ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Pattern of Dyslipidemia in Chronic Kidney Disease.

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ABSTRACT

Chronic Kidney Disease is one of the major causes leading to mortality and morbidity and its incidence and prevalence is also on the uptrend. One of the leading cause for death in stage 5 CKD patients is secondary cardiovascular problems associated with natural history of disease process. The aim of this study is to study the pattern of dyslipidaemia in patients suffering from chronic disease. In this study, 100 Chronic Kidney Disease patients attending the outpatient department or admitted in Rajiv Gandhi Government General Hospital were taken up for the study. This study revealed that there was a progressive increase in triglyceride and total cholesterol levels and a decrease in the levels of high density lipoproteins in patients suffering from Chronic Kidney Disease.

Keywords: Chronic Kidney Disease; Lipid Profile; Dyslipidaemia;

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ISSN: 0975-8585

INTRODUCTION

CKD is defined as "decline in renal function attributed to changes either in the structure of kidney or its function as evident by imaging or biochemistry respectively, in a person for more than 90 days duration" with its implications for health [1].

The term 'with implications for health' implies that decline in renal function secondary to changes either in structure or function is associated with its own consequences but all those really do not affect health of the individuals. Clinical evaluation helps to identify the varied manifestations associated with renal damage which are evident prior to declining renal function. In CKD, not only there is decline in excretory function, as the disease process affects the kidney as a whole which is evident by decline in other functions like endocrine functions (decreased erythropoietin production), metabolic functions (acid base balance).The best parameter to assess kidney function is GFR.

- Decreased GFR Less than 60 ml/min/1.73m^2
- Renal failure Less than 15 ml/min/1.73m^2

Globally, CKD contributes significantly to the disease burden. According to WHO, CKD is one among the major causes leading to mortality (12th major cause) and morbidity (17th major cause). Detection of new cases of stage 5 CKD is increasing at a rate of 8% per year [2].

The disease burden due to CKD in India in terms of prevalence remains elusive as the quality of data provided by the studies conducted on a small scale remains questionable.

A small beginning has been made by the start of CKD registry in India (www.ckdri.org). Screening and Early Evaluation of Kidney Disease (SEEK) study was started in 2006 in India which has reported a very high prevalence of 17.4% of CKD among 5,623 participants; 7% out of these were in CKD Stage 1; 4.3% were in CKD Stage 2; 5% were in CKD Stage 3 and 1.6% in CKD Stage 4 and 5.

Hypertension and Diabetes are the major forerunners of CKD. India one of the leading nation in terms of prevalence of diabetes and hypertension. So naturally ESRD burden will be increasing at an alarming pace. In 2030, India will have a prevalence of 79.4million cases [3].

CORDIOVASCULAR DISEASE IN CKD

One of the leading cause for death in stage 5 CKD patients is secondary cardio vascular problems associated with natural history of disease process. Relative risk of CVD in patients with CKD ranges between 10-200. This implies the chance of developing cardiovascular event is 10 to 200 times higher in CKD patients when compared to the control group of same age and sex. Relative risk of CVD varies in different stages of CKD. As a result, most patients with CKD succumb to cardiovascular disease before ever reaching stage 5 CKD. Thus, the focus of patient care in earlier CKD stages should be directed to the prevention of cardiovascular complications. The increased prevalence of vascular diseases in CKD patients derives from both disease related and common risk factors.

DYSLIPIDEMIA IN CKD

The most common dyslipidaemia seen in CKD patients are elevated TG and low HDL. This change seen in CKD patients highly favours and accelerates the process of atherosclerosis [4].Dyslipidaemia is a marker of disease progression per se regardless of the cause and contributes to high risk of CVD. Increased levels of lipoprotein (a) are also common in CKD10.

Dyslipidaemia is considered both as a cause and consequence of CKD, although the mechanisms for this relationship are not completely understood. Dyslipidaemia and abnormal levels of lipoprotein induce damage to mesangial cells as well as proliferation and atherosclerosis of renal arterioles, which results in excessive glomerular basement membrane deposition and glomerulosclerosis. These phenomena result in decreased renal function and further accentuate dyslipidaemia.

