ORIGINAL ARTICLE

UREMIA INDUCED CHANGES IN SERUM LIPID PROFILE AND EFFECT OF SELECTED VARIABLES ON PLASMA LIPIDS IN CHRONIC KIDNEY DISEASE

Shazia Tauqeer, Raeesa Naz, Nadia Haleem*, Muhammad Ayub**
Department of Physiology, *Biochemistry, Ayub Medical College, Abbottabad,
****Department of Physiology, AJK Medical College, Muzaffarabad, Pakistan**

Background: The course of chronic kidney disease (CKD) is complicated by dyslipidemia defined as changed plasma lipid levels and abnormalities of lipoproteins associated with early onset of atherosclerotic events. The altered pattern of lipid and lipoproteins metabolism results in rapid progression to end stage renal disease (ESRD) and atherosclerosis. The aim of this study was to see the pattern of dyslipidemia in CKD patients and to evaluate the effects of various sociodemographic variables on patterns of lipids and lipoproteins. **Methods:** This was a cross-sectional observational study conducted in Ayub Teaching Hospital, Abbottabad. In group-I, 313 patients of CKD were included in the study and 150 subjects with normal renal functions were taken as control. Serum lipid profile was evaluated for both groups. Effects of sociodemographic variables like age, sex, BMI, diabetes, hypertension and duration of renal failure was assessed. Data were analysed using SPSS-17 and $p<0.05$ was taken as significant. **Results:** Out of 313 subjects, 144 (46%) were female and 169 (54%) were male. The mean age of the patients was 48.48±14.78 years and it was 46.20±14.90 in controls. Most common type of dyslipidemia was hyperlipidemia of low density lipoprotein cholesterol (LDL-C) present in 90% patients. Hypertriglyceridemia was observed in 72% of patients. Low values for high density lipoprotein cholesterol (HDL-C) was observed in 28% of CKD group. Very low density lipoprotein cholesterol (VLDL-C) was found raised in 72% of CKD group. The most frequent dyslipidemia in combination was high LDL-C and high TG (201, 64%). Eighty-two (26%) of patients had a combination of high triglycerides (TGs) and low HDL-C. **Conclusion:** Significant dyslipidemia does develop in vast majority of chronic renal failure (CRF) patients. This is an important risk factor associated with early onset of atherosclerosis.

Keywords: Renal failure, CRF, dyslipidemia, Kidney disease, CKD, Lipid profile, LDL, HDL, Triglycerides

Pak J Physiol 2017;13(3):22–5

INTRODUCTION

Chronic Kidney Disease (CKD) is associated with many complex metabolic abnormalities, e.g., anaemia, cerebrovascular accidents, osteodystrophy, acid-base and electrolytes imbalance, volume overload hypertension and abnormal lipid profile or dyslipidemia.[1,2] Dyslipidemia is abnormal lipid profile, i.e., plasma concentration of various lipoproteins and lipids is relatively disturbed in relation with each other. Triglycerides (TGs) are elevated, high density lipoprotein cholesterol (HDL-C) decreases, while low density lipoprotein cholesterol (LDL-C) shows increase. This altered pattern of lipid metabolism accentuates the process of atherosclerotic events.[3] Elevation of plasma TGs is most frequent observation in CKD patients.[4] Elevated plasma TG in end-stage renal disease (ESRD) is usually accompanied with elevated plasma concentration of very low density lipoprotein (VLDL) as well as their impaired clearance associated with elevation and disturbed clearance of chylomicrons as well. This causes the accumulation of highly atherogenic chylomicrons remnants which are prone to oxidation.[5] In contrast the concentrations of LDL-C are found usually within normal range and are elevated in CKD only occasionally.[6,7] Plasma concentration of HDL-C is reduced frequently and conversion of HDL-3 which is poor in cholesterol esters, to a cardio-protective good cholesterol HDL-2, rich in cholesterol esters, is consistently impaired in CKD.[8,9]

