

The Role of Inflammatory Processes in Occurrence of Left Ventricular Failure in Patients with Chronic Kidney Disease

Abstract

Background: Recently, the relationship between increased level of inflammatory mediators and occurrence of left ventricular failure in patients with kidney disease has been suggested. The present study attempted to assess relationship between inflammatory mediators and occurrence of left ventricular failure in patients with chronic kidney disease. **Materials and Methods:** This cross-sectional study was performed at Noor and Hazrat Aliasghar hospital in Isfahan between September 2012 to September 2013 on patients aged >19 years that referred for following their chronic kidney disease. Serum level of inflammatory parameters including C-reactive protein (CRP) and Interleukin-6 (IL-6) was measured using spectrophotometer. All patients were also assessed using M-mode echocardiography to determine left ventricular ejection fraction (LVEF). **Results:** The group with significant reduced LVEF showed lower GFR when compared to the normal LVEF group ($40.73 \pm 20.61\%$ versus $44.43 \pm 17.98\%$, $P = 0.032$). Comparing GFR across the three groups with normal LVEF (>55%), with mild LV dysfunction (LVEF: 45 – 55) those with significant LV dysfunction (LVEF < 45%) showed significantly lower GFR level in latter group compared with normal LVEF and mild LV dysfunction group ($P = 0.026$). Although the level of serum CRP was significantly higher in patients with significant left ventricular failure than other groups ($P = 0.018$). **Conclusion:** Inflammatory processes can potentially affect left ventricular function in patients with chronic kidney disease. In this regard, increased level of CRP may be a main factor for predicting severity of left ventricular failure in these patients.

Keywords: Chronic kidney disease, ejection fraction, inflammation, left ventricle

Introduction

Nowadays, chronic kidney disease is one of the main causes of disability responsible for a high cost burden on healthcare systems in each society. This health problem not only has an increasing trend in most developed and developing countries, because of the necessity for prolonged dialysis or needing kidney transplantation, a considerable part of health budgets is being spent for managing and controlling this phenomenon.^[1,2] One of the main consequences of chronic kidney disease caused by progression of cardiovascular disease is left ventricular failure that affects about 75 percent of the patients in early stages of dialysis.^[3,4] The severity of left ventricular failure is directly associated with the level of renal failure progression.^[5] Moreover, left ventricular failure has been introduced as an independent factor for predicting high cardiovascular-related mortality in chronic kidney disease

patients. Besides, inflammatory processes have been well identified as the main background for both cardiovascular and kidney dysfunction leading left ventricular hypertrophy and heart failure.^[6] Numerous studies have recently shown strong evidences on association of increased level of inflammatory cell and mediators with different phases of coronary artery diseases. It has been also revealed that increased level of inflammatory biomarkers including c-reactive protein (CRP), tumor necrotizing factor (TNF- α), and interleukin-6 (IL-6) can be associated with increased risk for heart failure, even in those without any previous evidences of coronary heart diseases.^[7-9] In addition, inflammatory processes have been shown to be associated with deterioration of kidney dysfunction that can be accompanied with uremia, increased level of stress oxidative, protein loss, and increased susceptibility to infections. In this regard, the increase of CRP in patients undergoing hemodialysis is a powerful

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predictor for poor prognosis.^[10] Recently, the relationship between increased level of inflammatory mediators such as IL6 and CRP and occurrence of left ventricular failure in patients with kidney disease has been also suggested,^[11,12] however a few documents are available for this suggestion. Hence, the present study attempted to assess relationship between inflammatory mediators and occurrence of left ventricular failure in patients with chronic kidney disease.

Materials and Methods

Study population

This cross-sectional study was performed at Noor hazratiasghar hospital in Isfahan between September 2012 to September 2013 on patients aged >19 years that referred for following their chronic kidney disease. The main exclusion criteria included coronary artery disease, diabetes mellitus, peripheral vascular disease, any evidences of collagen-vascular diseases, acute infection on admission, under hemodialysis, or recently use of anti-inflammatory drugs. We excluded all reasons leading activation of inflammatory pathways. We also matched the groups in hypertension. The details of coronary artery disease were collected from available angiography reports. We aimed not to perform angiography for all participants; in fact, patients with negative coronary angiography underwent perfusion scan analysis to confirm the normal coronary condition. None of the patients with low LVEF had cardiomyopathy diagnosis. On admission, the aims of the study explained to the participants and written informed consent were received from all.

