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Exploring the Interplay of Homocysteine and Lipid Profile in End-Stage Renal Disease: Implications for Pathogenesis.

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ABSTRACT

End-Stage Renal Disease (ESRD) is an irreversible condition marked by progressive loss of kidney function, leading to the accumulation of metabolic waste and electrolyte imbalances. Present study evaluated homocysteine, a biomarker, lipid profile, and clinical parameters in individuals with ESRD and a control group. A case-control study was conducted to compare ESRD patients (n=180) and a control group (n=180) matched for age and sex. Baseline demographic data, blood samples for biochemical analysis were collected to assess biochemical parameters. Homocysteine was analysed using enzymatic method. No significant difference was found in age and gender between the two groups. However, ESRD patients exhibited significantly higher Body Mass Index (BMI) values. Hemoglobin and albumin levels were profoundly reduced in ESRD. Significantly elevated levels of urea, blood urea nitrogen (BUN), and creatinine, with a corresponding decrease in estimated glomerular filtration rate (eGFR) were demonstrated in ESRD patients. Furthermore, lipid marker analysis revealed significant differences, with ESRD patients exhibiting higher total cholesterol (TC), triglycerides (TG), and LDL cholesterol levels, as well as lower HDL cholesterol levels compared to controls. Additionally, homocysteine level was significantly higher in ESRD patients. The identified differences in lipid markers and homocysteine levels provide insights into the underlying pathophysiological mechanisms of ESRD. Ultimately, these findings contribute to a better understanding of ESRD and may guide future research and therapeutic interventions.

Keywords: End stage renal disease, ESRD, homocysteine, Lipid Profile

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INTRODUCTION

End-Stage Renal Disease (ESRD) is a chronic, irreversible condition that causes progressive kidney function loss and causes a significant amount of morbidity and mortality on a global scale [1,2]. It is a serious public health problem that has an enormous effect on healthcare systems and the standard of living for those who are impacted. Dialysis or kidney transplantation are required for ESRD patients in order to maintain essential physiological functions [2].

End-Stage Renal Disease (ESRD) is a serious global health burden, and its prevalence is increasing worldwide. The Global Burden of Disease Study estimates that ESRD caused about 1.3 million deaths worldwide in 2017, an increase of 32% from 2007 [3]. As a result of ageing populations, a high prevalence of chronic kidney disease, and better access to renal replacement therapies, developed nations like the United States, Japan, and Europe have higher rates of ESRD than developing countries [3, 4].

In the Indian context, ESRD has become a significant public health issue. Over the past ten years, ESRD prevalence has sharply increased in India. According to a 2017 study, India has an estimated 229 cases of ESRD per million people (pmp), with more than 220,000 new cases being reported yearly. Numerous factors, including the high prevalence of risk factors like diabetes mellitus, hypertension, and chronic kidney disease, contribute to the burden of ESRD in India. The difficulties in managing ESRD in India are further exacerbated by the country's limited access to healthcare resources, including diagnostic centres and renal replacement therapies [5-7].

To effectively address the rising burden of ESRD, healthcare planning and resource allocation depend on an understanding of both the global epidemiology and the particular Indian situation. To lessen the effects of ESRD on the health and wellbeing of the population, efforts should concentrate on early detection and management of risk factors, implementation of preventive strategies, and improving access to renal replacement therapies.

Chronic kidney disease progression, genetic predisposition, chronic kidney disease pathogenesis, vascular abnormalities, inflammation and oxidative stress all play complex roles in the multifactorial pathogenesis of ESRD. ESRD continues to be a difficult condition with few effective treatments, despite improvements in therapeutic interventions [8].

For effective disease management and the creation of cutting-edge therapeutic approaches, it is essential to comprehend the underlying biochemical and physiological alterations linked to ESRD. The pathophysiological mechanisms have been clarified and potential targets for intervention have been identified through the study of numerous biomarkers and clinical parameters [9]. As potential indicators of renal dysfunction and cardiovascular risk in ESRD patients, Homocysteine and lipid markers have all shown promise [10]. To provide a more thorough understanding of ESRD pathogenesis, however, there is a need for thorough investigations that simultaneously evaluate homocysteine and other clinical parameters.

The current study sought to assess homocysteine and lipid markers in ESRD patients and a control group in light of these factors. Age, body mass index (BMI), and various biochemical markers linked to kidney function and cardiovascular risk were also evaluated as clinical parameters. This thorough investigation was carried out for acquiring better knowledge of the biochemical and physiological changes linked to ESRD, possibly identifying new therapeutic targets and enhancing patient outcomes.

