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Study of Lipid Profile in Chronic Kidney Disease Patients of Non Diabetic Etiology and its Relation to Serum Calcium

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Abstract

Background: *Patients suffering from chronic kidney disease are prone to develop diseases related to the cardiovascular system owing to the accelerated rate of atherosclerosis due to a multitude of factors, one of them being the characteristic "atherogenic" lipid profile abnormality that they exhibit. Few studies have pointed out the role of secondary hyperparathyroidism as a contributing factor in the development of the abnormal lipid profile.*

Aim

1. *To study the pattern of lipid profile abnormalities in chronic kidney disease patients of non-diabetic aetiology and to assess the relation between the degree of renal impairment and the extent of alteration of lipid profile.*
2. *To study the association between the serum calcium and phophorous levels and hypertriglyceridemia.*

Materials and Methods: *150 patients were carefully selected after assessing their eligibility using the inclusion and exclusion criteria. History, clinical examination and biochemical investigations were performed .Blood for the assessment of lipid profile was collected after a minimum of 9 hours fasting and a light fat free diet on the previous day. Data was analysed using SPSS software.*

Results: *Patients with chronic kidney disease were likelier to have higher levels of triglyceride and lower HDL values and as the stage of CKD progressed, the abnormalities in TGL and HDL values increased. There is a positive correlation between the level of triglycerides and serum phosphorous in both stage 4 and 5 CKD and an inverse correlation between serum TGL and calcium in stage 4.Dialysed patients exhibit no alteration in their lipid profile as compared to non dialysed patients.*

Keywords: *Lipid Profile, Chronic Kidney Disease, Non-Diabetic Etiology, Calcium.*

Introduction

Cardiovascular disease is a major cause of mortality and morbidity in patients with chronic kidney disease (CKD). The prevalence of hyperlipidemia or dyslipidemia is much higher compared to the general population. The majority of patients with chronic kidney disease die of cardio vascular disease rather than of end stage renal disease. The KDOQI (Kidney Disease Outcomes Quality Initiative) guidelines on dyslipidemias in CKD suggest that all patients should therefore be evaluated for dyslipidemias. They should have a complete fasting lipid profile with total, LDL and high-density lipoprotein cholesterol, and triglycerides measured to identify those at risk and those who require treatment.

Generally, the treatment approach parallels that suggested by the National Cholesterol Education Program Adult Treatment Panel III guidelines, in which the main focus of treatment is the level of LDL cholesterol. The ideal values of LDL is less than 100 and that of triglycerides is less than 150. Patients with CKD should be considered a "very high risk" category and aggressive therapeutic intervention initiated to reduce the risk of cardiovascular events. In addition to its effect on the cardiovascular system studies in a variety of animal models have shown that hypercholester-olemia accelerates the rate of progression of kidney disease[1].

All patients with chronic kidney disease experience a secondary form of dyslipidemia that mimics the atherogenic dyslipidemia of insulin-resistant patients. This is characterized by an increase in serum triglycerides with elevated VLDL, small dense LDL particles, and low HDL cholesterol. All of these particles are characterized by triglyceride-rich apolipoprotein B (apoB)-containing complex lipoproteins, which have-a significant atherogenic potential[2]. The prevalence of elevated cholesterol levels (>240 mg/dl) in general population is 20% but in patients with CKD due to nephrotic syndrome it is 90% and not due nephrotic syndrome it is 30%.That of elevated -triglyceride (>200 mg/dl) in general population is 15%, in those with CKD due to nephrotic syndrome is 60% and those with CKD not due nephrotic syndrome is 40%[3].

Patients with CKD generally have reduced plasma HDL cholesterol concentrations compared with non-uremic individuals; also the distribution of HDL sub fractions is different. Because of the low apo-AIV level and decreased lecithin cholesterol acyltransferase activity , the esterification of free cholesterol and hence the conversion of HDL3 to HDL2 are diminished in uremia[4].

There are qualitative changes in LDL in patients with CKD and dialysis patients. The proportion of sdLDL (small density LDL) which is considered to be highly atherogenic is increased. Modified LDL particles, such as ox-LDL (oxidised LDL) and Malondialdehyde-modified LDL are taken up by macrophages via binding to several cell surface scavenger receptors. The accumulation of cholesterol leads to the transformation of macrophages into foam cells in the vascular wall and contributes to atherogenesis[5].