Study measurement

Baseline information including demographics, anthropometric indices, medical history, oral medication, and any available cardiovascular documents were collected. Participants also underwent a clinical examination that included measurement of height, weight, and arterial blood pressure (mean of two measurements performed with a standard sphygmomanometer in a sitting position after a 5-min rest) according to standardized protocols. Furthermore, blood samples were taken after at least 12 h of overnight fasting to measure inflammatory parameters including CRP and IL-6 determined by using ACE™ EIA KIT (USA) by ELISA method. Also, the serum level of serum creatinine and glomerular infiltration rate (GFR) were also assessed by $186 \times (\text{Creat}/88.4) - 1.154 \times (\text{Age}) - 0.203 \times (0.742 \text{ if female})$. Then, all patients were assessed using M-mode echocardiography according to the American Society of Echocardiography guideline with Vivid-3 instrument and adult probe to determine left ventricular ejection fraction (LVEF). In this study, the patients were categorized into three groups including those with significant left ventricular failure (LVEF <45%), with mild left ventricular failure (LVEF: 45-55%), normal control (LVEF >55%). Also, the rate of GFR was categorized into three groups with GFR ≤15, GFR 15–30, and GFR >30.

The ethics committee of Isfahan University of Medical Sciences approved the study and written informed consent was obtained from all patients.

Statistical analysis

Results were presented as mean ± standard deviation (SD) for quantitative variables and were summarized by absolute frequencies and percentages for categorical variables. Continuous variables were compared using One-way ANOVA test. Categorical variables were, on the other hand, compared using Chi-square test or Fisher's exact test when more than 20% of cells with expected count of less than 5 were observed. For the statistical analysis, the statistical software SPSS version 20.0 for windows (SPSS Inc., Chicago, IL) was used. *P* values of 0.05 or less were considered statistically significant.

Results

The Chi-square test and *t*-test showed that patients in the case group (LVEF <55%) and the control group (LVEF >55%) were matched for sex and age distribution as well as for mean weight, mean systolic and diastolic blood pressures, and also history of hypertension [Table 1]. The group with significant reduced LVEF showed lower GFR when compared to the normal LVEF group ($40.73 \pm 20.61\%$ versus $44.43 \pm 17.98\%$, *P* = 0.032), however no differences were found in the serum level of CRP and IL-6 between the two groups [Table 2]. We also compared study parameters across the three groups with normal LVEF (>55%), with mild LV dysfunction (LVEF: 45–55) those with significant LV dysfunction (LVEF <45%) [Table 3]. Comparing mean of GFR across the three groups using ANOVA *Post hoc* test showed significantly lower GFR level in latter group compared with normal LVEF and mild LV dysfunction group (*P* = 0.026). In this regard, the prevalence of

Table 1: Baseline characteristics in case and control groups

Characteristics	Case (N=44)	Control (N=43)	<i>P</i>
Age (year)	55±12	48±14	0.228
Weight (kg)	66±14.32	65±13.96	0.576
Sex (male/female)	27/17	25/18	0.878
Systolic blood pressure (mmHg)	132.5±12	133.4±14.2	0.446
Diastolic blood pressure (mmHg)	79.3±6.3	81.3±8.5	0.255
HX of hypertension	8/36	9/34	0.791

Table 2: Comparing study parameters in case and control groups

Characteristics	Case (N=44)	Control (N=43)	<i>P</i>
GFR	40.73±20.61	44.43±17.98	0.032
CRP (pg/ml)	8.42±3.41	7.87±3.37	0.453
IL6 (pg/ml)	8.64±0.54	8.53±0.62	0.353

GFR: Glomerular infiltration rate, CRP: C-reactive protein

GFR ≤ 15 was significantly higher in those with significant left ventricular failure than in those groups with mild left ventricular failure or in normal control group [Figure 1]. Although the level of serum CRP was significantly higher in patients with significant left ventricular failure than other groups ($P = 0.018$), but the difference in serum level of IL-6 was not significant between the three groups ($P = 0.420$) [Figure 2].

Discussion

Different mechanisms have been described in occurring left ventricular failure in chronic kidney disease patients. One of these mechanisms was related to increased pressure and volume overload in these patients that own may be affected by advanced age, activation of rennin-angiotensin axis, and stress oxidative.^[13-15] This pressure and volume overload can finally lead to left ventricular hypertrophy and even cardiomyopathy. In addition, anemia, systolic or diastolic hypertension, or hyperparathyroidism have been well known to affect overload and occurrence of left ventricular failure in chronic kidney disease patients.^[16] In this regard, the potential role of inflammatory markers in presence and progression of chronic kidney disease patients remained unclear.^[17] The present study could show a negative association between serum level of CRP and LVEF parameter as an applied index for assessing left ventricular function. On the other hand, activation of inflammatory processes in chronic kidney disease patients can gradually result in left ventricular dysfunction assessed by lowering EF. The role of inflammatory processes in stimulation

and progression of atherosclerosis has been clearly described.^[18-20] It seems that deterioration of left ventricular dysfunction can be indirectly mediated by the progression of coronary atherosclerosis caused by inflammatory processes activation.^[21] Furthermore, it has been now suggested that activation of these inflammatory processes may directly influence left ventricular function by it's directly effect on left ventricular mass and thus on its function.^[22] In this line, chronic renal failure strongly link to cardiovascular functional state so that not only coronary disease can gradually cause renal dysfunction by misbalancing supply and demand, but also the presence of renal failure can lead to volume overload and thus can directly affect outcome of patients with cardiovascular disease.^[23] On the other hand, both progression of renal dysfunction and also activation of inflammatory mechanisms can disturb left ventricular function in renal failure patients.^[24,25]

