio (r=+0.736; p=0.017) and negative correlation with IL-10 (r=-0.562; p<0.001).

Determination of Significant Contributors for ED in CKD Patients

Univariate linear regression analysis to assess the principal determinants of ED showed that IL-6 (β=-0.038; p=0.002), was independently associated with ED [Table/Fig-6]. Other adipokines adiponectin, leptin, IL-10 and TNF-α were not associated with ED. Also, there was no significant association between inflammatory marker hsCRP and ED marker NO (p=0.514).

Parameter	r-value	p-value
Adiponectin Vs Leptin	0.207	0.027
Adiponectin Vs IL-10	-0.480	<0.001
Adiponectin Vs IL-6	0.449	<0.001
Adiponectin Vs TNF-α	0.305	0.001
Adiponectin Vs IL-6/IL-10	0.612	<0.001
Leptin Vs IL-6	0.357	<0.001
Leptin Vs IL-6/IL-10	0.329	0.001
IL-6 Vs TNF-α	0.374	<0.001
IL-6 Vs IL-6/IL-10	0.872	<0.001
TNF-α Vs IL-6/IL-10	0.368	<0.001
IL-10 Vs IL-6	-0.327	0.001
IL-10 Vs IL-6/IL-10	-0.722	<0.001
Creatinine Vs Adiponectin	0.649	<0.001
Creatinine Vs Leptin	0.222	0.017
Creatinine Vs IL-6	0.553	<0.001
Creatinine Vs IL-10	-0.562	<0.001
Creatinine VsTNF-α	0.262	0.006

[Table/Fig-4]: Correlation analysis in CKD patients.
Correlation between variables were made using spearman's correlation
IL-6: Interleukin-6; IL-10: Interleukin-10; TNF-α: Tumour necrosis factor-α

Parameter	r-value	p-value
Group I (Stage I, II)		
IL-6VsIL-6/ IL-10	0.924	<0.001
Group II (Stage III, IV)		
IL-6 Vs IL-6/IL-10	0.756	<0.001
IL-10 VsIL-6/IL-10	-0.800	<0.001
hs CRP Vs NO	-0.422	0.057
Group III (Stage V)		
Adiponectin Vs IL-10	-0.354	0.029
IL-6 Vs IL-6/IL-10	0.605	<0.001
IL-6 Vs NO	-0.557	0.005
IL-10 Vs IL-6/IL-10	-0.654	<0.001
hs CRP Vs NO	-0.411	0.051

[Table/Fig-5]: Correlation analysis at various groups (stages) of CKD patients.
Correlation between variables were made using spearman's correlation
IL-6: Interleukin-6; IL-10: Interleukin-10; TNF-α: Tumour necrosis factor-α

Independent variable		B±SE	95% CI	p
1.	IL-6	-0.038±0.11	-0.061-0.015	0.002
2.	IL-10	-0.616±6.71	-14.580-13.348	0.928
3.	TNF-α	-5.745±6.596	-19.389-7.900	0.393
4.	hs CRP	1.772± 2.671	3.574-7.297	0.514

[Table/Fig-6]: Factors contributing to endothelial dysfunction.
*Dependent Variable: Nitric Oxide;
B: unstandardized coefficient; SE: standard error;CI: confidence interval
IL-6: Interleukin-6; IL-10: Interleukin-10; TNF-α: Tumour necrosis factor-α; hs CRP: high sensitive C reactive protein

DISCUSSION

Adipokines

In the present study, adiponectin levels were significantly lower in CKD patients than healthy controls (p=0.037). However, the levels were significantly elevated as the renal function deteriorates and the levels were higher in group III (stage V). A possible explanation for this can be decreased renal adiponectin clearance in patients with CKD [10,15-17]. Further, adiponectin directly correlated with serum creatinine (r=0.649; p<0.001), in CKD patients which indicates an increase in adiponectin with decreasing renal function. In the present study, adiponectin showed a positive correlation with leptin, IL-6 and TNF-α in CKD patients (r=0.207; p=0.027, r=0.449; p<0.001 and r=0.305; p=0.001) and thus, it is possible that adiponectin may play a compensatory role in the presence of an inflammatory milieu as an anti-inflammatory factor [17,18].