ISSN: 0975-8585

In CKD there is progressive increase in levels of TG and decrease in HDL levels. The TG/HDL ratio is a far better indicator of insulin resistance and adverse cardiovascular events than the other lipid parameters including LDL, TG or the ratio of total cholesterol to HDL. Further, the ratio of TG/HDL correlates very well with concentration of small, dense LDL particles, which are more prone to oxidization and are highly atherogenic. Thus, it is conceivable that elevated TG/HDL ratio may also indicate the progression and development of CKD, since similar pathologic mechanisms are involved in both atherosclerosis and glomerulosclerosis.

MATERIALS AND METHODS

STUDY POPULATION:

Hospital based 100 CKD patients in Government General Hospital (out-patient & in-patient) for a period of 6 months.

CONTROL POPULATION:

Age & sex matched 100 normal healthy controls are selected from the same hospital, who came with different illness other than the study disease.

SELECTION CRITERIA FOR CASES:

CKD patients in stage III - V, irrespective of aetiology except nephrotic proteinuria and diabetes mellitus on conservative management.

EXCLUSION CRITERIA FOR BOTH CASES AND CONTROLS:

Exclude patients who are obese, with diabetes mellitus, those on beta- Blockers and oral contraceptive pills, pregnant patients, renal transplant patients, patients on dialysis.

Diabetes mellitus is ruled out by fasting and post-prandial blood sugar. Patients are excluded if they have FBS > 100mg/dl.

Urine spot PCR in early morning urine sample is used to exclude nephrotic proteinuria. Urine protein in mg and urine creatinine in mg is noted & their ratio is calculated. Cases were excluded if the ratio was >3.5 (correlates with 3.5 gm protein/24 hrs. urine sample).

Obese patients are excluded since they have high VLDL & reduced HDL13. Obesity classification was based on Body Mass Index (BMI). BMI = weight in kg / height in m2. If BMI was > 30 kg/m2, patients were excluded.

Pregnant patients were excluded since VLDL is elevated in pregnancy [5].

Those on OCPs were excluded, since the oestrogen component increases HDL [5].

Beta blockers elevate VLDL & reduce HDL13, hence patients consuming it were excluded.

In the proforma, detailed history regarding the presenting symptoms like fatigue, weakness, pruritis, anorexia, nausea, vomiting, nocturia, polyuria, oliguria, insomnia, oedema, difficulty in breathing, etc., was enquired. Past history & history of dialysis was obtained. General examination including pallor, pulse rate, blood pressure, height & weight were noted & BMI calculated. Cardiovascular system, respiratory system, per abdomen examination & central nervous system examination including fundus examination was done.

The following laboratory investigations were obtained - haemoglobin (g/dl), blood sugar - fasting & post prandial (mg/dl), urea (mg/dl), creatinine (mg/dl), electrolytes - sodium, potassium, chloride & bicarbonate (mEq/L). Creatinine clearance was calculated. Ultrasonography of the abdomen was done to measure the kidney size. Fasting lipid profile was done - Total Cholesterol, Triglycerides and High Density Lipoproteins (HDL) were measured and Low Density Lipoproteins, & TG/HDL ratio were calculated.

ISSN: 0975-8585

Electrocardiogram, urine analysis & spot urine protein creatinine ratio were also done. All the data collected were analysed using SPSS (Statistical Package for the Social Science) system.

Table 1. Indian Data

S.no	Place	Prevalence	Incidence
1.	Chennai	86 /10000	-
2.	Delhi (creatinine >1 .8mg/dl were included as cases)	79/10000	-
3.	Bhopal		151/million population (ESRD alone)[4]

Table 2: Distribution of LDL With Stage Of CKD

S.no	LDL (mg/dl)	Stage of CKD			Total
		3	4	5	
1.	<100	17	11	5	33
2.	100-129	2	0	0	2
3.	130-159	9	0	0	9
4.	>159	0	30	26	56
Total		28	41	31	100

Table 3: Distribution of TGL With Stage Of CKD

S.no	TGL (mg/dl)	Stage of CKD			Total
		3	4	5	
1	<150	19	11	5	35
2	150-199	9	30	12	51
3	>200	0	0	14	14
Total		28	41	31	100

Table 4: Distribution Of TC With Stage Of CKD

S.no	TC (mg/dl)	Stage of CKD			Total
		3	4	5	
1.	<200	19	11	5	35
2.	200-240	9	10	0	19
3.	>240	0	20	26	46
Total		28	41	31	100

