

Original Research Article

Study of Serum Homocysteine and Lipid Profile Parameters in Patients of Chronic Renal Failure

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ABSTRACT

Objective: The aim of the study was to evaluate the serum homocysteine level and correlate it with lipid profile in chronic renal failure patients.

Study Design: Cross-sectional study

Methods: Total 150 individuals comprising of male & female age group of 18-70 years were studied between Dec 2012- Jan 2014. They are divided into 3 groups: 50 diagnosed were of chronic renal failure without dialysis in group I, 50 diagnosed case of chronic renal failure on dialysis from 3 month or more in group II and 50 healthy individuals as control in group III.

Results: It was observed that serum homocysteine level were significantly increased on both the chronic renal failure patient either in dialysis or without dialysis condition but it was noted that serum homocysteine level were more elevated in patients of renal failure on dialysis compared to without dialysis renal patients.

Key Words: Homocysteine, GFR, Chronic renal failure, Dialysis, Glomerulonephritis.

INTRODUCTION

Chronic kidney disease (CKD) is a deterioration of renal function, which results from diminished effective functioning of renal tissue. [1] The kidneys (Latin: ren, Greek: nefros) serve several essential roles in humans, not only filtering the blood and excreting waste products but also playing a crucial role in regulatory functions such as maintaining blood pressure, water balance, electrolyte levels and acid-base balance. [2] The kidneys also play a major role in degradation of proteins as well as producing hormones affecting red blood cells production and mineral turnover. [2,3]

CKD is a worldwide serious health problem. According to World Health organization (WHO) Global Burden of Disease project, diseases of the kidney and urinary tract contribute to global burden

with approximately 850,000 deaths every year and 115,010,107 disability adjusted life years. CKD is 12th leading cause of death and 17th cause of disability¹. It has been recently estimated that the age-adjusted incidence rate of end stage renal disease (ESRD) in India to be 229 per million populations (pmp), and more than 100,000 new patients enter renal replacement programs annually in India. [4]

In adults, leading cause of kidney disease are diabetes, hypertension and glomerulonephritis. Other causes of renal failure include kidney inflammation, genetic diseases, autoimmune diseases, and birth defects. [5]

Cardiovascular disease is a major cause of morbidity and mortality among patients with chronic renal failure. [4] As compared with the general population,

dialysis patients have more than a 10 times higher relative risk for cardiovascular mortality. [6]

Homocysteine is a sulphur containing intermediary amino acid which is derived by the demethylation of methionine. The normal range of serum homocysteine is 5 to 15 $\mu\text{mol/L}$. [7] Elevated serum homocysteine beyond the normal range ($>15 \mu\text{mol/L}$) is traditionally referred to as hyperhomocysteinemia.

Hyperhomocysteinemia may be due to genetic insufficiencies of the enzymes needed for its metabolism, to nutritional deficits in vitamin cofactors, or to other circumstances such as drugs and medical conditions like diabetes. [8] Similarly, low intake and plasma concentrations of folate and vitamins B6 and B12 have been associated with increased plasma homocysteine levels. [9]

Hyperhomocysteinemia, is defined as total homocysteine concentrations elevated above 15 $\mu\text{mol/L}$. Plasma homocysteine concentration exhibits a strong relationship with (indices of) renal function. Hyperhomocysteinemia has been implicated in patients with CKD. There are several indications that whole body homocysteine metabolism is altered in renal insufficiency. [10] Stable isotope studies in dialysis patients have shown a decreased homocysteine clearance by transsulfuration and decreased homocysteine remethylation and methionine transmethyltion. [11] Hyperhomocysteinemia has been also associated with the pathogenesis of cardiovascular disease. [12,13] Deficiencies of the vitamins folic acid, pyridoxine (B6), or B12 (cyanocobalamin) can lead to hyperhomocysteinemia. [14,15]

Glomerular filtration rate (GFR) is measured in mL/min and is usually normalised to a body surface area of 1.73 m^2 . In a healthy young adult, GFR is 100 to $130 \text{ mL/min}/1.73 \text{ m}^2$. GFR decreases with increasing age, but opinions differ about when the age-related decline begins. Starting from 40 to 50 years of age, GFR appears to decrease approximately $10 \text{ mL/min}/1.73 \text{ m}^2$

per decade. Methods to estimate GFR have been developed as alternatives to measuring GFR. The most common is based on creatinine. The plasma concentration of creatinine increases as GFR decreases; an elevated concentration is thus a rough indicator of impaired kidney function. However, the concentration of creatinine in plasma also depends on muscle mass and several formulas have been developed to estimate GFR from the report. Methods to Estimate and Measure Renal Function (Glomerular Filtration Rate) creatinine while taking into consideration age, sex, and in some cases ethnicity, weight, and height. Which creatinine equation yields the most accurate estimate of GFR in different situations and in different disorders is still an open question. [16]

