International Journal of Biochemistry Research & Review
14(1): 1-9, 2016, Article no.IJBCRR.29218
ISSN: 2231-086X, NLM ID: 101654445

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Serum Prolactin Level and Inflammation in Chronic Kidney Disease

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Authors' contributions

This work was carried out in collaboration between all authors. Authors KSM and EM designed the study, wrote the protocol and supervised the work. Authors DL and KSM carried out all laboratories work and performed the statistical analysis. Author DL managed the analyses of the study and wrote the first draft of the manuscript. Authors KSM & EM managed the literature searches and edited the manuscript. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/IJBCRR/2016/29218
Editor(s):
(1) Yi-Ren Hong, College of Medicine, Kaohsiung Medical University, Taiwan.
Reviewers:
(1) Brijesh Mukherjee, Sambalpur University, India.
(2) Christopher Drummond, University of Toledo, Medicine, USA.
Complete Peer review History: http://www.sciencedomain.org/review-history/16419

Original Research Article

Received 29th August 2016
Accepted 24th September 2016
Published 3rd October 2016

ABSTRACT

Back Ground and Objectives: Chronic Kidney Disease (CKD) is a major prevalent disease worldwide associated with low grade systemic inflammation, which predisposes individuals to higher incidence of atherosclerotic complications. The pituitary hormone prolactin has recently been regarded as a local regulator of macrophage responses. Both prolactin clearance and production are altered in CKD. Emerging evidences suggests that prolactin participates in atherosclerotic processes in cases of peri /post partum cardiomyopathy and hypertension. Given the elevated cardiovascular risk of CKD, this study is intended to estimate the levels of prolactin and tumor Necrosis Factor α, an inflammatory marker in CKD and to decipher if there is are significant interactions between these variables.

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Methods: The study population included 45 CKD and 45 healthy controls of either gender. Fasting Blood Sugar (FBS) and Serum creatinine were measured in the fasting sample collected from both the groups. Estimated Glomerular Filtration Rate (eGFR) was calculated using MDRD formula. Serum prolactin levels and tumor necrosis factor α was estimated by ELISA method.
Results: The study found highly significant increase in serum TNF-α levels (8.64±4.97/2.06±1.34 pg/ml, p<0.001) and serum prolactin levels (61.65±28.9/11.76±8.55 ng/ml, p<0.001) in cases when compared to controls There was no correlation between eGFR and prolactin of cases in different stages of CKD. No correlation was found between prolactin and TNF in all the stages of CKD.
Interpretation and Conclusion: The increased prolactin levels acts independently in increasing the risk of cardiovascular diseases in cases of CKD superimposing on low grade inflammation.

Keywords: Atherosclerosis; chronic kidney disease; inflammation; prolactin.

1. INTRODUCTION AND NEED FOR THE STUDY

Chronic kidney disease is one of the global health problems with a prevalence of 17.2% as per a cohort study done in India [1]. Chronic kidney disease (CKD) has gained epidemic proportions worldwide due to increase in the predominance of systemic arterial hypertension, diabetes mellitus and dyslipidemia, which are found to be associated with elevated risk for cardiovascular disease [2]. Cardiovascular disease is the leading causes of morbidity and mortality in all stages of chronic kidney disease.

Subclinical inflammation has been considered to play an important role in the progression of chronic diseases [2]. Activation of the immune system has been reported in various stages of CKD [3]. Inflammation, associated with the effects of oxidative stress and endothelial dysfunction are considered as cardiovascular risk factors for CKD population [4].

Prolactin is a multifunctional pituitary hormone and has other metabolic actions that are not confined to the lactating mammary gland. Prolactin has biologic actions that contribute to the atherosclerotic process subsequently predisposing individuals to essential hypertension, acute phase of coronary syndromes, ischemic strokes. Increased expression of prolactin receptors were also found in advanced human atherosclerotic plaque [5]. High levels of serum prolactin in the body can modulate immune function including its involvement in autoimmune disease. At present, little is known about the implications of hyperprolactinemia in CKD.

In CKD, the combination of impaired immune response coupled with persistent immune stimulation and disturbed cytokine network plays a predominant role in low grade systemic inflammation [6]. However the relation of prolactin with inflammation attributing to risk of cardiovascular disease in CKD has not been proved yet. This study is intended to know the levels of prolactin and Tumor Necrosis Factor α, an inflammatory marker in CKD and to find out if there are significant interactions between these variables.