Similarly, a significant increase in leptin was observed in comparison with preceding group in CKD patients and the levels were higher in group III (p<0.001). Leptin is cleared by kidney. Increased levels in CKD patients (p=0.004) may be due to deficient renal metabolism and also possibly by increased leptin production which in turn may result from increased IL-6 and TNF-α levels in the state of enhanced systemic inflammatory milieu [19,20]. In the present study, leptin was positively correlated with increased IL-6 and IL-6/IL-10 ratio (r=0.357; p<0.001; r=0.329; p<0.001) in CKD patients, suggesting that inflammation and hyperleptinaemia are associated in CKD [21].

In the present study, IL-6 was significantly elevated in CKD patients compared to healthy controls (p<0.001). Also, IL-6 was significantly higher in group III (stage V) compared to group I (stage I&II) and II (stage III&IV) CKD patients. Similarly, TNF-α levels were elevated in group III (stage V) CKD patients compared to group I (stage I&II) and II (stage III&IV) (p<0.001). These observations are in agreement with previous reports [2,13,16,22-24]. The elevated plasma IL-6 and TNF-α level in CKD patients may be related to loss of kidney function, and activated monocytes and macrophages [11]. Further, it is possible that an increased IL-6 production is an early response to renal disease rather than a mere accumulation phenomenon attributable to loss of renal function [24]. Both IL-6 and TNF-α were directly correlated with serum creatinine (r=0.553; p<0.001 and r=0.262; p=0.006), indicating that reduced GFR could lead to their defective clearance from the plasma [22]. A strong positive correlation between IL-6 and TNF-α was observed (r=0.374; p<0.001). This indicates both could be responsible for production of each other [23].

The levels of IL-10 were increased in CKD patients compared to controls. In contrast to the above result, in CKD patients, there was a decrease in IL-10 levels from group I to group III CKD patients and the levels were significant in comparison with preceding group (p<0.001). A significant negative correlation of IL-10 with IL-6 and IL-6/IL-10 ratio was observed in CKD patients (r=-0.327; p=0.001 and r=-0.722; p<0.001) Further, a significant negative correlation with renal function (serum creatinine) was observed in CKD patients

(r=-0.562; p<0.001). These findings suggest that beneficial effects of IL-10 plasma levels are restricted in patients with CKD by elevated plasma levels of IL-6, TNF-α and hsCRP, which is an indication of an enhanced systemic inflammatory response [25].

IL-6/IL-10 Ratio

The IL-6/IL-10 ratio may reflect a proinflammatory/anti-inflammatory balance. Therefore, we examined IL-6/IL-10 ratio in CKD patients and found that there was a significant increase in CKD patients compared to controls (p=0.002). Moreover, the IL-6/IL-10 ratio significantly increased among the CKD patients with progression of disease (p<0.001) indicating a systemic pro-inflammatory state in these patients. The altered IL-6/IL-10 ratio in CKD patients may be due to decreased IL-10 secretion, especially at high CRP levels observed thereby, accentuating the inflammatory process by inhibiting IL-10 and stimulating IL-6, TNF-α [26].

hsCRP

In the present study, the inflammation was assessed by hsCRP which was significantly increased in CKD patients when compared to controls (p<0.001). A similar observation has been reported previously [19,27]. Circulating hsCRP levels elevated in CKD patients may be due to renal function deterioration as well as increase in IL-6 which stimulates production of CRP in the liver [5]. However, there was no change among the three CKD groups. This could be due to that CRP levels fluctuate over time, being mainly influenced by co-morbidity and subclinical infections [28].

Endothelial Dysfunction in CKD

In the present study, ED was analysed by estimating plasma NO levels. In accordance with the earlier reports [29-31] in the present study also, NO levels were significantly lower in CKD patients than controls (p<0.001). NO is decreased in renal disease due to impaired endothelial and renal NO production. Many mechanisms are likely to be responsible, including substrate limitation due to decreased renal synthesis of L-arginine, utilization by arginase, and loss of renal NO production due to reduced renal neuronal NO synthase α (nNOS-α) activity [32]. However, no significant change was observed among the CKD groups. This decline in NO can lead to elevated levels of proinflammatory components (IL-6 and TNF-α) in CKD resulting in attenuated prothrombotic potential of endothelial cells which may lead to the development of ED [33].

Adipokine, Inflammation and Endothelial Dysfunction

In the present study, adiponectin, leptin, IL-10 and TNF-α did not show significant correlation with NO which is contrary to our expectations.