MATERIALS AND METHODS

Sources of the data

The present study was a hospital based cross sectional study carried out in department of Biochemistry, Aurangabad, Maharashtra during the period of Dec 2012 to July 2014. The selected study subjects were from the Medicine department, out Patient Department (OPD) wards, ICCU & dialysis unit. The study group patients with CKD were diagnosed with history of kidney damage or decreased kidney function with decreased glomerular filtration rate for more than three or more months. Total 150 individuals age groups of 18-70 years were studied. The Study population was divided into 3 groups:

Each group consists of individuals of age between 18-70 years.

- Group 1: 50 Diagnosed cases of chronic renal failure without dialysis
- Group 2: 50 Diagnosed cases of chronic renal failure on dialysis from 3 months or more
- Group 3: 50 healthy individuals as control.

Participants were selected on the basis of detailed history, clinical examination and laboratory investigations. Detailed history of participants including

age, sex, marital status, history of any medications, addictions, physical activities, eating habits and lifestyle was taken.

Sample Collection

After written informed consent, 12 hour fasting venous blood samples were collected from all participants in fluoride and plain bulbs. Serum was separated after 1 hour by centrifugation at 3000 rpm for 10 minutes, and was tested for following parameters

Inclusion criteria:

- New or old chronic kidney disease patients with GFR <60 ml/min.
- Chronic kidney disease patients on conservative treatment and/or on maintenance hemodialysis from 3 months or more.
- Person ready to follow protocol guideline, and to give inform consent.

Exclusion criteria:

- Patients not willing to give consent.
- Acute renal failure
- nephrotic syndrome
- H/o ishaemic heart diseases
- Drug affecting study parameters
- Patients with H/o abnormal TFTs and LFTs

Methods

Serum Homocysteine was done by chemiluminescence immunoassay (CLIA) method. Blood Glucose was done by glucose oxidase peroxidase end point method (GOD-POD). Serum Total cholesterol and Serum Triglyceride was done by Cholesterol oxidase peroxidase & Glycerophosphate oxidase (GPO) end point method respectively. HDL was estimated using HDL direct reagent based on modified polyvinyl sulfonic acid (PVS) and PEGME coupled classic precipitation method with the improvements in using optimised quantities of PVS/PEGME and selected detergents. Serum VLDL and LDL was calculated by Friedewalds formula. Serum Urea and Serum Creatinine was estimated by GLDH-UREASE METHOD & Modified Jaffe's method respectively.

Statistical Analysis

The results were interpreted as mean \pm S.D. One way ANOVA Variance test for comparing all three groups & Unpaired t test was applied to analyze the differences of studied characters in between two study groups and correlation coefficients were calculated (r value). P value was obtained from unpaired t test and <0.05 was considered statistically significant.

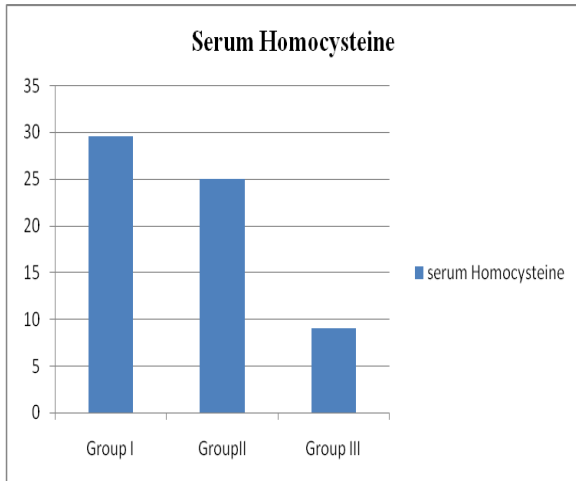
RESULTS

Table 1: shows comparison of Homocysteine and other biochemical parameters in studied groups.