2. MATERIALS AND METHODS

The study was conducted at M.S. Ramaiah Medical College, Bangalore after obtaining ethical clearance from the ethical review board of the institution and informed consent was taken from the study population before the collection of the sample The study population included 45 clinically diagnosed cases of chronic kidney disease in the age group 20-50 years, who were attending the outpatient clinic of the department of nephrology and 45 healthy individuals as controls, in the age group 20-50 years who visited hospital for routine health check up and were willing to be a part of this study. The exclusion criteria for the recruitment of cases included CKD patients with history of diabetes mellitus, who were on medications like anti inflammatory drugs, ACE inhibitors, angiotensin receptor blockers, known cases of cardiovascular disease, with acute illness or infection, chronic kidney disease patients on dialysis. The control subjects also had same exclusion criteria as CKD cases. A detailed history, including drug history and anthropometric measurement was taken from the both the groups. Systemic examination was done and appropriate laboratory investigations were included. 5ml of venous blood sample was collected after overnight fasting of about 10-12 hours from control subjects and CKD patients. The sample collected in vacutainer with EDTA as anticoagulant was used for estimation of

hemoglobin as early as possible. The sample collected in yellow vacutainer with clot activators was allowed to clot and then centrifuged at 5000 rpm for eight minutes. The serum was separated at the earliest and used for the estimation of fasting blood sugar (FBS), blood urea nitrogen (BUN), serum creatinine, uric acid, prolactin and TNF –α level. Blood glucose by hexokinase, Serum creatinine by alkaline picrate, kinetic rate blanked, traceable to IFCC IDMS standardized, BUN by urease-GLDH method and uric acid by uricase method on Roche Cobas 6000**.** Hemoglobin concentration is estimated in whole blood by the cyanide free- sodium lauryl sulphate method. The Calbiotech, Inc. (CBI) prolactin ELISA kit is used for the quantitative measurement of prolactin in human serum. This a solid phase sandwich ELISA assay method, based on a streptavidin-biotin principle. The quantitative determination of serum TNF-α was carried out by the Diaclone TNF-α ELISA kit [7]. This is based on sandwich enzyme-linked immunosorbent assay (ELISA) with monoclonal antibody, Streptavidin-horseradish peroxidase (HRP) conjugate and recombinant cytokines as the standard were used. The plate was read at 450 nm in an ELISA reader (CPC diagnostics, Stat Fax 4700, microstrip reader).

Estimated GFR (eGFR) was calculated by using the Modification of Diet in Renal Disease (MDRD) Formula [8].

eGFR (mL/min/1.73 m^2) = 175 × $(S.cr)^{-1.154}$ × $(Age)^{-0.203}$ × (0.742 if female) × (1.212 if African American).

CKD patients were grouped based on eGFR calculated by MDRD formula:

Stage I CKD - eGFR: ≥ 90mL/min with demonstrable kidney damage

Stage II CKD - eGFR: 60-89 mL/min

Stage III CKD - eGFR: 30-59 mL/min

Stage IV CKD - eGFR: 15-29 mL/min

Stage V CKD - eGFR: < 15 mL/min

2.1 Statistical Methods

The results were expressed as mean ± SD. Significance was assessed at 5% level of significance. Categorical data was represented in the form of number (n) and percentage (%). Student "t" test (two tailed, independent) was used to find the significance of study parameters. Pearson correlation was used to study the relation between the various parameters. Statistical analysis was performed using SPSS 12.0 software.

3. RESULTS

The data of controls and chronic kidney disease cases are compared with respect to serum creatinine, BUN, uric acid, FBS, hemoglobin, serum prolactin, Tumor necrosis factor- α and calculated parameters like eGFR and BMI. Out of 45 cases included in the study, 65% were males and 35% females (Table 1). There is no evident variation in age, height, weight, BMI, waist and hip circumference between controls and CKD cases as shown in Table 1.

Blood urea, S. creatinine, uric acid, eGFR was found to be increased in CKD cases as compared to controls with a p value of <0.001 (Table 2). The blood urea nitrogen levels of both the groups are shown in Fig. 4. In CKD, due to compromise in renal functions there is retention of nitrogenous wastes including increase in serum concentration of blood urea nitrogen. As evident from the above Table 2, there is significant increase in mean values of serum creatinine, uric acid and BUN (p <0.001**). The study populations recruited were based on the deranged S. creatinine levels for the CKD cases.