Because we excluded other causes of CHF such as coronary artery disease, the main cause of CHF was cardiomyopathy caused by renal failure. In fact, more increase of inflammatory in CHF patients indicates the concomitantly role of inflammation in CHF patients. Thus, treatment of inflammation in CKD patients can prevent occurrence of cardiomyopathy in these patients.

A limitation of the study was the relatively small sample size. So these findings cannot be generalized to the broader community based on this study alone. Because of confounding effects of advanced age on CKD, we attempted to exclude very old persons to achieve reliable results. This inclusion selecting led to include a small number of patients.

Table 3: Comparing study parameters across the three groups

Characteristics	(LVEF <45% (N=29)	(LVEF: 45-55) (N=15)	(LVEF >55%) (N=43)	P
GFR	40.12±16.15	41.34±17.75	44.43±17.98	0.026
CRP (pg/ml)	9.91±3.99	7.66±2.85	7.87±3.37	0.018
IL6 (pg/ml)	8.58±0.51	8.76±0.59	8.53±0.62	0.420

GFR: Glomerular infiltration rate, CRP: C-reactive protein, LVEF: Left ventricular ejection fraction

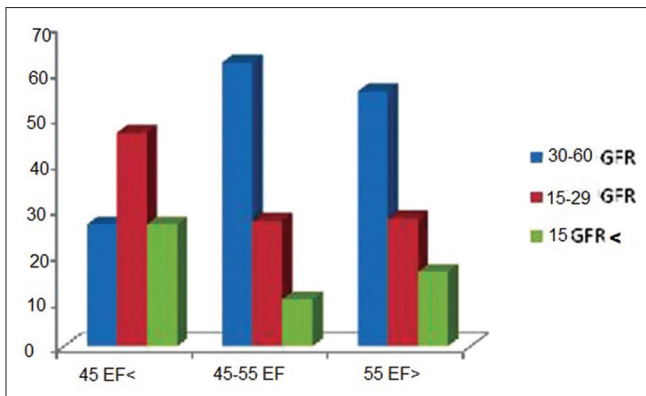


Figure 1: The GFR value in three LVEF subgroups

Conclusion

In conclusion, inflammatory processes can potentially affect left ventricular function in patients with chronic kidney disease. In this regard, increased level of CRP may be a main factor for predicting severity of left ventricular failure in these patients.

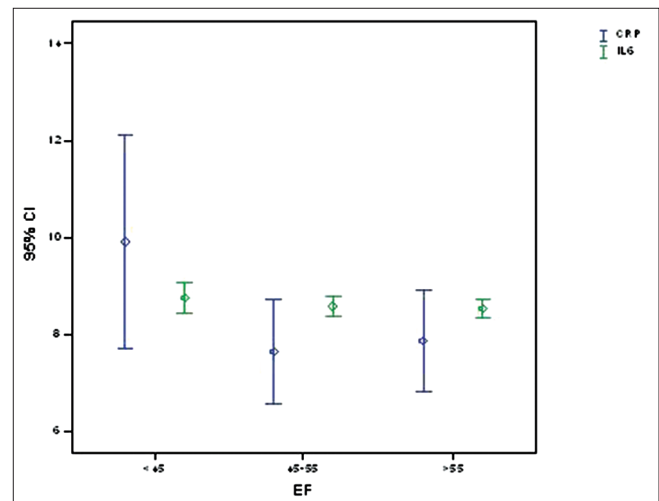


Figure 2: The level of CRP and IL6 in different LVEF subgroups

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Conflicts of interest

There are no conflicts of interest.