Hypercholesterolemia, less commonly observed, is more likely to be present in patients receiving continuous ambulatory peritoneal dialysis than those receiving hemodialysis probably because of glucose absorption from the dialysate and peritoneal protein loss 5-15 g/day[6].

The most common dyslipidemia in chronic kidney disease is hypertriglyceridemia. The diminished clearance of triglycerides, which can lead to hypertriglyceridemia stems both from an alteration in the composition of circulating triglycerides (which become enriched with apolipoprotein C-III) and, perhaps later, from reductions in the activity of lipoprotein lipase and hepatic triglyceride lipase, which are involved in triglyceride removal[7,8,9].Why lipoprotein lipase activity is reduced in CKD is not well understood, but has been thought to reflect increased inhibitor activity. The associated secondary hyperparathyroidism may play a contributory role, perhaps by increasing calcium accumulation within the cells in the liver and adipose tissue[10].Studies in humans and experimental animals with CKD suggest that parathyroidectomy can normalize serum triglyceride levels and hepatic lipase activity[11]. In experimental animals, benefit can also be achieved with verapamil by a similar mechanism, although this has not been confirmed in humans[12] but two studies conducted in chronic kidney disease patients showed no relationship between the levels of parathyroid hormone and the degree of derangement of lipid profile[13,14]. Another possible mechanism for hypertriglyceridemia in CKD is retention of a circulating inhibitor of lipoprotein lipase, such as pre-beta-high density lipoprotein (HDL)[15]. Pre-beta-HDL is a form of apolipoprotein A-I found in the non- lipoprotein fraction of normal plasma.

The levels of lipoprotein a is also significantly higher in patients with chronic kidney disease as compared to general population and it is well established that the high levels of lipoprotein a correlates with increased risk of atherogenesis and cardio vascular mortality[16].

Indian studies on lipid profile abnormalities in chronic renal failure (CRF) have varied from no abnormalities at all to significant abnormality (hypertriglyceridemia and reduced HDL) as described in the Western literature.

Significant hypertriglyceridemia does develop in a majority of CRF patients. The abnormality probably improves with dialysis treatment and renal transplantation.

A lower Apo Al/Apo B ratio in CRF patients may account for higher risk of atherosclerosis[17.]

Statins significantly reduced the risk of all-cause and cardiovascular mortality in CKD patients who are not receiving renal replacement therapy. They do not impact on the decline in renal function as measured by creatinine clearance, but may reduce protein excretion in urine. Statins appear to be safe in this population. Guidelines recommen-dations on hyperlipidemia management in CKD patients could therefore be followed targeting higher proportions of patients receiving a statin, with appropriate monitoring of adverse events[18].

Materials and Methods

The study was an observational study done during the period, 18th Jan. 2015 to 18th Nov. 2015 at GMCH Kottayam.

After attaining clearance from the Institutional Review Board, this hospital based observational study was conducted in the patients admitted in the ward under the Department of General Medicine and department of nephrology. A total of 150 subjects was selected after explaining the purpose of the study and procedure in detail and, after attaining their consent in written format. Data collection done by clinical history, examination and investigations. The patients included in the study were non- diabetic patients who were diagnosed to have chronic kidney disease according to KDOQI (Kidney dialysis outcome quality initiative) criteria. Definition of Chronic Kidney Disease according to KDOQI Criteria

Kidney damage for 3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifest by either: Pathological abnormalities; Markers of kidney damage, including abnormalities in the composition of the blood or urine, or abnormalities in imaging tests. GFR <60 mL/min/1,73m^2 for 3 months, with or without kidney damage.

Staging Of Chronic Kidney Disease (KDOQI)

Stage	GFR
0	>90(With Risk Factors For CKD)
1	>90(With Demonstrated Kidney Damage)
2	60-89
3	30-59
4	15-29
5	<15

Estimated GFR is calculated by means of Cockroft-Gault equation.