There was significant decrease in hemoglobin concentration (gm %) in CKD cases when compared to controls (p <0.001**). In renal disease there is decrease in the production of hemoglobin resulting in anemia as erythropoietin is secreted by peri-tubular fibroblasts of kidney.

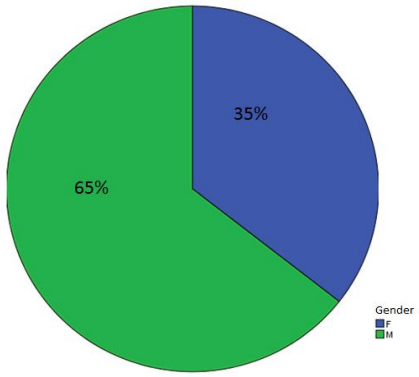

Fig. 1. Percentage of male and female gender in CKD cases

In the study mean eGFR was 13.24±8.84 ml/min/1.73 m^2 in CKD cases and 109±27.96 ml/min/1.73 m^2 in controls (Table 3). There is highly significant decrease in eGFR in CKD cases as compared to controls. As CKD progresses, there is fall in glomerular filtration rate with decrease in clearance of various substances.

Table 1. Demographic and anthropometric measurements of CKD cases and controls (mean±SD)

Profiles	CKD cases	Controls	P value
Age (years)	36.1±9.5	35.1±8.7	0.605
Height (cms)	163.5±7.4	164.5±6.8	0.509
Weight (kg)	64.3±10.6	65.2±10.3	0.692
BMI (Kg/m^2)	24±3.6	24±2.8	0.977
Waist circumference (cm)	73.6±11.6	78±13.2	0.096
Hip circumference (cm)	82.4±12.2	86.2±13.8	0.178
Waist Hip Ratio	0.9±0.1	0.9±0.0	0.207

Table 2. Comparison of biochemical parameters among CKD cases and controls (mean±SD)

Biochemical Parameters	CKD cases (mean±SD)	Controls (mean±SD)	P value
Fasting Blood Glucose (mg/dl)	93.9±17.9	90.5±10.5	0.276
Serum Creatinine (mg/dl)	7.9±5.7	0.8±0.2	<0.001**
Serum Uric Acid (mg/dl)	7.7±2.5	4.5±1.5	<0.001**
Blood Urea Nitrogen (mg/dl)	62.1±35.5	8.6±4	<0.001**
Hemoglobin (gm%)	9.2±2.3	13.6±1.9	<0.001**

Table 3. eGFR in CKD cases and controls (mean±SD)

Parameter	CKD cases	Controls	P value
eGFR(ml/min/1.73m^2)	13.24±8.84	109±27.96	<0.001**

Table 4. Serum TNF-α (pg/ml) and prolactin (ng/ml) level in CKD cases and controls (mean±SD)

Parameter	CKD cases	Controls	P value
S. TNF- α (pg/mL)	8.64±4.97	2.06±1.34	<0.001**
S. Prolactin (ng/ml)	61.65±28.9	11.76±8.55	<0.001**

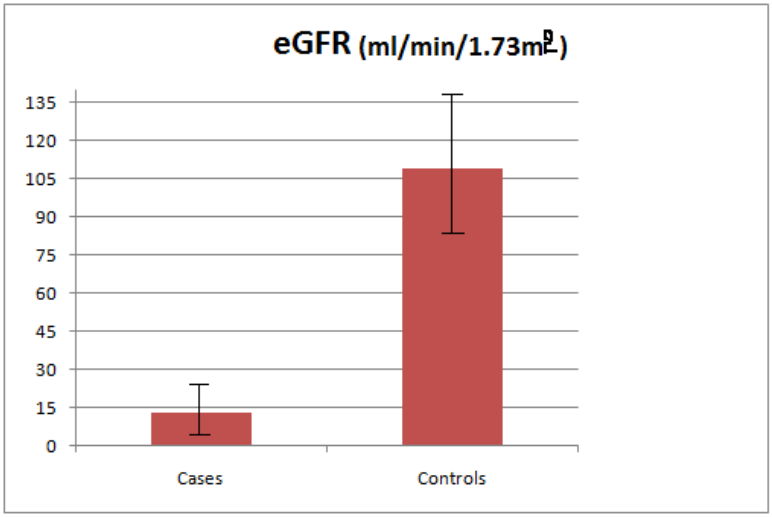

Fig. 2. Diagram showing eGFR in CKD cases and controls (mean±SD)

Serum TNF-α level (pg/ml) and prolactin levels (ng/mL) in CKD cases and controls are shown in Table 4. It is observed that there is increase in serum TNF-α and prolactin in CKD patients when compared to controls. Increased production from activated monocytes and decreased excretion from the diseased kidneys subsequently leads to increased levels of serum TNF-α.