A negative correlation of IL-6 with NO was observed in group III (stage V CKD) (r=-0.557; p=0.005). Further, in regression analysis also IL-6 was independently associated with NO in CKD patients, which implies adipokines may contribute to ED in CKD.

Apart from adipokines, inflammatory marker hsCRP showed a negative correlation with NO in group II (stage III, IV) and group III (stage V) CKD patients (r=-0.422; p=0.057 and r=-0.411; p=0.051). This supports a direct role of pro inflammatory state in the development of ED [34].

CONCLUSION

In conclusion, the present study demonstrates that, CKD leads to the abnormal concentration change of adipokines due to renal function deterioration. The concentration changes were more pronounced at advanced stages of CKD compared with earlier stages of CKD. There is a substantial increase in inflammation and a pro inflammatory/anti-inflammatory imbalance from initial stages to advanced stages of CKD. The ED was accelerated from earlier to final stages of CKD. Moreover, a significant association was observed for adipokines with inflammation and ED in CKD patients. Thus, CKD leads to disruption in levels for adipokines which in association with an exaggerated inflammation may contribute to the ED and an excess of CV risk in pre dialysis patients from initial to advanced stages of CKD.

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REFERENCES

[1] Ritz E. Cardiovascular disease in patients with chronic kidney disease-An update. *Hipertensriesgovas.* 2010;27:75-79.
[2] Suliman ME, Stenvinkel P. Contribution of inflammation to vascular disease in chronic kidney disease. *Saudi J Kidney Dis Transplant.* 2008;19(3):329-45.
[3] Malyszko J. Mechanism of endothelial dysfunction in chronic kidney disease. *Clin Chim Act.* 2010;41:1412-20.
[4] Axelsson J, Stenvinkel P. The emerging biology of adipose tissue in chronic kidney disease: from fat to facts. *Nephrol Dial Transplant.* 2008;2:3041-46.
[5] Chudek J, Wiecek A. Adipose tissue, inflammation and endothelial dysfunction. *Pharmacol Rep.* 2006;58:S81-88.
[6] Kaisar OM, Johnson DW, Prins JB, Isbel N. The role of novel biomarkers of cardiovascular disease in chronicKidney disease: focus on adiponectin and leptin. *Curr Cardiol Rev.*2008;4:287-92.
[7] Stenvinkel P, Ketteler M, Johnson RJ, Lindholm B, Pecoits-Filho R, Riella M. IL-10, IL-6, and TNF-α: Central factors in the altered cytokine network of uraemia-The good, the bad, and the ugly. *Kidney Int.* 2005;67:1216-33.
[8] Zoccali C. Endothelial dysfunction in CKD: a new player in town? *Nephrol Dial Transplant.* 2008;23:783-85.
[9] Ruster C, Wolf G. Adipokines promote chronic kidney disease. *Nephrol Dial Transplant.* 2013;28(Suppl4):iv8–14.
[10] Kir HM, Eraldemir C, Dervisoglu E, Caglayan C, Kalender B. Effects of chronic kidney disease and type of dialysis on serum levels of adiponectin, TNF-alpha and high sensitive C-reactive protein. *Clin Lab.* 2012;58(5-6):495-500.
[11] Dounousi E, Koliousi E, Papagianni A, Ioannou K, Zikou X, Katopodis K, et al. Mononuclear leukocyte apoptosis and inflammatory markers in patients with chronic kidney disease. *Am J Nephrol.* 2012;36(6):531-36.
[12] Lemos MM, Jancikic AD, Sanches FM, Christofalo DM, Ajzen SA, Carvalho AB, et al. Intima-media thickness is associated with inflammation and traditional cardiovascular risk factors in non-dialysis-dependent patients with chronic kidney disease. *Nephron Clin Pract*. 2010;115(3):189-94.
[13] Yeo ES, Hwang JY, Park JE, Choi YJ, Huh KB, Kim WY. Tumour necrosis factor and C-reactive protein are positively associated with the risk of chronic kidney disease in patients with type 2 diabetes. *Yonsei Med J.* 2010;51(4):519-25.
[14] Cortas NK, Wakid NW. Determination of inorganic nitrate in serum and urine by kinetic cadmium reduction method. *Clin chem.*1990;36(8):1440-43.
[15] Zoccali C, Mallamaci F. Adiponectin and renal disease progression: another epidemiologic conundrum? *Kidney Int.* 2007;71:1195-97.
[16] Sedighi O, Abediankenari S. Relationship between plasma adiponectin level with inflammatory and metabolic markers in patients with chronic kidney disease. *Nephro Urol.* 2014;6(1):11743.
[17] Chitalia N, Raja RB, Bhandara T, Agrawal P, Kaski JC, Jha V, et al. Serum adiponectin and cardiovascular risk in chronic kidney disease and kidney transplantation. *J Nephrol*. 2010;23(1):77-84.
[18] Robinson K, Prins J, Venkatesh B. Clinical review: Adiponectin biology and its role in inflammation and critical illness. *Crit Care.* 2011;15:221.
[19] de Oliveira RB, Liabeuf S, Okazaki H, Lenglet A, Desjardins L, Lemke HD, et al. The clinical impact of plasma leptin levels in a cohort of chronic kidney disease patients. *Clin Kid J.* 2013;6:63-70.
[20] El-Mougi HM, El-Yazeed SA, Yousry ZA, Fattah AA. Serum leptin in patients with chronic renal failure on different modes of management. *The Egy J off Hosp Med.* 2006;25:610-19.
[21] Mak RH, Cheung W, Cone RD, Marks DL. Leptin and inflammation associated cachexia in chronic kidney disease. *Kidney Int.* 2006;69:794-97.
[22] Barreto DV, Barreto FC, Liabeuf S, Temmar M,Lemke HD, Tribouilloy C. Plasma interleukin-6 is independently associatedwith mortality in both haemodialysis and pre-dialysispatients with chronic kidney disease. *Kidney Int.* 2010;77:550-56.
[23] Teplan V, Vyhnanek F, Gurlich R, Haluzik M, Racek J, Vyhnankova I. Increased proinflammatory cytokine production in adipose tissue of obese patients with chronic kidney disease. *Wien Klin Wochenschr*. 2010;122(15-16):466-73.
[24] Spoto B, Leonardis D, Parlongo RM, Pizzini P, Pisano A, Cutrupi S, et al. Plasma cytokines, glomerular filtration rate and adipose tissue cytokines gene expression in chronic kidney disease patients. *Nutr Metab Cardiovasc Dis.* 2012;22(11):981-88.
[25] Biswas S, Ghoshal PK, Mandal SC, Mandal N. Relation of Anti- to Pro-Inflammatory Cytokine Ratios with Acute Myocardial Infarction. *Korean J Intern Med.* 2010; 25:44-50.
[26] Singh U, Devaraj S, Dasu MR, Ciobanu D, Reusch J, Jialal I. C-reactive protein decreases interleukin-10 secretion in activated human monocyte-derived

