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Research article

Cardiovascular diseases risk factors among chronic kidney diseases male patients

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Key words: Cardiac risk factors, Chronic kidney disease, CKD, Lipids, Electrolytes.

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Abstract

Individuals with chronic kidney disease (CKD) are at a very high risk for the development of cardiovascular disease. In order to improve the prognosis of individuals with CKD, it is important to identify modifiable cardiovascular diseases risk factors and treat them. **Objectives:** In this study we tried to discover the correlation between progression of chronic kidney disease and traditional and nontraditional cardiac risk factors. **Methods:** This study was conducted on 40 male patients with chronic renal failure from January to Jun 2013 and a group of 20 healthy male individuals as a control group in El-Zahraa hospital in the west of Libya. **Results:** The results of this study concluded that, there is a correlation between estimated glomerular filtration rate and serum potassium, cholesterol, and uric acid, also this study proved that there a correlation between serum creatinine concentrations and potassium, cholesterol, triglycerides, and uric acid significantly, on the other hand, no correlation between serum urea levels and all of the tested cardiac risk factors.

Introduction

Cardiovascular disease (CVD) is one of these poor outcomes, which is related to death in chronic kidney disease (CKD) patients even before end-stage kidney disease (ESRD). Cardiovascular events in CKD can be brought under control with proper risk assessment and early detection of CVD-related factors. Besides cardiomyopathy and two subtypes of arterial vascular disease, atherosclerosis and arteriosclerosis, risk for sudden cardiac death secondary to arrhythmia is markedly increased in CKD [1].

Individuals with CKD are at a very high risk for the development of cardiovascular disease [2]. In order to improve the prognosis of individuals with CKD, it is important to identify modifiable CVD risk factors and treat them. Cardiac risk factors in CKD can be divided into traditional and nontraditional risk factors. Traditional risk factors as older age, male gender, hypertension, higher total cholesterol, higher LDL and lower HDL, diabetes, smoking, physical inactivity, menopause, left ventricular hypertrophy. The nontraditional risk factors are albumin urea, hyperhomocysteinemia, anemia, abnormal Ca/Phosphate metabolism, extracellular fluid volume overload and electrolyte imbalance, oxidative stress, inflammation, malnutrition, thrombogenic factors, sleep disturbances, altered nitric oxide/endothelin balance [3].

Cardiovascular risk factors promote the development of endothelial dysfunction that has a central role in the pathogenesis of CVDs together with inflammation, atherosclerosis, and mineral bone disease. Indeed vascular calcification and left ventricular hypertrophy are the most commonly encountered clinical challenges and the most prevalent reasons for morbidity and mortality [4-6]. Nontraditional risk factors, such as hyperhomocysteinemia and hyperuricemia, have a high prevalence in renal disease and are associated with endothelial dysfunction and vascular damage [4-6]. Therefore, the identification of early markers of CVDs in this population is an important task for nephrologists.

The study of Lai *et al.* [7], aimed to investigate the relation among serum cardiac biomarkers (N-terminal pro-brain natriuretic peptide (NT-proBNP), cardiac troponin T (cTnT),nontraditional cardiovascular risk factors (serum uric acid, homocysteine), inflammatory indexes(C-reactive protein (CRP) serum ferritin, fibrinogen) and noninvasive predictors of atherosclerosis

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(carotid intima-media thickness (cIMT), brachial artery flow mediated dilation (baFMD), and left ventricular mass index (LVMI)) in CKD patients. This study showed an increase of NT-proBNP and the serum cTnT, of serum uric acid and homocysteine with a positive correlation with the increase of cIMT and LVMI and reduced baFMD compared with the controls. This study concluded that serum cardiac biomarkers and nontraditional cardiovascular risk factors increase already in the stage 2/3 KDOQI contributing to explain the high cardiovascular morbidity and mortality of these patients. The NT-proBNP seems to have arisen earlier compared with serum cTnT; however, both seemed to be a useful clinical biomarker for evaluating noninvasive predictors of atherosclerosis in CKD patients.