Progressive deterioration of kidney functions is a direct consequence of dyslipidemia which can accelerates the disease progression by various mechanisms, e.g., reabsorption of fatty acids, various phospholipids and cholesterol which are found in the filtered lipoproteins and albumin, by the epithelial cells of renal tubules which initiates the inflammation of renal tubules and interstitium and other forms of tissue injury, oxidative damage[10] and foam cell formation[11]. Renal glomerular cells, glomerular basement membranes and renal tubular cells are all exposed to abnormal lipoproteins present in plasma[12] which promote matrix production in

glomerular mesangium and glomerulosclerosis[13]. The production of matrix proteins is specifically stimulated by LDL-C from the cultured renal mesangial cells and LDL also promotes generation of cytokines that promote inflammation. As a result vasoconstriction and proliferation of mesangial cell takes place resulting in lipoprotein associated glomerulopathy, characterized by formation of intraglomerular lipoprotein induced thrombi and ultimately glomerulosclerosis.[14,15]

The aim of this study was to see the pattern of dyslipidemia in CKD patients and to evaluate the effects of various sociodemographic variables on patterns of lipids and lipoproteins.

MATERIAL AND METHODS

This was hospital based cross-sectional comparative observational study conducted in Medical Units A, B, C, and Urology and Dialysis Units of Ayub Teaching Hospital (ATH) Abbottabad, from June 2012 to June 2015. Total 313 known patients of CKD diagnosed on basis of history, examination and laboratory assessment of renal function were included in the study. Anthropometric data of the patients were recorded and analysed according to uniform requirements for Asians.[16] Patients were grouped according to gender and duration of renal failure into 3 groups <5 years, 5–10 years, 10–15 years.

All diagnosed cases of chronic renal failure (CRF) irrespective of age and sex were included in the study. Patients receiving any lipid lowering therapy, known cases of familial hypercholesterolemia, kidney transplant, patients with thyroid disorders, acute infections, patients taking oral contraceptives, hormonal replacement therapy and steroids were excluded from the study.

The subjects included in control group were healthy individuals who were selected randomly and age, sex and BMI matched. History and physical examination of the patients were recorded on proforma. Serum lipid profile was assessed. SPSS-17 was used for data analysis. Results were analysed as Mean±SD for categorical variables and descriptive for continuous variables. Student's *t*-test and the Chi-square test for categorical parameters were applied and $p \leq 0.05$ was taken as statistically significant.

RESULTS

Total 313 subjects were included in the CKD group (46% females and 54% males). Their age ranged from 18 to 76 years (mean age 48.48±14.78 Years) and for controls it was 46.20±14.90 Years. Serum lipid profile included serum total cholesterol (TC), TGs, LDL, HDL and VLDL with statistically significant difference in two groups (p=0.000) in each case. (Table-1).

Frequency of hypercholesterolemia was 44%, hyper-triglyceridemia was 72%, low HDL-C 28%, borderline high in 90% and raised VLDL-V was present in 72% cases. (Table-2).

In addition to isolated dyslipidemia various combinations were also analysed and it was observed that most frequent dyslipidemia in combination was high LDL-C and high TG 64% then second most common type was high LDL-C and low HDL-C 62%. Twenty-six percent of CKD patients had a combination of high TGs and low HDL-C while rest of the patients has dyslipidemias of all five types in combination 24% in all. (Table-3).

Various clinical and sociodemographic variables affected dyslipidemia in quite significant way (Table-4). Older people had greater preponderance of high LDL-C and VLDL-C. Females had high incidence of high LDL-C, VLDL-C, and low HDL-C while males showed increasing trend in serum total cholesterol. Smoking strongly associated with high LDL-C and VLDL-C. Diabetes is most frequent cause of CKD as well as dyslipidemia of CKD with rise in TC, LDL-C and VLDL-C followed by hypertension (p<0.05). BMI has significant difference for high TGs, LDL-C, VLDL-C and low HDL-C in obese. Duration of renal failure significantly predicted high TC (p=0.03) and high LDL-C (p=0.002), with longer duration of illness (Table-4). Use of antihypertensive, beta blockers, hypoglycaemic agents and stage of CKD did not significantly predict dyslipidemia so they have been removed from results.