Table 5: Distribution Of HDL With Stage Of CKD

S.no	HDL (mg/dl)	Stage of CKD			Total
		3	4	5	
1	>40	19	11	5	35
2	<40	9	30	26	65
Total		28	41	31	100

ISSN: 0975-8585

Table 6: Prevalence of Abnormal Lipid Profile in Study Group

Stage of CKD	Lipid profile		Total
	Abnormal	Normal	
3	9 (9%)	19 (19%)	28
4	30 (30%)	11 (11%)	41
5	26 (26%)	5 (5%)	31
Total	65	35	100 (100%)

DISCUSSION

CKD is a worldwide health problem and one of the growing, silent epidemic of non-communicable diseases. For a long time, dyslipidaemia in CKD patients was an underestimated problem. Diabetes, nephrotic syndrome, thiazide diuretics and many secondary causes of dyslipidaemia are well known to us and obviously CKD due to the above disorders (diabetes being the most common aetiology) will have dyslipidaemia. This study was hence undertaken to look, whether chronic kidney disease per se, possess a risk of dyslipidaemia (without the above secondary causes of dyslipidaemia) by excluding obesity, diabetes, patients with nephrotic range of proteinuria, those on beta-blockers, & OCPs, pregnant patients, renal transplant patients and CKD patients on HD.

The fact that ratio of triglyceride/high density lipoprotein is a surrogate marker of insulin resistance and its elevation in diabetic patients is well known. This ratio represents the concentration of highly atherogenic small density LDL in the body. This study was conducted to assess the association between the ratio of triglyceride/high density lipoprotein in non-diabetic CKD patients.

100 CKD patients were selected (who satisfied the above exclusion & inclusion criteria) and 100 age and sex matched, hospital based controls were also chosen and lipid profile was done on a fasting sample. The results obtained were statistically analysed using chi square test in study group and unpaired student t test for comparing study group with control group.

AGE DISTRIBUTION:

Age of the patients varied from 16 yrs. to 72 yrs. In our study group of 100 patients, clustering of cases was observed between the age group 30-60 years (82%). Of this, 40-50 years had maximum percentage (33%) in our study population. Association between age group and stage of CKD was statistically significant (p value= 0.004).

SEX DISTRIBUTION

In our study, males were 86% remaining 14% were females. It appears as if there was a considerable gender prevalence among CKD patients. But the association between gender and prevalence of CKD was statistically not significant (p value =0.977).

Even though the majority of patients in our study group belonged to the male sex, distribution of different stages of CKD among males and females did not have gross variability. In males, distribution of stage 3, stage 4 and stage 5 CKD was 27.9%, 40.7% and 31.4% respectively. In females, distribution of stage 3, stage 4 and stage 5 CKD was 28.57%, 42.86% and 28.57% respectively

DISTRIBUTION OF LDL

In our study, lowest value of LDL was 19.6 mg/dl and the highest value was 195.8 mg/dl. Their mean value was 134.67 mg/dl and standard deviation was 55.61. 33 % of the patients had normal values of LDL. The remaining proportion had elevated levels of LDL. Of this group, about 56 % had abnormally high values of LDL >159 mg/dl. The association between rise in serum LDL levels and stages of CKD was statistically significant (p value < 0.001). In controls, the mean and SD were 131.30 and 157.054 respectively. However in comparison study, student t value was calculated and P value was statistically not significant (p value=0.840) when compared with controls. This shows that the elevated LDL levels in the study group was statistically

insignificant when compared with the control group. Similar results of statistically insignificant (p value >0.05) LDL- elevation in CKD patients (not on dialysis) when compared with control group was reported in a study conducted by A.Madhusudhana Rao et al [6].

Elevated LDL levels was seen in study conducted by Diana M Lee et al [7]. But most studies find that CKD patients usually have normal or slightly reduced concentrations of LDL levels and they exhibit important disturbance in the density distribution of LDL sub fraction that is characterized by predominance of small dense LDL particles [8].