Parameters	Group I n=50	Group II n=50	Group III n=50	P value
Total Homocysteine (μ mol/L)	29.56 \pm 10.81	24.92 \pm 10.09	9.04 \pm 2.89	<0.0001**
Total cholesterol(mg/dl)	196.52 \pm 48.87	176.54 \pm 44.78	168.38 \pm 51.24	<0.01*
Triglycerides(mg/dl)	223.45 \pm 54.98	202.08 \pm 30.48	138.26 \pm 37.27	<0.0001**
HDL (mg/dl)	29.48 \pm 7.28	36.69 \pm 9.79	42.42 \pm 10.37	<0.0001**
LDL (mg/dl)	123.60 \pm 50.53	109.60 \pm 47.45	95.27 \pm 45.97	<0.05*
VLDL(mg/dl)	44.69 \pm 10.99	40.51 \pm 6.30	27.66 \pm 7.44	<0.0001**
eGFR (ml/min/1.73m ²)	11.06 \pm 4.78	5.8 \pm 2.56	126.42 \pm 27.32	<0.001**

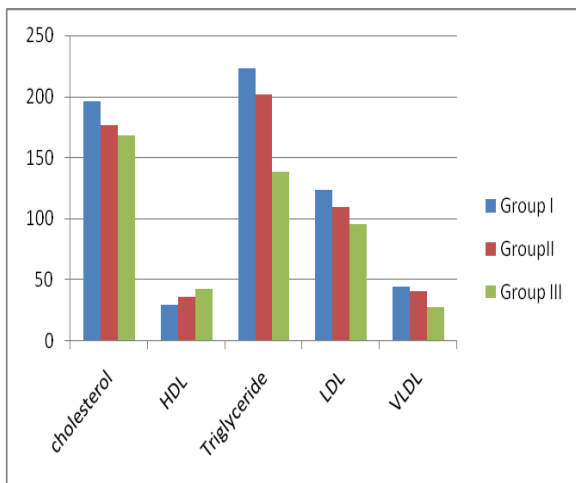
Table shows mean serum cholesterol, LDL, TG, VLDL levels found to be significantly higher in first 2 groups than group 3 and mean serum levels of HDL in first 2 groups were significantly lower than group 3. Table also shows mean values of eGFR (p= 0.001) [calculated by creatinine based MDRD formula]

significant difference among all the 3 studied groups. eGFR of group I and II is very low as compared to Group III (control). eGFR of group I and II is comparably equal and in group III it is in range of normal GFR. (125 -135 ml/min)



Graph 1: Graphical Comparison of Serum homocysteine in studied groups

Graphic shows the mean values of Serum homocysteine ($p=0.0001$) are significantly differ among all the 3 groups studied. Serum homocysteine levels in group I, II are increased significantly than group III.



Graph 2: Graphical representation of mean values of Lipid profile parameters among the studied groups

Table 2: Correlation coefficients (r value) in Group 1: Individuals of chronic renal failure with Dialysis

Sr. No.	Parameter	Parameter	Pearson "r"	P value
1	Homocysteine	Cholesterol	0.2903	0.040*
2	Homocysteine	HDL	-0.3025	0.0328*
3	Homocysteine	LDL	0.3044	0.0316*
4	Homocysteine	TG	0.288	0.04*
5	Homocysteine	VLDL	0.1056	0.4654ns
6	Homocysteine	eGFR	-0.2980	0.0356*

Table correlates the serum homocysteine and other parameters in chronic renal failure with Dialysis i.e group I. homocysteine is positively correlated with

serum cholesterol, Serum Triglycerides, Serum LDL and negatively with serum HDL and eGFR. No significant correlation with VLDL.

Table 3: Correlation coefficients (r value) in Group 2: Individuals of chronic renal failure without Dialysis

Sr. No.	Parameter	Parameter	Pearson "r"	P value
1	Homocysteine	Cholesterol	0.5241	<0.0001***
2	Homocysteine	HDL	-0.3755	0.0072*
3	Homocysteine	LDL	0.3569	0.0110*
4	Homocysteine	TG	0.2837	0.0459*
5	Homocysteine	VLDL	0.2722	0.0559ns
6	Homocysteine	eGFR	-0.2805	0.0485*

Table correlates the serum homocysteine and other parameters in chronic renal failure without Dialysis i.e. group 2. homocysteine is positively correlated with serum cholesterol, Serum Triglycerides, Serum LDL and negatively with serum HDL and eGFR. No significant correlation with VLDL.