References

- Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, *et al.* Prevalence of chronic kidney disease in the United States. *JAMA* 2007;298:2038-47.
- Ramirez SP, McClellan W, Port FK, Hsu SI. Risk factors for proteinuria in a large, multiracial, southeast Asian population. *J Am Soc Nephrol* 2002;13:1907-17.
- Imai E, Horio M, Iseki K, Yamagata K, Watanabe T, Hara S, *et al.* Prevalence of chronic kidney disease (CKD) in the Japanese general population predicted by the MDRD equation modified by a Japanese coefficient. *Clin Exp Nephrol* 2007;11:156-63.
- US Renal Data Systems. *USRDS 2006 Annual Data Report: Atlas of End-Stage Renal Disease in the United States*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2007.
- Ansell D, Feest T, Hodsman A, Rao R. *UK Renal Registry, The Renal Association, The Ninth Annual Report*. Bristol, UK: UK Renal Registry; 2006.
- Lamb EJ. United Kingdom guidelines for chronic kidney disease. *Scand J Clin Lab Invest Suppl* 2008;241:16-22.
- Zimmermann J, Herrlinger S, Pruy A, Metzger T, Wanner C. Inflammation enhances cardiovascular risk and mortality in hemodialysis patients. *Kidney Int* 1999;55:648-58.
- Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis* 1998;32(Suppl 3):S112-9.
- London GM. Left ventricular hypertrophy: Why does it happen? *Nephrol Dial Transplant* 2003;18(Suppl 8):viii2-6.
- U.S. Renal Data System, *USRDS 2006 Annual data report*. Bethesda (MD): NIH, National Institute of Diabetes and Digestive and Kidney Diseases; 2007.
- Harnett JD, Foley RN, Kent GM, Barre PE, Murray D, Parfrey PS. Congestive heart failure in dialysis patients: Prevalence, incidence, prognosis and risk factors. *Kidney Int* 1995;7:884-90.
- Malik J, Tuka V, Mokrejsova M, Holaj R, Tesar V. Mechanisms of chronic heart failure development in end-stage renal disease patients on chronic hemodialysis. *Physiol Res* 2009;58:613-21.
- Rasic S, Kulenovic I, Haracic A, Catovic A. Left ventricular hypertrophy and risk factors for its development in uraemic patients. *Bosn J Basic Med Sci* 2004;4:34-40.
- Furman MI, Gore JM, Anderson FA, Budaj A, Goodman SG, Avezum A, *et al.* Elevated leukocyte count and adverse hospital events in patients with acute coronary syndromes: Findings from the Global Registry of Acute Coronary Events (GRACE). *Am Heart J* 2004;147:42-8.
- Cesari M, Penninx BW, Newman AB, Kritchevsky SB, Nicklas BJ, Sutton-Tyrrell K, *et al.* Inflammatory markers and onset of cardiovascular events: Results from the Health ABC study. *Circulation* 2003;108:2317-22.
- Wu CK, Yang CY, Lin JW, Hsieh HJ, Chiu FC, Chen JJ, *et al.* The Relationship Among Central Obesity, Systemic Inflammation, and Left Ventricular Diastolic Dysfunction as Determined by Structural Equation Modeling. *Obesity (Silver Spring)* 2012;20:730-7.
- Kovesdy CP, Kalantar-Zadeh K. Do genes allow inflammation to kill or not to kill? *J Am Soc Nephrol* 2009;20:1429-31. Available at: <https://www.uptodate.com/contents/inflammation-in-renal-insufficiency>. [Last access on 2014 May 02].
- Yeun JY, Levine RA, Mantadilok V, Kaysen GA. C-Reactive protein predicts all-cause and cardiovascular mortality in hemodialysis patients. *Am J Kidney Dis* 2000;35:469-76.
- Erten Y, Tulmac M, Derici U, Pasaoglu H, Altok RK, Bali M, *et al.* An association between inflammatory state and left ventricular hypertrophy in hemodialysis patients. *Ren Fail* 2005;27:581-9.
- Cottone S, Nardi E, Mule G, Vadala A, Lorito MC, Riccobene R, *et al.* Association between biomarkers of inflammation and left ventricular hypertrophy in moderate chronic kidney disease. *Clin Nephrol* 2007;67:209-16.
- Hosseinpanah F, Kasraei F, Nassiri AA, Azizi F. High prevalence of chronic kidney disease in Iran: A large population-based study. *BMC Public Health* 2009;9:44.
- Fenga C, Cacciola A, Martino LB, Calderaro SR, Di NC, Verzera A, *et al.* Relationship of blood lead levels to blood pressure in exhaust battery storage workers. *Ind Health* 2006;44:304-9.
- Libby P, Braunwald E. *Braunwald's heart disease: A textbook of cardiovascular medicine*. Amsterdam, Netherlands: Elsevier Saunders; 2007.
- Keller C, Katz R, Cushman M, Fried LF, Shlipak M. Association of kidney function with inflammatory and procoagulant markers in a diverse cohort: A cross-sectional analysis from the Multi-Ethnic Study of Atherosclerosis (MESA). *BMC Nephrol* 2008;9:9.
- Wannamethee SG, Shaper AG, Lowe GD, Lennon L, Rumley A, Whincup PH. Renal function and cardiovascular mortality in elderly men: The role of inflammatory, procoagulant, and endothelial biomarkers. *E Heart J* 2006;27:2975-81.