Based on eGFR value staging of CKD is done. Table 5 shows mean eGFR in CKD cases and are grouped under different stages.

Table 5. eGFR level of cases in different stages of CKD (mean±SD)

CKD stages	N	eGFR (ml/min/1.73m^2) (mean±SD)
Stage 1	3	81.93±27.68
Stage 2	1	60.00±0.00
Stage 3	5	42.96±3.31
Stage 4	14	22.71±4.46
Stage 5	22	9.55±3.56

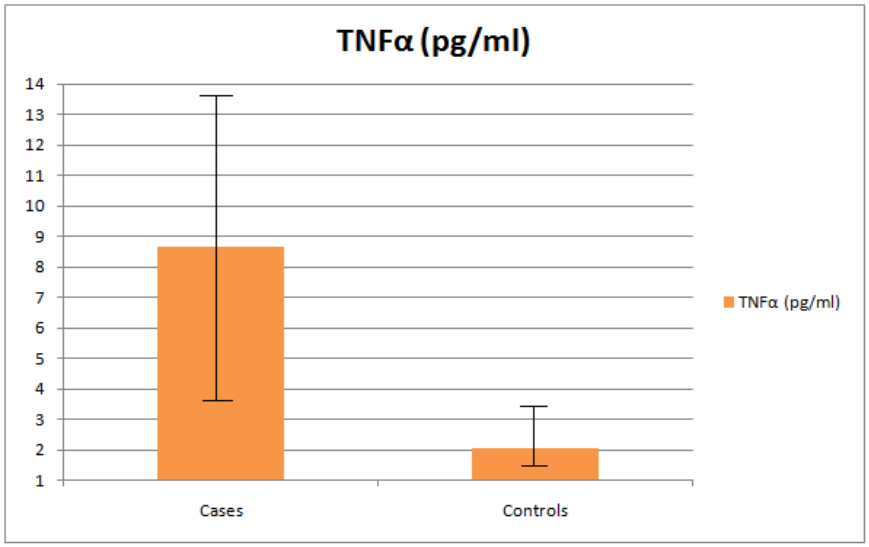

Fig. 3. Serum TNF-α in CKD cases and controls (mean±SD)

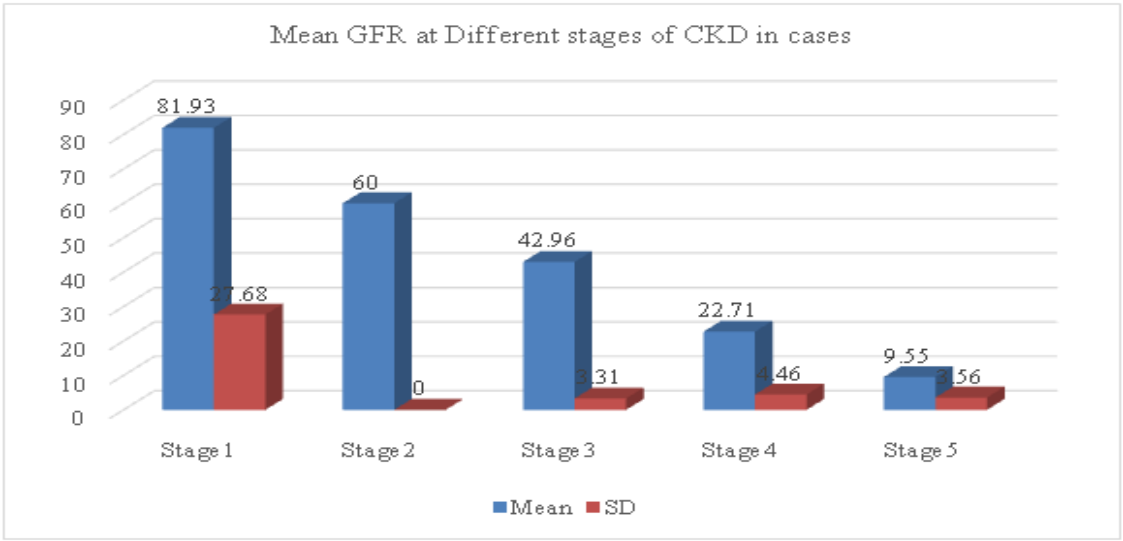

Fig. 4. Diagram showing eGFR of cases in different stages of CKD (mean±SD)

Tables 6 and 7 show decrease in GFR and elevation in S. prolactin level in CKD cases, but there is no significant correlation in the present study. The mechanism influencing the rise in S. prolactin and TNF-α are independent of each other.