DISCUSSION

Ischemic heart disease and other complications of atherosclerosis are the most common cause of death in patients with chronic renal failure. The pathogenesis of cardiovascular diseases in these patients is of multifactorial. Dyslipidemia and hyperhomocysteinemia are important factors associated with the early onset of atherosclerosis. Chronic renal failure is often associated with dyslipoproteinemia, high levels of cholesterol and triglycerides, as well as a decrease in the polyunsaturated fatty acids. Each of these abnormalities has been identified as an independent risk factor for atherosclerosis. On the other hand, an increment of plasma homocysteine concentration is highly prevalent among patients under hemodialysis, and it is considered an independent risk factor for atherosclerotic complications of end-stage renal disease.

Homocysteine contains a reactive sulfhydryl group, and undergoes oxidation to disulfide at physiological pH in the presence of O_2 . It has been suggested that this pro-oxidant activity of homocysteine is also responsible for the oxidation of LDL

cholesterol and damaging of vascular cells and tissues. Total plasma homocysteine concentration ($>14.5\mu\text{mol/L}$) increase the risk of vascular events independent of other known risk factors such as diabetes, hypertension, hypercholesterolemia and smoking. In addition to CVD risk factors, a new hypothesis has recently been aroused related to “new” factors involved in the development of atherosclerosis in the uremic patients; these are the homocysteine, inflammation and oxidative stress.

To study serum homocysteine and various Lipid profile parameters in patients of chronic renal failure (CRF) at one point of time was the aim of our study. Also we aimed at correlating these parameters with each other.

Serum Homocysteine:

Serum homocysteine was increased significantly in both group of CRF than controls ($p<0.001$). (Graph 1) Further the increase of serum homocysteine in patients on dialysis over without dialysis is statistically significant ($p<0.05$) and this rise correlates with reduction of GFR ($r=-0.2980/p=0.0356$ in dialysis patients and $r=-0.2805 /p=0.0485$ in without dialysis patients). (Table 1&2)

This finding is in agreement with that demonstrated by

Yu YM et al 2004, in their study showed levels of total homocysteine in the non-dialysis CRF patients were significantly higher than those in the healthy controls and increased with the progression of renal insufficiency. Compared with the pre-dialysis patients, hemodialysis patients exhibited higher levels of total homocysteine and they concluded that Hyperhomocysteinemia in CRF patients may accelerate oxidative stress, and lipid peroxidation may be involved in the occurrence of micro inflammation state. The complex interaction between hyper homocysteinemia, oxidative stress and micro inflammation may result in accelerated atherosclerosis seen in CRF. [17]

Plasma homocysteine (Hcy) levels are increased significantly in patients with

moderate renal failure and increase markedly in patients with end-stage renal disease. An increase in plasma Hcy level theoretically could be caused by an increased production rate (i.e., transmethylation), a decreased rate of removal by transsulfuration or remethylation, or a decrease in the excretion of Hcy. Current evidence indicates that the major mechanism for hyperhomocysteinemia in renal failure is a decrease in Hcy removal from the body. However, it is debated whether this effect is the result of a decrease in the renal metabolic clearance or a result of extrarenal metabolic changes. The human kidney plays a major role in the removal of several aminothiols or homocysteine related compounds from the circulation (e.g., cysteine-glycine, glutathione, AdoMet, and AdoHcy). However, the glomerular filtration of homocysteine seems to be restricted because of protein binding. Besides glomerular filtration, the normal kidney can remove homocysteine by plasma flow and peritubular uptake. The flow through the transsulfuration pathway is reduced if related to Homocysteine levels in uremia; in addition, the remethylation pathway also is impaired. Besides the potential effect of the reduced renal mass on homocysteine removal, available evidence suggests the occurrence of a generalized down-regulation of the methionine cycle and catabolism in uremia. [18]

Thus considering our finding we can say that as the CKD progresses; the serum homocysteine estimation is useful as a marker of severity of kidney disease.

In our study, we concluded that there is significant rise in serum homocysteine level in cases of chronic renal failure than controls ($p<0.0001$). (Table 1) (Graph 1) Serum homocysteine shows significant negative association with GFR in both Groups ($r=-0.2980/P=0.0356$ in dialysis patients and $r=-0.2805 /P=0.0485$ in without dialysis patients). (Table 2 & 3)

Lipid profile

Dyslipidemia was found in both the groups of chronic Renal Failure. There was significant rise of serum cholesterol ($p < 0.01$), serum triglycerides, serum VLDL ($p < 0.0001$), and serum LDL ($P < 0.05$) and significant lower values of HDL ($P < 0.0001$) were found in cases compared to controls. (Graph 2)