Table-1: Comparison of serum lipid profiles of two groups (patients=313, controls n=150)

Lipid Profile	Groups	Mean±SD	*p*
(TC, mg/dl)	Controls	170.06±22.66	0.000
	CKD	213.22±45.18	
(TG, mg/dl)	Controls	112.37±30.73	0.000
	CKD	206.90±96.19	
(HDL-C, mg/dl)	Controls	53.92±9.27	0.000
	CKD	43.29±9.23	
(LDL-C, mg/dl)	Controls	93.40±18.59	0.000
	CKD	128.91±37.75	
(VLDL-C, mg/dl)	Controls	22.92±5.44	0.000
	CKD	41.38±19.24	

Table-2: Frequency of individual lipid profiles

Lipid Profile	CKD patients n (%)	Controls n (%)	*p*
Hypercholesterolemia	138 (44)	15 (10)	0.001
High TG	226 (72)	18 (12)	0.00
Low HDL-C	88 (28)	6 (4)	0.01
Borderline High LDL-C	282 (90)	51 (34)	0.01
High VLDL-C	226 (72)	21 (14)	0.00

Table-3: Pattern of combined dyslipidemias in CKD patients

Dyslipidemia	Frequency	Percentage
High LDL+High TG	201	64
High LDL+Low HDL	195	62
High TG + Low HDL	82	26
High TC+High LDL + Low HDL+High TG + High VLDL	76	24

Table-4: Effects of selected variables on serum lipid profiles of CKD patients [n (%)]

		Hypercholesterolemia	High Triglycerides	Low HDL	High LDL-C	High VLDL-C
Age	Group I (20–40 Years)	31 (9.9)	56 (17.9)	57 (18.2)	38 (12)	57 (18)
	Group II (40–60 Years	38 (12.14)	94 (30)	51 (16.2)	56 (17.9)	13 (4)
	Group III (≥60 Years)	44 (14)	65 (21)	12 (4)	19 (6)	13 (4)
	p-value	0.490	0.678	0.767	0.002	0.000
Gender	Female	67 (22)	113 (36)	38 (12)	63 (20)	106 (34)
	Male	75 (24)	116 (37)	25 (8)	44 (14)	119 (38)
	p-value	0.001	0.190	0.02	0.000	0.000
Smoking	Yes	125 (40)	194 (62)	47 (15)	96 (30)	188 (60)
	No	19 (6)	35 (11.1)	16 (5)	13 (4)	38 (12)
	p-value	0.000	0.321	0.07	0.000	0.002
Cause of CKD*	Diabetes	44 (14)	4 (1.2)	16 (5)	32 (10.2)	67 (22)
	Hypertension	36 (12)	25 (8)	16 (5)	19 (6)	50 (15.9)
	Miscellaneous	13 (4)	22 (7)	4 (1.2)	13 (4)	25 (8)
	p-value	0.000	0.463	0.165	0.000	0.000
BMI (Kg/meter^2)	Normal (18.5–22.9)	44 (14)	176 (51)	69 (22)	219 (70)	176 (56)
	Underweight (<18.5)	–	7 (2.2)	–	19 (6)	7 (2.1)
	Overweight\(23–24.4)	16 (5.1)	18 (5.9)	19 (6)	44 (14)	38 (12)
	Obese(>25)	–	4 (1.2)	–	–	7 (2.1)
	p-value	0.071	0.000	0.028	0.000	0.000
Duration of CKD*	<5 years	13 (4.1)	50 (16)	50 (16)	–	50 (16)
	5–10 years	100 (32)	150 (48)	206 (66)	81 (26.6)	150 (48)
	10–15 years	25 (8)	25 (8)	25 (8)	6 (2)	25 (8)
	p-value	0.030	0.244	0.002	0.092	0.244

*Use of beta blockers, anti-hypertensives, oral hypoglycaemic agents did not significantly predict dyslipidemia, so have been removed from this model. $p \leq 0.05$ is significant.