The study of Yenigun *et al.* [8] showed that QT, QTc and QTd, markers of arrhythmia risk and sudden death, are prolonged in patients with acidosis. This increased risk is independent of serum electrolyte levels. Correction of metabolic acidosis by sodium bicarbonate supplementation is useful not only to reduce the hazard of CKD progression, bone disease and inflammation but also to improve the QT interval, which is a predictor of total and cardiovascular mortality.

Inflammation and increased atherosclerosis, decreased albumin synthesis [9],insulin resistance, increased bone resorption and decreased bone formation, increased β2micro globulin, rapid CKD progression are some of the problems related to metabolic acidosis. Metabolic acidosis also causes decreased myocardial contractility as a result of decreased Na^+-K^+-ATPase activity in myocardial cells [10].

Experimental

This study was conducted on 40 male patients with chronic renal failure from January to Jun 2013 and a group of 20 healthy male individuals as a control group. Ethical approve and patients consent statement were taken from everyone and the study was performed in El-Zahraa hospital in the west of Libya. At first, all patients with proven chronic renal failure were included in study. Patients with especial established disorders such as endocrinopathies, and hepatosplenomegaly were excluded from study. In order to eliminate effects of age on comparison between cases and control groups, age were selected in each of groups of patients and control as similar as possible. Demographic and anthropometric data including age, sex, weight, height, BMI and blood pressure were measured for the participants. All of patients and normal participants were Libyans, above 18 years of age, and free from chronic degenerative diseases such as cancer or peritonitis.

Five mL of blood was drawn by venous puncture. Collected blood sample was emptied in plain vial for biochemical tests. After clotting of blood in the plain vial, serum was separated, within an hour; by centrifugation at 3000-5000 g for 5 min. Serum was used for measurements of urea, creatinine, uric acid, cholesterol, triglycerides, Sodium, Potassium, Calcium, Phosphorous and glucose levels. Laboratory standard operation procedures were maintained for all laboratory analysis. Internal quality control sera, both normal and pathological, were also run for each lot of the test, for the validation of the results. Biochemical studies were performed using commercially available kits from Biomeriux (France) according to the manufacturer's instructions. Sodium and potassium ions were determined using Na^+ and K^+ filter of flame photometer (Jenway PFP7. ESSEX.UK.).

Defining variables

CKD was defined as reduced excretory function with an estimated GFR (eGFR) <60 mL/min/1.73 m^2 as a marker of kidney dysfunction. Furthermore, CKD was defined and classified into five stages of CKD as per National Kidney Foundation guidelines. The formula of Cockcroft and Gault equation was used to calculate eGFR[11]. eGFR = [140 - age (in years)] x weight (in kg) /[72 x serum creatinine (mg/dl)].

Statistical analysis

The data was analyzed by using Excel 2010, and graph Pad Prism software version 5. Association between cardiac risk factors and chronic kidney disease was tested by Pearson's correlation test. Comparison of mean value of continuous data was tested by t test. p-value of <0.05 (two-tailed) was used to establish statistical significance.

Results and Discussion

The patients of this study are 40 males were diagnosed as chronic kidney disease patients by physical and laboratory investigations. By estimating GFR, most of patients were in stage five of chronic kidney disease (80%), as illustrated in figure (1). The patients who within stage four limits are 17.1% but there is very low percentage of patients who within stage three limits (2.9%), on the other hand, no patients within limits of stages one or two. In this study we compared the patient's renal function test results with the results of control healthy persons and tabulate these data in table (1). These data indicate the classical changes in kidney function tests as increase in serum urea, creatinine and uric acid by 592%, 1095% and 73% respectively. The estimated glomerular filtration rate, serum sodium and calcium were reduced in these patients by -91%, -4.3% and -8.5% respectively. The data tabulated in table (1) also showed the increase of Potassium, Phosphorus and Ca*Ph product by 37%, 103%, and 104% respectively. The classical

cardiac risk factors as total cholesterol, triglycerides, and fasting blood sugar (FBS) were also increased in CKD patients in this study by 9%, 61% and 75% respectively on comparing with control healthy persons.