Estimated creatinine clearance (ml/mg) = [(140-age) x body weight in kg] / (72xCr in mg/dl) multiply by 0.85for women.

For our study, chronic kidney disease was diagnosed by means of clinical examination, biochemical analysis and sonological abnormalities.

Procedure in Detail

Those patients meeting the criteria for chronic kidney disease was selected carefully excluding those with diabetes, chronic liver disease, those on hypolipidemic drugs, those with nephrotic range proteinuria and those with hypothyroidism. Detailed history and clinical examination was performed and routine hematological and biochemical investigations was performed which include hemoglobin, total leukocyte count, differential count, ESR, platelet, blood urea, serum creatinine, serum calcium, phosphorous, magnesium, uric acid. USG scanning was done to assess renal echotexture and size. All those not

meeting the criteria were excluded. Blood samples were drawn from all the patients after a minimum of nine hours of fasting, the subjects were asked to have a light fat free diet on the day prior to sampling. The samples were analyzed on the same day for the levels of trigycerides, HDL, LDL, and total cholesterol levels.

Statistical analysis was done using appropriate software to look for any association between lipid profile and the various clinical features and biochemical parameters.

Results

Tabie 1: GFR*TGL

Corelation between GFR and TGL in non-dialysed patients

		GFR	TGL
GFR	Pearson Correlation	1	* -.188
	Sig. (2-tailed)		.040
	N	120	120
TGL	Pearson Correlation	-.188*	1
	Sig. (2-tailed)	.040	
	N	120	120
*. Correlation is significant at the 0.05 level (2-tailed).			

Table 2: GFR*HDL

Corelation between GFR and HDl in non-dialysed patients

		GFR	HDL
GFR	Pearson Correlation	1	.467**
	Sig. (2-tailed)		.000
	N	120	120
HDL	Pearson Correlation	**.467	1
	Sig. (2-tailed)	.000	
	N	120	120
**. Correlation is significant at the 0.01 level (2-tailed).			

Table 3: GFR*(TC&LDL)

Corelation between GFR and LDL and total cholesterol in non-dialysed patients

		GFR	TC	LDL
GFR	Pearson Correlation	1	.094	.031
	Sig. (2-tailed)		.309	.733
	N	120	120	120
TC	Pearson Correlation	.094	1	** .822
	Sig. (2-tailed)	.309		.000
	N	120	120	120
LDL	Pearson Correlation	.031	** .822	1
	Sig. (2-tailed)	.733	.000	
	N	120	120	120
**. Correlation is significant at the 0.01 level (2-tailed).				

Table 4: Proportion of Patients with TGL>150 in Stage 5 Vs Non-Stage 5 CKD

		TGL		Total
		<150	>150	
GFR	<= 15.0 Stage 5	21	54(72%)	75
	> 15 Other stages	35	40(53.3%)	75
Total		56	94	150

The higher percentage (72) of hypertrygly-ceridemia in Stage V CKD as compared to other status (53.3%) is statistically significant with a P value of 0.028.

Table 5: Stage HDL Group

Corelation with stage of CKD and HDL

HDL				Total
		<50in females and <40 in males	>50 in females and >40 in males	
Stage	STAGE 2	5(25%)	15	20
	STAGE 3	10(50%)	10	20
	STAGE4	18(51.3%)	17	35
	STAGE5	55(73.3%)	20	75
Total		88	62	150

Increasing percentage of patients with low HDL as the stage of CKD advances is statistically significant with a P value of <0.01.

Table 6: Correlation between TGL and S.Calcium in Stage 5 Nondialysed CKD Patient

		serum calcium	TGL
serum calcium	Pearson Correlation	1	-.143
	Sig. (2-tailed)		.348
TGL	Pearson Correlation	-.143	1
	Sig. (2-tailed)	.348	

There is an inverse correlation between calcium and triglyceride in stage V, but not statistically significant.

Table 7: Correlation between S.TGL and Phosphorous in Stage 5 Nondialysed CKD Patient

		serum phosphorus
TGL	Pearson Correlation	.496**
	Sig. (2-tailed)	.001

There is a positive correlation between serum TGL and phosphorous levels in stage V CKD and statistically significant with a P value of <0.01.