DISCUSSION

Dyslipidemia is abnormal lipid profile, i.e., plasma concentration of various lipoproteins and lipids is relatively disturbed in relation with each other. TGs are elevated, HDL-C decreases while LDL-C shows moderate increase. Cardiovascular mortality among patients of ESRD who are dialysis-dependent, is 10–30 folds higher in comparison to general population.[17] In an epidemiological survey of Indian population with ESRD, who are maintained on haemodialysis (HD) treatment, it was found that 44% of the mortality in these patients is due to acute cerebrovascular accidents and MI.[18] The higher risk of cerebrovascular disease (CVD) in ESRD is attributable to numerous factors. The important ones include inflammation, oxidative stress, high blood pressure, and altered pattern of nitric oxide metabolism, metabolism of various lipids and lipoproteins, carbohydrates, phosphate and calcium metabolism.[18] A cluster of metabolic abnormalities like hypertriglyceridemia, hypercholesterolemia, low HDL-C and elevated sd-LDL levels greatly marked in CRF are independent risk factors of CVD in general population.[5] We included 313 known cases of chronic renal insufficiency who showed characteristic abnormalities of lipoproteins composition which are typically observed in renal failure population[19].

In our study mean value for TC was significantly higher than normal. Hypertriglyceridemia and hypercholesterolemia was most frequent observation in CKD population as consistent with the studies conducted at the Department of Nephro-Urology, Liaquat University Hospital, Hyderabad, Pakistan.[6] Frequency of hypercholesterolemia was 44% of diseased population and hypertriglyceridemia was observed in 72% of CKD patients in our study population. A little increased trend in raised serum cholesterol and triglyceride is because none of our patients were on lipid lowering treatment, the fact that is attributable to CRF alone[3–6].

The most common type of dyslipidemia was borderline high dyslipidemia of LDL cholesterol which was present in 90% of CKD patients LDL-C mean value was 128.91±37.75 mg/dl ($p<0.05$). Desirable values are 60–130 mg/dl and borderline high is 130–159 mg/dl according to the NCEP Adult Treatment Panel III lipid risk category revised in May 2001. Our study group is in borderline high group mostly near lower limit of borderline high group and consistent with other studies[9].

Mean HDL-C was 53.92±9.26 mg/dl in normal subjects and 43.29±9.23 mg/dl ($p=0.00$) in CKD group. According to the NCEP guidelines desirable range is up to 60 mg/dl, borderline high risk is 35–45 mg/dl, and <35 mg/dl is associated with high risk for CVD. Low values for HDL-C was observed in 28% of CKD group in our study. HDL cholesterol concentration is frequently reduced, and the conversion of HDL-3 which is poor in cholesterol esters, to a cardio-protective good cholesterol HDL-2, rich in cholesterol esters, is consistently impaired in CKD. Disturbances in these concentrations of apolipoproteins apo-AI, apo-AII, function of LPL enzymes, CETP receptors, other classes of lipoproteins apoE and apo-C can all may have major effect on anti-atherosclerotic property of HDL-C.[19] VLDL-C concentration was 22.91±5.44 mg/dl in normal subjects as opposed to CKD group's mean 41.38±19.23 mg/dl majority lying in high risk group.

Hypertriglyceridemia is in particular, a strong risk predictor of CVD.[20] Elevated plasma TG in CKD is usually associated with elevated concentration of plasma VLDL-C, results in consistence with our study group. This causes the accumulation of chylomicrons remnants which are specially prone to oxidation and are atherogenic.[21] Above mentioned dyslipidemias are found at all stages of CKD and duration of CRF as there was significant difference in serum total cholesterol and LDL-C with longer duration of illness. Serum triglycerides are persistently impaired after 5 years of renal metabolic derangements.[15]

Gender group showed significantly raised total cholesterol in males and elevated LDL-C, VLDL-C and low HDL-C in females (p<0.05).Our results signify that impact of uraemia on chronic dysregulation surpass hormonal influences. Females usually have cardio-protective lipid profile with high HDL and low LDL-C as compared to men[22], finding that is not consistent with our study group, possible explanation may be different effect of exercise, dietary habits, intercurrent hormonal problems, control of diabetes and hypertension which are not encountered in present study. Further research is therefore needed to completely understand the complex relationship between atherosclerosis causing lipoproteins and associated adverse outcomes in advance ESRD.

CONCLUSION

Significant dyslipidemia develops in vast majority of CRF patients. Optimal targets of different serum lipids in CKD and haemodialysis patients are not known. Available data on CKD population are too sparse to draw a conclusion regarding use of lipid lowering agents in these patients. Further research is needed to clarify this relationship and to regress the CVD in CKD patients.