MATERIALS AND METHODS

The present study was carried out in Department of Biochemistry, Government Medical College, Miraj. This study aimed to evaluate homocysteine and lipid profile as well as clinical parameters in individuals with End-Stage Renal Disease (ESRD) and a control group. A case-control design was employed to compare the two groups. The study included ESRD patients (n=180) and a control group (n=180) matched for age and sex. Baseline demographic data, including age, height & weight were collected. Body mass index (BMI) was measured as kg/m^2.Estimated glomerular filtration rate (eGFR) was calculated with the help of recommended equation using serum creatinine, age, sex and body weight

according to guidelines of National Kidney Foundation [Kidney Dialysis Outcomes Quality Initiative (KDOQI)][11].

Blood samples were obtained from all participants, and biochemical analyses were performed such as hemoglobin by cyanmethemoglobin method, albumin, urea, blood urea nitrogen (BUN), creatinine, total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol by using kits with biochemistry autoanalyser [ERBA XL640], homocysteine level by enzymatic method.

Thyroid disorders, Cushing's syndrome, Pregnancy, systemic illnesses like malignancies were excluded from the study.

The study was approved by institutional ethics committee and informed consent was obtained from all participants prior to their inclusion in the study. Data confidentiality and privacy were ensured throughout the research process.

The data was analysed using SPSS version 26.0. The continuous variables were presented as mean ± SD, and compared between the groups using unpaired students't'test. The significance level was set at $p<0.05$.

RESULTS

The presented table 1 illustrates a comprehensive comparative analysis between individuals afflicted with End-Stage Renal Disease (ESRD) and a control group, focusing on crucial biomarkers and clinical parameters. Age, though similar in both cohorts, demonstrates nostatistically significant ($p=0.9141$) difference. However, ESRD subjects exhibit significantly ($p<0.0001$) higher Body Mass Index (BMI) values. Hemoglobin and albumin levels are profoundly ($p<0.0001$) reduced in ESRD. ESRD participants manifest significantly ($p<0.0001$) elevated levels of urea, blood urea nitrogen (BUN), and creatinine.

Table 1: Comparison of demographical and clinical parameters among ESRD patients and controls

	ESRD		Controls		p value
	Mean	SD	Mean	SD	
AGE	54.75	6.14	54.68	5.57	0.9141
BMI (kg/m²)	27.01	1.46	23.38	2.85	<0.0001
Hemoglobin	7.53	0.66	15.47	1.40	<0.0001
Albumin	3.14	0.19	3.86	0.30	<0.0001
Urea	186.93	9.50	26.71	6.30	<0.0001
Blood urea nitrogen	87.70	4.34	12.44	2.93	<0.0001
Creatinine	10.87	1.43	0.75	0.07	<0.0001
eGFR	4.60	2.86	100.76	5.14	<0.0001

The analysis of lipid markers between individuals diagnosed with End-Stage Renal Disease (ESRD) and the control group revealed significant ($p<0.0001$) differences. ESRD patients exhibit significantly ($p<0.0001$) higher levels of total cholesterol compared to controls. Similarly, triglyceride levels were significantly ($p<0.0001$) elevated in the ESRD group compared to the control group. Conversely, HDL cholesterol levels were significantly ($p<0.0001$) lower in ESRD compared to controls. Additionally, LDL cholesterol levels were significantly ($p<0.0001$) higher in ESRD compared to controls. Homocysteine levels were also significantly ($p < 0.0001$) higher in ESRD compared to controls. Additionally, estimated glomerular filtration rate (eGFR) is significantly ($p<0.0001$) decreased in ESRD and found significant negative correlation with homocysteine level ($r = -0.678$, $p<0.0001$).The findings of homocysteine and lipid parameters in ESRD patients and controls are depicted in table 2.

Table 2: Comparison of homocysteine and lipid markers among ESRD patients and controls

	ESRD		Controls		p value
	Mean	SD	Mean	SD	
Homocysteine	26.67	7.12	10.85	9.35	<0.0001
Total cholesterol	275.26	20.30	172.34	19.35	<0.0001
Triglycerides	240.49	21.67	139.86	6.08	<0.0001
HDL cholesterol	32.33	1.71	57.81	15.88	<0.0001
LDL cholesterol	178.62	11.00	82.59	7.97	<0.0001

Correlation analyses were performed to investigate the relationship between homocysteine level, and lipid parameters. Homocysteine level exhibited positive correlations with TC ($r = 0.679$, $p < 0.0001$) and TG ($r = 0.718$, $p < 0.0001$). Conversely, HDL cholesterol showed a negative correlation with homocysteine level ($r = -0.558$, $p < 0.0001$). LDL cholesterol (LDL) exhibited positive correlations with homocysteine level ($r = 0.715$, $p < 0.0001$).