There was no significant correlation between tumor necrosis factor- alpha and prolactin in different stages of CKD (Table 8). Though there has been increase in serum levels of tumor necrosis factor-alpha and prolactin in chronic kidney disease cases but no significant correlation is evident in the present study indicating the rise in their levels are independent of each other. The mechanism underlying for their elevation is not interdependent of each other.

4. DISCUSSION

Chronic kidney disease is found to be associated with low grade inflammation and resulting in increased production of atherogenic and proinflammatory compounds [9]. In the present study there is increase in serum prolactin and tumor necrosis factor alpha in chronic kidney disease. There is gradual increase in inflammation with the progression of CKD. There are reports which indicate prolactin was able to modulate the inflammatory response, stimulate adhesion of mononuclear cells to endothelium and enhance vascular smooth muscle cell proliferation thereby modulate the inflammatory response [10]. Vasoconstrictive effects of prolactin via *β*2-adrenergic and nitric oxide mechanisms further predispose towards increased cardiovascular risk. There are studies which indicate that endothelial dysfunction and arterial stiffness are not the sole mechanisms of action mediating this effect [11]. Correro et al [5] have reported selective deteriorating effect of prolactin toward arteriosclerosis.

Prolactin retention leads to inhibition of gonadotropic hormone production including testosterone deficiency in male CKD patients and has been linked to increased atherosclerotic plaque occurrence, systemic inflammation, cardiovascular risk and mortality [12]. In the present study there is fivefold increase in serum prolactin level in CKD cases as compared to controls. Increased prolactinemia can be consequent to decreased dopaminergic activity, which can lead to increased norepinephrine release and can have adverse effects on endothelial function and on other organs consequently predisposing to cardiovascular comorbidities [5].

Table 6. Correlation of serum prolactin with TNF-α and eGFR in CKD cases

Biochemical parameters	R value	P value
Prolactin and TNF-α	-0.117	0.467
Prolactin and eGFR	-0.169	0.26

Table 7. Correlation between eGFR and S. prolactin of cases in different stages of CKD

Stages	eGFR(ml/min/1.73m^2) (mean±SD)	Prolactin (ng/ml) (mean±SD)	No of cases(n)	Correlation coefficient (r)	P value
Stage 1	81.93±27.68	4.04±1.8	3	---	---
Stage 2	60.00±0.00	4.86	1	---	---
Stage 3	42.96±3.31	6.3±1.89	5	0.52	0.36
Stage 4	22.71±4.46	11.11±8.4	14	-0.002	0.99
Stage 5	9.55±3.56	63.15±31	22	-0.04	0.85

Table 8. Correlation between TNF-α and prolactin in different stages of CKD

Stages	TNF-α (pg/ml) (mean±SD)	Prolactin (ng/ml) (mean±SD)	No of cases (n)	Correlation coefficient (r)	P value
Stage 1	4.35±2.6	4.04±1.8	3	---	---
Stage 2	4.2	4.86	1	---	---
Stage 3	4.68±3.02	6.3±1.89	5	**-0.86**	**0.06**
Stage 4	5.19±2.57	11.11±8.4	14	-0.22	0.45
Stage 5	10.36±5.27	63.15±31	22	0.14	0.53

The secretion of prolactin is influenced by various substances including monoamines, endogenous opiates and can be altered in uremia [13,14]. Hyperprolactinemia in CKD can be either due to reduced renal clearance or increased production of prolactin [15]. Serum prolactin level rise correlates with decline in glomerular filtration rate. Increased serum prolactin levels are also reported in several systemic as well as organ-specific autoimmune diseases. Its elevation can be due to increased release of prolactin from the anterior pituitary due to inflammatory cytokines, reduced production of suppressive dopamine or due to increased production of prolactin in immune system cells [16]. Prolactin-receptors are present in T and B lymphocytes, natural killer cells and intestinal epithelial cells. The rise in serum prolactin increases the ability of the immune cells to proliferate and produce cytokines such as TNF-alpha, IL-6, IL-1 beta [16,17]. Prolactin due to its immune modulatory action can interfere with lymphocyte activation and cytokine production [18]. Oxidative stress can bring about proteolytic cleavage of prolactin into a potent antiangiogenic, proapoptotic and proinflammatory 16-kD subform that may initiate the atherosclerotic-related complications [19]. In the present study increase in serum prolactin level is very evident in later stages of CKD, as in stage IV and stage V.