REFERENCES

1. Minnaganti VR, Cumha BA. Infections associated with uremia and dialysis. Infect Dis Clin North Am 2001;15(2):385–406.
2. Smogorzewski M. Central nervous dysfunction in uremia. Am J Kidney Dis 2001;38:122.
3. Nosratola D, Vaziri, Norris K. Lipid disorders and their relevance to outcomes in chronic kidney disease. Blood Purification 2011;5:189–96.
4. Lodh M, Lal S, Goswami B, Karamkar P, Parida AK. Dyslipidemia in chronic renal failure: Cause or effect? Asian J Med Sci 2016;7(5):42–6.
5. Vaziri ND. Dyslipidemia of chronic renal failure: The nature, mechanism and potential consequences. Am J Physiol Renal Physiol 2006;290:262–72.
6. Maheshwari N, Ansari MR, Darshana MS, Lal K, Ahmed K. Pattern of lipid profile in patients on maintenance hemodialysis. Saudi J Kidney Dis Transpl 2010;21(3):565–70.
7. Cibulka R, Racek J. Metabolic Disorders in Patients with Chronic Kidney Failure. Physiol. Rev 2007; 56: 697–705.
8. Tsimihodimos V, Dounousi E, Siamopoulos KC. Dyslipidemia in Chronic Kidney Disease: an approach to pathogenesis and treatment. Am J Nephrol 2008;28:958–73.
9. Majumdar A, Wheeler D. Lipid abnormalities in renal disease. J R Soc Med 2000; 93:178–82.
10. Brunskill N. Albumin signals the coming of age of proteinuric nephropathy. J Am Soc Nephrol 2004;15:504–5.
11. Magil A. Interstitial foam cells and oxidized lipoprotein in human glomerular disease. Mod Pathol 1999;12:33–40.
12. Kaysen GA: Hyperlipidemia in chronic kidney disease. Int J Artif Organs 2007;30:987–92.
13. Vaziri ND, Sato T, Liang K: Molecular mechanism of altered cholesterol metabolism in focal glomerulosclerosis. Kidney Int 2003;63:1756–63.
14. Kwan BC, Kronenberg F, Beddhu S, Cheung AK. Lipoprotein metabolism and lipid management in chronic kidney disease. J Am Soc Nephrol 2007;18:1246–61.
15. Moradi H, Pahl MV, Elahimehr R, Vaziri ND. Impaired antioxidant activity of HDL in Chronic kidney disease. Transl Res 2009;153:77–85.
16. Robert H, Eckle: Relationship of Overweight and Obesity to Risk Factors for and Incidence of Cardiovascular Disease. Obesity Circulation 2005;111:e257–9.
17. Keith D, Nichols G, Gullion C, Brown J, Smith D. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. Arch Intern Med 2004;164:659–63.
18. Shah B, Nair S, Sirasat R. Outcome of end stage renal disease: experience at a private hospital. Indian J Nephrol New Series 1992;2:151–3.
19. Attman P, Samuelsson O, Johansson A, Moberly J, Alaupovic P. Dialysis modalities and dyslipidemia. Kidney Int 2003;84:110–2.
20. Amin K, Javed M, Iqbal NM, Qayyum A. Pattern of dyslipidemia in patients with CRF. Professional Med J 2006;13(1):79–84.
21. Nesto R. Beyond low-density lipoprotein: addressing the atherogenic lipid triad in type 2 diabetes mellitus and the metabolic syndrome. Am J Cardiovasc Drugs 2005;5:379–87.
22. Magkos F, Mohammed BS, Mittendorfer B. Effect of obesity on the plasma lipoprotein subclass profile in normoglycemic and normolipidemic men and women. Int J Obes (Lond) 2008;32:1655–64.

Address for Correspondence:

Dr Shazia Tauqeer, Assistant Professor Physiology, Ayub Medical College, Abbottabad, Pakistan. **Cell: +92-**333-5286502
Email: Shazia_tauqeer@hotmail.com

Received: 26 Jul 2017 Reviewed: 15 Sep 2017 Accepted: 20 Sep 2017