The data in table (2) indicate the correlation between renal function tests as urea, creatinine and eGFR and traditional cardiac risk factors as dyslipidemia and diabetes, also the nontraditional risk factors as electrolyte imbalance and uric acid. These data showed correlation when we use Pearson correlation test, two tailed P value, confidence interval 95%, between eGFR and total cholesterol ($P < 0.01$), also there are correlations between eGFR and Potassium and uric acid significantly ($P < 0.05$). In the same time serum creatinine levels were showed correlation with potassium with high significant degree ($P < 0.01$) and with cholesterol, triglycerides, and uric acid with significant degrees ($P < 0.05$), on the other hand the correlation tests between serum urea and all cardiac risk factor did not show any significant correlation.

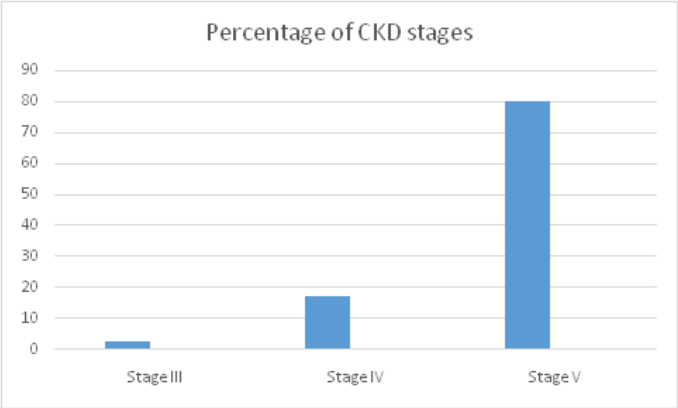


Figure 1. Percentages of CKD stages among patients

Table 1. Biochemical parameters in chronic kidney diseases male patients and healthy persons

Groups		Urea	Creatinine	eGFR	Na	K	Ca	Ph	Ca*Ph product	Cholesterol	Tri-glycerides	FBS	Uric acid
Control	Mean ± SD	25 ± 5.5	0.92 ± 0.21	130 ± 5.8	140 ± 2.2	4 ± 0.5	9.4 ± 0.6	3.2 ± 0.4	27.4 ± 2.4	144 ± 11.5	120 ± 32.5	88 ± 18.8	4.4 ± 0.56
Patients	Mean ± SD	173** ± 52	11** ± 3.6	11** ± 5.6	134** ± 6.0	5.5** ± 1.1	8.6 ± 1.6	6.5** ± 2.7	56** ± 26	157 ± 27	194* ± 100	154** ± 87	7.6** ± 1.4
	% of Mean differences	592%	1095%	-91%	-4.3%	37%	-8.5%	103%	104%	9%	61%	75%	73%

(*) significant difference compared to control group ($P < 0.05$).
(**) highly significant difference compared to control group ($P < 0.01$).

Table 2. Correlation between renal function tests and traditional and nontraditional cardiac risk factors

	Parameter	Na	K	Ca	Ph	Ca*Ph product	Cholesterol	Triglycerides	FBS	Uric acid
Correlation of eGFR with Cardiac risk factors	Pearson r	0.072	-0.42	-0.25	-0.12	-0.17	-0.46	-0.23	0.044	-0.39
	P value (two-tailed)	0.6915	0.0118	0.1469	0.5004	0.3234	0.0076	0.2393	0.8162	0.0220
	P value summary	Ns	*	Ns	Ns	Ns	**	Ns	Ns	*
Correlation of Creatinine with Cardiac risk factors	Pearson r	0.25	0.45	0.14	0.20	0.21	0.36	0.44	-0.13	0.43
	P value (two-tailed)	0.1486	0.0064	0.4188	0.2608	0.2286	0.0422	0.0161	0.4743	0.0105
	P value summary	Ns	**	Ns	Ns	Ns	*	*	Ns	*
Correlation of Urea with Cardiac risk factors	Pearson r	-0.35	0.27	0.16	0.086	0.20	-0.0086	-0.0091	0.089	0.31
	P value (two-tailed)	0.0506	0.1412	0.3772	0.6470	0.2746	0.9642	0.9642	0.6398	0.0895
	P value summary	Ns	Ns	Ns	Ns	Ns	Ns	Ns	Ns	Ns