CKD is associated with deleterious effect on physiological and metabolic functions including worsening of kidney function, uremia, acidosis, malnutrition and others. The progression of metabolic and cellular dysfunction, both systematically and locally within kidney tissue in CKD eventually can result in increased production of proinflammatory cytokines. These proinflammatory cytokines can increase the production of reactive oxygen species (ROS) which sequentially can further activate cytokine production resulting in detrimental effects on renal function [20]. Prolactin is metabolized in the kidneys and liver and in case of renal failure due to decreased renal clearance results in accumulation of prolactin in the blood leading to hyperprolactinemia. Morgan et al [21] have mentioned that proinflammatory cytokines increase the production of ROS and are themselves regulated in a positive feedback loop via the nuclear factor kappa beta (NF-κB) pathway. Nian et al [22] have reported the cellular damage caused by the proinflammatory response stimulates the ROS production cycle and in turn activating further cytokine production. In CKD, the combination of impaired immune response coupled with persistent immune stimulation and disturbed cytokine network plays a predominant role in low grade systemic inflammation which mediates the process of monocyte influx, proliferation of macrophages and matrix expansion resulting in glomerular sclerosis and tubulointerstitial injuries [23]. These tissue resident macrophages promote the production of pro inflammatory cytokines like C reactive protein, interleukin 6, tumor necrosis factor α and others.

TNF α binds to TNF cell surface receptors on target cells and induces expression of adhesion molecules, chemokines for leucocytes and apoptosis in susceptible cells [24]. TNF α can mediate progressive renal injury and can be used as marker of inflammation. In the present study there is nearly four times increase in TNF-α levels in CKD cases as compared to controls. Tonelli et al [25] have reported C reactive protein and TNF-α are elevated in the initial stage of renal dysfunction and are independently associated with accelerated rate of loss of kidney function. TNF-α is a proinflammatory cytokine whose production is stimulated by angiotensin II, and which is associated with interstitial fibrosis through myofibroblast differentiation and NF-κB activation.

Cytokines induce local proliferation of tubular and interstitial cells, synthesis of extracellular matrix, pro-coagulant endothelial activity, formation of oxygen reactive species and increased expression of adhesion molecules and biologically active lipids in renal tissues [26]. Cytokine release is also related to the hemodynamic and local effects of the activation of the renin-angiotensin system (RAS). The RAS plays a central role in intracellular signaling processes, possibly by modulating the inflammatory response associated with renal disease progression and susceptibility to cardiovascular dysfunction. RAS and cytokine may lead to modified expression of inflammatory cytokines and, consequently, to renal disease progression and the development of cardiovascular dysfunction in CKD patients [27,28]. Though there is significant rise in prolactin and TNF-α level in later stages of CKD, that is in stage IV, and stage V but there is no significant correlation between serum prolactin and TNF-α. In the present study though there is increase in serum prolactin and TNF-α, but the elevation of their levels are independent of each other.

However, studies need to be carried out to confirm, if therapeutic intervention of hyperprolactinemia can improve cardiovascular-related outcomes including reduction in arterial pressure. The limitations of the present study include single measurement of the proinflammatory cytokines and prolactin which may not represent average levels of these biomarkers overtime. In conclusion, inflammation and alteration in immune response can aggravate the pathological consequence in chronic kidney disease. Modulation of the immune-inflammatory response can be targeted towards management of CKD treatment to reduce cardiovascular risk.

5. CONCLUSION

There is increase in inflammatory markers in CKD which can predispose to endothelial dysfunction, vascular wall inflammation and subsequently to atherogenesis. CKD is associated with increased serum levels of hormone prolactin. The increased prolactin levels acts independently in increasing the risk of cardiovascular diseases in cases of CKD superimposing on low grade inflammation.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
http://sciencedomain.org/review-history/16419