Table 3: Correlation of homocysteine level with lipid parameters

		Homocysteine
Total Cholesterol	r	0.679
	p	<0.0001
Triglyceride	r	0.718
	p	<0.0001
HDL Cholesterol	r	-0.558
	p	<0.0001
LDL Cholesterol	r	0.715
	p	<0.0001

DISCUSSION

A severe and permanent condition known as end-stage renal disease (ESRD) is characterized by the progressive loss of kidney function. It is the terminal stage of a number of kidney diseases, including chronic kidney disease (CKD), and survival requires renal replacement therapy, such as dialysis or kidney transplantation. Millions of people around the world are affected by ESRD, which places a significant financial and medical burden on society [12]. Due to the kidneys' impaired filtration, excretion, and regulatory functions, ESRD is linked to a wide range of complications and systemic manifestations [13].

The kidneys are essential for maintaining fluid and electrolyte balance, eliminating waste, and producing hormones that control blood pressure and help the body make red blood cells [14, 15].

Therefore, the dysfunction of these crucial renal functions in ESRD results in a chain reaction of physiological issues all over the body [16, 17].

In spite of same age groups, significantly raised BMI in ESRD patients suggest a possible correlation between ESRD and elevated BMI.The study's examination of hematological and biochemical parameters revealed notable variations between the ESRD patients and the control group. Significantly lower levels of hemoglobin and albumin were found in patients with ESRD, which may indicate malnutrition. As expected, the markers of impaired kidney filtration and clearance i.e. urea, blood urea nitrogen (BUN), and creatinine were significantly higher in ESRD. The kidney function indicator known as estimated glomerular filtration rate (eGFR) significantly declined in ESRD patients.

Lipid markers were evaluated in our study, and the results showed significant differences between the ESRD patients and the control group. Total cholesterol and triglyceride levels were significantly higher in ESRD patients, indicating dyslipidemia related to ESRD. However, ESRD patients had significantly lower levels of HDL cholesterol than controls, which may increase their risk of cardiovascular complications. Furthermore, ESRD patients had significantly higher LDL cholesterol levels, emphasizing the dyslipidemic profile linked to ESRD.

The kidney is the major site of homocysteine metabolism. Most (80%) of the homocysteine binds to plasma proteins, and only the unbound form is subject to glomerular filtration and tubular reabsorption. [18] Hyperhomocysteinemia found in this study may be because of impaired renal metabolism and / or reduced renal excretion. Elevated plasma homocysteine levels were more likely to lower the eGFR and increase the prevalence of CKD.

Elevated level of homocysteine may be involved in the pathogenic action of progression of vascular damage. Hyperhomocysteinemia may produce endothelial dysfunction & promotes oxidative stress by increasing levels of asymmetric dimethylarginine an endogenous inhibitor of nitric oxide synthase, by inhibiting its catabolising enzyme dimethylarginine dimethylamino hydrolase [19]. Also, homocysteinemia promote the proliferation of smooth muscle cells leading to several interactions with platelets, clotting factors, and lipids, and indeed might contribute to the scavenger receptor-mediated uptake of oxidized-LDL by macrophages resulting in foam cell formation in atherosclerosis. These pathways end to amplify the atherosclerotic process and the inflammatory state, which can contribute to development and progression of cardiovascular disease. Hyperhomocysteinemia is an independent interpreter of cardiovascular morbidity and mortality in end-stage renal disease [20].

In our study, Patients with ESRD had significantly higher homocysteine levels, which are linked to a higher risk of cardiovascular diseases. Additionally, we found a significant correlation between the homocysteine and lipid parameters in ESRD. Homocysteine induces endoplasmic reticulum stress which activates genes for coding enzymes in cholesterol and triglycerides biosynthesis [21].

Hyperhomocysteinemia leads to increase in hepatic synthesis of cholesterol and triglycerides synthesis,decrease in levels of HDLand accumulation in endothelial cells and this can be considered as link between increased homocysteine level and development of atherosclerosis [22].

CONCLUSION

In the present study, our results highlight the significant effects of ESRD on a number of physiological parameters, including haematological, biochemical, and lipid profile. The observed changes emphasize how complicated ESRD is and how it affects the entire body in addition to just the kidneys. For effective management and targeted interventions to improve the outcomes of ESRD patients, it is essential to comprehend these changes.

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