Discussion

Cardiovascular disease is the cause of death in adults with CKD patients [2]. We tried in this study to cover the presence of correlation between chronic kidney disease and traditional and nontraditional risk factors as serum cholesterol, triglycerides, glucose, uric acid and electrolytes. Early appearance of vascular disease in patients with CKD is attributed to the combination of two parallel processes: atherosclerosis and arteriosclerosis. High prevalence of traditional cardiovascular risk factors, such as hypertension and dyslipidemia, are responsible for the formation of the intimal atherosclerotic plaque. In this study CKD patients did not show significant difference in serum cholesterol on comparing to control, but there is a significant correlation between eGFR and creatinine in one side and total cholesterol concentration in the other side. The percentage of mean difference of serum triglycerides between CDK patients and healthy persons in this study is 61% and the correlation of triglycerides with serum creatinine is significant, which prove the hyperlipidemic effect of chronic renal disease, which means the cardiovascular risk factor.

The case of hypertriglyceridemia may be caused by reduced activity of lipoprotein lipase and hepatic triglyceride lipase, which is the major enzyme responsible for the esterification of free cholesterol, also insulin resistance may cause hypertriglyceridemia. Reduced HDL levels may reflect alterations in cholesteryl ester transfer protein or lecithin: cholesterol acyltransferase (LCAT), which regulates the exchange of triglyceride ester between VLDL and HDL. Triglyceride-enriched HDLs are cleared more rapidly from the plasma [12].

Vascular diseases are either intimal atherosclerosis or medial arteriosclerosis, these two clinical entities differ with respect to risk factors, mechanism of disease, histological findings and clinical manifestations [13]. The cause of atherosclerosis is by intimal plaque formation, secondary to traditional vascular disease risk factors. The clinical manifestations occur as a result of alterations in the conduit function of the arteries. Medial arteriosclerosis is caused by diffuse mineral deposition in the tunica media of the arterial wall, as a result of high calcium–phosphate product, suppression of natural crystallization inhibitors and vascular smooth muscle cell phenotypic changes leading to osteoblastic differentiation. In the present study, as showed [14]. Together they create a permissive environment for nucleation of Ca–P crystals. The known risk factors, in addition to the Ca–P-related parameters, are cumulative doses of Ca containing Phos binders and vitamin D analogs. Clinically, arteriosclerosis causes vascular stiffness and secondarily results in hypertension, increased pulse pressure and LVH. These studies are in correlation with the present study which showed a highly significant increase in both Phosphorus concentration in serum and Ca*Ph product in patients compared to control.

On the other hand there is no correlation between renal function tests and Calcium or phosphorus concentrations by using Pearson correlation test.

Many studies concluded that elevated uric acid levels increases the risk for new onset kidney disease, independent of eGFR, components of the metabolic syndrome, gender, age and antihypertensive drugs [15]. Also, our findings are consistent with previous studies pointing to the deleterious effect of uric acid on endothelial function and arterial stiffness, even when uric acid levels are within the normal range. Mechanistically, experimental animal models have suggested that high uric acid levels may induce primary hypertension, probably by causing renal afferent arteriolopathy [16]. The data in our study indicate a highly significant difference in serum uric acid between CDK patients and control, in the same time there are correlations between eGFR and creatinine progression and serum uric acid as a nontraditional cardiac risk factor.

Many studies have shown that hyperuricemia is associated with increased risk for cardiovascular mortality, and also, it is found to be associated with hypertension, coronary heart disease, metabolic syndrome and chronic kidney disease**.** Cardiovascular disease is the main cause of mortality and morbidity among CKD and in end stage renal disease patients [17].We found that, serum uric acid was significantly higher in CKD patients than in Control persons ($p<0.01$).Also, there was a negative significant correlation between serum uric acid and eGFR ($p<0.05$).Both results support that hyper-uricema is linked to deterioration of renal function. Our results agreed with studies which reported that high serum uric acid level is associated with decline in renal function and GFR [17,18]**.** The mechanism of damaging action of uric acid to kidney includes glomerular hypertension and cortical vasoconstriction, which may induce glomerular damage and tubular ischemia, in addition to uric acid cause stimulation of inflammatory response [19].