Discussion

150 patients were studied of which 101 were males and 29 were females. The mean age of the patients studied was 52.37 +_ 10.062 with a minimum age of 28 and maximum 78. 30 of the stage 5 CKD patients were undergoing dialysis.

Triglyceride: In non dialysed patients, there is an inverse co relation between the serum triglyceride levels and GFR and the correlation is statistically significant. There is an increasing percentage of patients with higher triglyceride values as the stage of CKD increases, but it not found to be statistically significant. But there was a higher percentage of patients with abnormal triglyceride values in CKD stage 5 as compared to non stage 5 patients and was found to be statistically significant with a p- value of 0.028.

In a study by Kasiske BL[3] 40 % of the patients with CKD not due to nephrotic syndrome has triglyceride values more than 200, which is comparable to our study, with 62.7 % of patients having triglyceride more than 150.

In the study "Prevalence of dyslipidemia in urban and rural India" the ICMR-INDIAB study conducted by Shashank R et.al , the prevalence of hyper triglycerideamia in the general population of India was found to be 29.5 %. Hyper triglycerideamia is one of the most common lipid profile abnormalities observed in CKD patients as reported by Attman PO et al[18] and Vazirin ND et al[19]

HDL: 58.7% of all patients studied have HDL value less than 50 in females and less than 40 in males. The mean value of HDL decreases as the stage of CKD advances and statistically significant with a p-value less than 0.01.Attman et al[20] and Deighan et al[21] observed that the HDL values decrease in patients with CKD.

LDL: Our study shows no significant association with LDL and stage of CKD or GFR in any of the statistical analysis performed .Moore K.J et al has observed that while the total S.LDL values remain largely unaltered as is observed in our study, the proportion of sdLDL which is considered to be highly anthrogenic is increased[5].

Total Cholestrol: Our study shows no significant association with total cholesterol values and stage of CKD and this correlates well with the existing studies. Attman et al[26] and Deghan et al[27] observed that total cholesterol values may remain the same or decrease in patients with CKD.

Corelation between TGL and S.Calcium and S.Phosphorus (non-dialysed patients): There is an inverse correlation between GFR and S.Calcium in CKD, but not statistically significant. But there is a positive correlation between GFR and S.Phosphorus in CKD and is statistically significant with p-value less than 0.001.

Effects of Haemodialysis on lipid profile

Overall no difference in lipid profile abnormalities are observed between dialysed and non-dialysed patients. Attman *et al*[26] and Deghan *et al*[27] demonstrate that the liquid profile abnormalities of dialysed and non-dialysed patients remain essentially the same. Wheeler D.C reports that abnormalities of lipoprotein metabolism that are associated with renal failure are not corrected by renal replacement therapy[17]

Conclusion

- Patients with ckd due to non-diabetic aetiology tend to have low HDL, high triglyceride values, and unaltered levels of total cholesterol and LDL and HDL decreases and triglyceride increases as GFR declines and the stage of CKD advances.
- There is a statistically significant positive correlation between TGL and serum phosphorous in both stage 4 and stage 5 of ckd and an inverse correlation between s.ca and TGL in stage4 and 5,but the correlation is not statistically significant in stage 5.
- There is no difference between the lipid profiles of dialysed and non dialysed, nondiabetic CKD patients.

Recommendations

- Patients with chronic kidney disease tend to have an atherogenic lipid profile, that is low HD and high TGL. In addition to the various proatherogenic factors in play in chronic kidney disease, this pattern of lipid profile accelerates the sclerotic process and eventually lead to the high incidence

of cardiovascular mortality and morbidity observed in these groups of patients. Studies also prove that the lipid profile abnormalities as such accelerates the progression of ckd, Thus it is imperative to pay close attention to lipid parameters of patient with ckd and treat accordingly.

- It should also be pointed out that abnormalities of calcium and phosphorous metabolism may contribute to the lipid profile abnormalities, and thus indirectly and directly increase atherosclerosis. Timely treatment of ckd patients with phosphate binders ,calcium and vit D may attenuate the lipid profile abnormalities contributed to by hyperparathyroidism. More research needs to be done in this field.

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