DISTRIBUTION OF TGL

In our study group, TG values ranged between 80 mg/dl to 240 mg/dl. Mean and standard deviation of study group were 154.93 and 45.128 respectively. In the study population, 65% of patients had TG levels more than 150 mg/dl. Of this, 14 cases had TG values more than 200 mg/dl, interestingly all those were stage 5 CKD patients. Association between rising TG levels and progression in the stage of CKD was found to be statistically significant (p value < 0.0001). In controls, the mean and standard deviation were 108.23 and 19.357. Student 't' test was performed and t value was calculated (t=9.510) P value was significant (P < 0.0001). This shows that the TG levels are significantly raised in CKD patients compared to the control group.

Shah et al [9] & most western studies demonstrated that hypertriglyceridemia was the abnormality found in CKD patients. Gupta DK et al [10], Das BS et al [11], Bagdade J [12], Chan MK et al [13] also found hypertriglyceridemia was the major abnormality in their studies.

DISTRIBUTION OF TOTAL CHOLESTEROL

Range of TC levels in study group was 100 mg/dl to 262 mg/dl. The mean value of study group was 207.19 and standard deviation was 207.19. In the study group, 65 Patients out of 100 had abnormal levels of total cholesterol more than 200 mg/dl. Levels more than 240 mg/dl was seen in stages 4 and 5 of CKD (n-46). This association between the elevation of LDL and progression of CKD was found to be statistically significant (p value <0.001). The mean and standard deviation of control group was 204 and 156.71 respectively. T value was calculated (t = 7.395). P value was (P<0.0001) significant. This shows that total cholesterol levels are significantly elevated in study population compared to the control group.

Similar elevation in cholesterol was found in study conducted by Diana M Lee et al. In a prospective study [14], marked elevation in TC, LDL and apo (B) lipoprotein was seen in non-diabetic CKD patients and it was strongly associated with deterioration of renal function. In another study [15], rise in TC levels and proteinuria had positive cholesterol with severity of CKD. But most studies state that hypercholesterolemia is not a common feature of CKD. It is commonly found in nephrotic syndrome.

DISTRIBUTION OF HDL

Serum HDL values ranged between 25 mg/dl to 68 mg/dl in the study group. In this group, mean value was 41.53 and standard deviation was 12.176. In the study population, decreased levels of HDL (<40 mg / dl) was observed in all stages of CKD. 65% of patients had values < 40mg/dl. The association between decreasing HDL levels and the progression in stage of CKD was statistically significant (p value < 0.001).

In control group the mean was 51.31 and standard deviation was 7.484. T value was calculated using student t test and it was 6.843. P value (<0.0001) was statistically significant. This shows that there was a significant reduction in HDL levels in patients with CKD than that of controls. Similar findings was found in the conducted by Diana M Lee et al. and MDRD study [16].

DISTRIBUTION OF TG/HDL RATIO

In CKD patients, the mean of this ratio was 4.309 and standard deviation was 2.104. Increasing TG levels and decreasing HDL levels in CKD patients are reflected as rising TG / HDL ratio with progression of the severity of CKD from stage 3 to stage 5. In our study group, 35% had ratios less than 3.5. About 20 patients had

TG/ HDL ratio in the range of 3.5-5, 45 patients had TG/HDL ratio >5. This association between the rise in TG/HDL ratio and progression of CKD was found to be statistically significant (p value <0.0001).

In control group the mean was 2.215 and standard deviation was 0.823. T value was calculated using student t test and it was 9.266. P value (<0.0001) was statistically significant. This shows that the TG/HDL ratio was significantly elevated in CKD patients when compared with the control group. Studies have shown that this ratio was significantly associated with the prevalence of CKD and its rise correlates with the severity of CKD [17].

CONCLUSION

Following results were obtained from our study.

- Elevated TG levels in stages 3, 4 and 5 of CKD which was found to be statistically significant when compared with control group.
- Decrease in HDL levels in stages3-5 of CKD was found to be statistically significant when compared with control group.
- Progressive rise in TG and decline in HDL as reflected as Increasing TG/HDL ratio from stage 3-5 was found to be statistically significant when compared with control group.
- TG/HDL ratio correlates with the progression and severity of CKD. Hence this ratio can be taken as a marker of disease severity.
- Elevated TC levels in stages 3-5 of CKD was statistically significant when compared with control group.
- Elevated LDL levels in stages 3, 4 and 5 of CKD was statistically not significant when analysed with control group.

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