macrophages via inhibition of cyclic AMP production. *Arterioscler Thromb Vasc Biol.* 2006;26(11):2469-75.
[27] Nand N, Aggarwal HK, Yadav RK, Gupta A, Sharma M. Role of high-sensitivity C-reactive protein as a marker of inflammation in pre-dialysis patients of chronic renal failure. *JIACM.* 2009;10:18-22.
[28] Fisman EZ, Tenenbaum A. The ubiquitous interleukin-6: a time for reappraisal. *Cardiovasc Diabetol.* 2010;9:62.
[29] Schmidt RJ, Baylis C. Total nitric oxide production is low in patients with chronic renal disease. *Kidney Int.* 2000;58(3):1261-26.
[30] Baylis C. Arginine and arginine analogs and nitric oxide production in chronic kidney disease. *Nat Clin Pract Nephrol.* 2006;2:209-20.
[31] Sowjanya N, Bitla AR, Suchitra MM, Siva Kumar V, SrinivasaRao PVLN. Endothelial dysfunction in early stages of chronic kidney disease: a pilot study. *J Clin Sci Res.* 2012;1:109-10.
[32] Baylis C. Nitric oxide deficiency in chronic kidney disease. *Am J Physiol Renal Physiol.* 2008;294:F1-F9.
[33] Bautista LE. Inflammation, endothelial dysfunction, and the risk of high blood pressure: epidemiologic and biological evidence. *J Hum Hypertens.* 2003;17(4):223-30.
[34] Zyga S, Hutchison CA, Stringer S, Gil APR, Christopoulou G, Giata P, et al. Inflammation and Endothelial Dysfunction in the Initiation and Propagation of Cardiovascular Disease in Patients with Chronic Kidney Disease. *Br J Med & Med Res.* 2014;4(13):2568-80.

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