In CKD patients, Kamel *et al.* [17] found a highly significant correlation between serum uric acid level and both systolic and diastolic blood pressures which reflects the correlation of hyperuricemia to hypertension. There was also a negative significant correlation between eGFR and systolic blood pressure accompanied by a highly significant negative correlation between eGFR and diastolic blood pressure**.** The mechanism of elevated blood pressure was shown to be caused by a reduction in endothelial nitric oxide levels and stimulation of renin expression which mediated by uric acid.

In this study we found that 48.75% of patients were diabetic. The mechanisms underlying the pathophysiology of diabetic nephropathy have been suggested and include hyperglycemia and the increased production of advanced glycation end products; glomerular hyperfiltration; hypoxia-

inflammation and the activation of cytokines. Hyperfiltration commonly occur in early in the course of diabetes and involves glucose-dependent dilation of the afferent arteriol, and the enhanced filtration area secondary to the increase in the number of mesangial cells and capillary loops [20]. Molecular level action involves vasoactive mediators like insulin-like growth factor 1, transforming growth factor beta, nitric oxide, prostaglandin, glucagon and vascular endothelial growth factor, also, diabetic nephropathy include nodular diabetic glomerulosclerosis and diffuse glomerulosclerosis, mediated at least in part by inflammatory processes and immune cells activity [21]. Early in diabetic, nephropathy interstitial fibrosis and tubular atrophy are also seen, with the underlying pathogenetic mechanism being similar to those in progressive non diabetic renal disease [22].

Potassium excretion is determined by the sum of three renal processes: the rate of potassium filtration, the rate of potassium reabsorption by the tubules, and the rate of potassium secretion by the tubules. The normal rate of potassium filtration is about 756 mEq/day (GFR, 180 L/day multiplied by plasma potassium, 4.2 mEq/L); this rate of filtration is usually relatively constant as a result of the auto-regulatory mechanisms for GFR and the precision with which plasma potassium concentration is regulated. In cases of sever reduction in GFR as in certain renal diseases, however, can cause serious potassium accumulation and hyperkalemia. In our study on CKD patients, the serum level of Potassium was increased significantly on comparing with healthy persons as a result of reduction of GFR. Insulin is One of the most important factors that increase cell potassium uptake after a mealm In people who have insulin deficiency owing to diabetes mellitus, the rise in plasma potassium concentration after eating a meal is much greater than normal, this is showed in this study, where 48.75% of patients were diabetic which may be the reason of elevated Potassium level in patient group.

Increased potassium intake also stimulates secretion of aldosterone, which increases cell potassium uptake. Excess aldosterone secretion (Conn's syndrome) is almost invariably associated with hypokalemia, due in part to movement of extracellular potassium into the cells. Conversely, patients with deficient aldosterone production (Addison's disease) often have clinically significant hyperkalemia as a result of accumulation of potassium in the extracellular space as well as to renal retention of potassium, also in case of renal failure and disturbances in renin-angiotensin system, as in our patients, this leads to elevation in serum potassium. Metabolic acidosis increases extracellular potassium concentration, in part by causing loss of potassium from the cells, whereas metabolic alkalosis decreases extracellular fluid potassium concentration. Although the mechanisms responsible for the effect of hydrogen ion concentration on potassium internal distribution are not completely understood, one effect of increased hydrogen ion concentration is to reduce the activity of the Na^+-k^+-ATPase pump which leads to decrease of cellular uptake of potassium and raises extracellular potassium concentration [23]. Potassium plays a critical role in conducting nerve impulses and controlling of cardiac muscle contractility and excitability, thus any changes in serum potassium level leads to cardiac arrhythmia and heart attack.

Conclusion

The results of this study concluded that, there is a correlation between estimated glomerular filtration rate and serum potassium, cholesterol, and uric acid, also this study proved that there a correlation between serum creatinine concentrations and potassium, cholesterol, triglycerides, and uric acid significantly, on the other hand, no correlation between serum urea levels and all of the tested cardiac risk factors.

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