This finding is in agreement with that demonstrated by

Maheshwari N 2010 Found in their study that Serum TG and lipoprotein-a (LPa) were significantly increased ($P = < 0.001$ for each) while HDL-c was significantly lower ($P = < 0.001$) in maintenance hemodialysis patients than in the control group. Their study suggests that patients on maintenance hemodialysis show abnormalities of lipid metabolism like hypertriglyceridemia, elevated lipoprotein-a and low HDL-c, which could contribute to atherosclerosis and cardiovascular disease that may increase the morbidity and mortality in these patients. [19]

Chronic renal failure (CRF) results in profound lipid disorders, which stem largely from dysregulation of high density lipoproteins (HDL) and triglyceride-rich lipoprotein metabolism. Specifically, maturation of HDL is impaired and its composition is altered in CRF. In addition, clearance of triglyceride-rich lipoproteins and their atherogenic remnants is impaired, their composition is altered, and their plasma concentrations are elevated in CRF. Impaired maturation of HDL in CRF is primarily due to down regulation of lecithin-cholesterol-acyltransferase and, to a lesser extent, increased plasma cholesteryl ester transfer protein (CETP). Triglyceride enrichment of HDL in CRF is primarily due to hepatic lipase deficiency and elevated CETP activity. The CRF induced hypertriglyceridemia, abnormal composition, and impaired clearance of triglyceride-rich lipoproteins and their remnants are primarily due to down regulation of lipoprotein lipase, hepatic lipase, and the very low density lipoprotein

receptor, as well as, up regulation of hepatic acyl-CoA cholesterol acyltransferase (ACAT). In addition, impaired HDL metabolism contributes to the disturbance of triglyceride-rich lipoprotein metabolism. These abnormalities are compounded by down regulation of apolipoproteins apoA-I, apoA-II and apoC-II in CRF. Together, these abnormalities may contribute to the risk of atherosclerotic cardiovascular disease and may adversely affect progression of renal disease and energy metabolism in CRF. [20]

Homocysteine and lipid profile

Helal I et al 2010 in their study; lipid profile, homocysteine (Hcy) and C reactive protein (CRP) were measured. When compared to a healthy population, Haemodialysis patients displayed a marked atherogenic profile, and found increased levels of total cholesterol (TC), triglycerides (TG), low-density lipoprotein-cholesterol (LDL-C), apolipoprotein A (Apo A), CRP, Homocysteine and lower concentrations of high-density lipoprotein-cholesterol (HDL-C), Apo B, albumin (ALB). [21]

In our study, we also concluded that there is significant hyper homocysteinemia ($P < 0.0001$) (Graph 1) in cases which was positively correlated with serum Triglyceride ($r = 0.288 / P = 0.04$ in dialysis CRF patients and $r = 0.2837 / P = 0.0459$ in without dialysis CRF patients). Serum cholesterol is also positively correlated with serum homocysteine ($r = 0.2903 / P = 0.04$ in dialysis CRF patients and $r = 0.5241 / P < 0.0001$ in without dialysis CRF patients). There is significant positive correlation between serum LDL and serum Homocysteine ($r = 0.3044 / P = 0.0316$ in dialysis CRF patients and $r = 0.3569 / P = 0.0110$ in without dialysis CRF patients). Serum HDL is significantly lower ($P < 0.0001$) in cases, and negatively correlated with serum homocysteine ($r = -0.3025 / P = 0.0328$ in dialysis patients and $r = -0.3755 / P = 0.0072$ in without Dialysis patients). (Table 2 & 3)

All these findings need to be ascertained in the larger and well

systematized study with prospective approach so as to test the utility of estimation of serum homocysteine and Lipid Profile to study the deterioration in kidney function and to predicting cardio vascular risk in chronic renal Failure patients

CONCLUSION

In present study, we have observed serum homocysteine levels were significantly increased in patients of chronic renal failure on Dialysis and without Dialysis. Serum homocysteine levels in Patients of chronic renal failure on dialysis were elevated than Patients of chronic renal failure without dialysis. Considering the results of this study which point of the fact that serum homocysteine, cholesterol, Triglyceride, LDL, VLDL values are significantly higher and HDL-C are lower in patients with CRF, in comparison to the population with regular renal function, It can be concluded that the determination of homocysteine and Lipid profile parameters would be advisable for a more complete risk assessment of premature atherosclerotic development, but also of possible further progression of CRF.

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