



# Comparison of Cardiovascular Risk Between Diabetic & Non-Diabetic End Stage Renal Disease (ESRD) Patients Undergoing Haemodialysis

Priya K.<sup>1</sup>, Sangeeta K.<sup>2</sup>

<sup>1</sup>Department of Biochemistry, Govt. Medical College, Kannauj, India; <sup>2</sup>Department of Biochemistry, TMMC & RC, TMU, Moradabad, India.

## ABSTRACT

**Background:** This study proposes to see whether end stage renal disease (ESRD) patients undergoing haemodialysis with additional diabetes mellitus exhibit increased cardiovascular risk markers in comparison to end stage renal disease (ESRD) patients undergoing haemodialysis without diabetes mellitus.

**Objectives:** In this study, an attempt has been made to compare the Lipid profile and fibrinogen as inflammatory markers for assessing cardiovascular risk between diabetic and non-diabetic end stage renal disease (ESRD) patients undergoing maintenance haemodialysis.

**Material and Methods:** We enrolled 32 patients of both sex suffering from diabetes mellitus end stage renal disease undergoing haemodialysis and 32 non-diabetic end stage renal disease undergoing haemodialysis for this study.

**Results:** We found that there is significant increase in the parameters like plasma fibrinogen, plasma glucose concentration, atherogenic index (TC/HDLc), serum lipid profile (TC, LDLc, TG, VLDLc) and decrease in serum HDLc in diabetic ESRD patients in comparison to non-diabetic ESRD patients undergoing maintenance haemodialysis.

**Conclusion:** We conclude that elevation in plasma fibrinogen level, serum lipid profile and atherogenic index (TC/HDLc) in diabetic ESRD patients undergoing maintenance haemodialysis which indicates higher risk of adverse cardiac events and atherosclerosis as a major cause of coronary heart disease in diabetic ESRD patients.

**Key Words:** Plasma Fibrinogen, Haemodialysis, Diabetes

## INTRODUCTION

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both. It is a chronic disease that causes serious health complications including renal (kidney) failure, heart disease, stroke and blindness. Diabetes mellitus is associated with a number of changes in thrombotic and fibrinolytic coagulation factor level or activity, which collectively increases the risk of thrombus formation. Hyperglycaemia and insulin resistance induce qualitative and quantitative changes in clotting factors, resulting in dense and compact clot structure and resistance to fibrinolysis

[1]. Fibrinogen is the major coagulation protein in blood by mass, the precursor of fibrin and an important determinant of blood viscosity and platelet aggregation [2]. As a clotting factor, fibrinogen is an essential component of the blood coagulation system, being the precursor of fibrin.

Fibrinogen has been identified as a major independent risk factor for cardiovascular disease. There are several mechanisms by which fibrinogen may increase cardiovascular risk. First, it binds specifically to activate platelets via glycoprotein IIb/IIIa, contributing to platelet aggregation. Second, increased fibrinogen levels promote fibrin formation. Third, it is a major contributor to plasma viscosity. Finally,

### Corresponding Author:

Priya K., Department of Biochemistry, Govt. Medical College, Kannauj, India  
E-mail: priyayadav199025@gmail.com

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it is an acute phase reactant that is increased in cardiovascular diseases [6]. High fibrinogen levels are associated with more compact clot structure, whereas elevated plasminogen activator inhibitor – I (PAI-I) levels impairs the fibrinolytic process. In addition to the quantitative changes, qualitative changes in clotting factors can affect the structure of the clots. High serum glucose has been shown to increase glycation of fibrinogen and clots formed from glycated fibrinogen have a more compact structure and increased resistance to lysis. A by-product of protein glycation that is glycoaldehyde induces post-translational modifications in fibrinogen, which impairs the fibrinolytic process, other post-translational modifications in fibrinogen such as oxidation, a known pathogenic process in diabetes mellitus, can also modify clot structure [1]. Diabetes mellitus is associated with an increase in low density lipoprotein cholesterol, and triglycerides, and low high density lipoprotein cholesterol levels. The alterations in the level and properties of LDL and HDL together contribute to the increased risk for Coronary artery disease (CAD) in diabetics [7].

Cardiovascular morbidity and mortality is markedly increased in diabetes mellitus with end stage renal disease (ESRD) patients undergoing haemodialysis (HD). As atherogenesis is mediated by inflammation of vessel walls and as evidence evolves that atherosclerosis and diabetes mellitus share a common inflammatory basis. Lipid profile and fibrinogen level has been compared as inflammatory markers for assessing cardiovascular risk between diabetic and non-diabetic end stage renal disease (ESRD) patients undergoing maintenance haemodialysis in this study. Atherogenic index (TC/HDLc) has also been determined and compared between control group and diabetes mellitus patients.

Hence, this study proposes to see whether end stage renal disease (ESRD) patients undergoing haemodialysis with additional diabetes mellitus exhibit increased cardiovascular risk markers in comparison to end stage renal (ESRD) patients undergoing haemodialysis without diabetes mellitus.

## EXPERIMENTAL SECTION

**Study Design and Subjects:** This study was conducted in the Department of Biochemistry Teerthanker Mahaveer Medical College and Research Centre and Dialysis unit of Teerthanker Mahaveer Hospital, Moradabad, U.P, and India. The investigation was conducted on 32 patients of both sex suffering from diabetes mellitus end stage renal disease undergoing haemodialysis and 32 non-diabetic end stage renal disease undergoing haemodialysis.

**Inclusion criteria:** Patients undergoing maintenance HD for atleast one year.

**Exclusion criteria:** Patients with any infective diseases such

as AIDS, Hepatitis B and Hepatitis C, and treatment with cholesterol lowering drugs, tissue plasminogen activator (tPA), anticoagulant therapy, pregnant women, and post-menopausal state conditions (which can alter the plasma fibrinogen and serum lipid profile level) were excluded from the study.

**Sample collection:** Blood samples were collected from an antecubital vein between 8 and 9 AM after an overnight fast from all subjects and dispensed into following vials for various biochemical tests:

1. Fluoride oxalate vial for fasting plasma glucose estimation.
2. Plain vial for Total cholesterol, Total triglycerides and High density lipoprotein cholesterol.
3. Vial containing 3.8% tri sodium citrate for fibrinogen estimation.

## Analysis of Sample:

- Estimation of Plasma fibrinogen level by Kjeldahl-Nesslerization method.
- Estimation of fasting blood sugar (FBS) level by GOD-POD method (Glucose oxidase and peroxidase).
- Estimation of serum Cholesterol by end point CHOD-PAP method.
- Estimation of serum triglycerides by end point GPO-TRINDER method.
- Estimation of serum HDLc by end point TRINDER reaction.

## Calculation

- $VLDLc = [TG/5]$
- $LDLc = [Total\ Cholesterol] - [HDLc] - [(TG/5)]$  (Friedewald equation)
- $Atherogenic\ index = [TC/HDLc]$

## Statistical analysis

Mean  $\pm$  SD were calculated for all the parameters analyzed and were compared by Student's t-test (2 tailed) using SPSS.

P-values considered significant were as follows:-

P < 0.05 – As significant

P < 0.001 – As highly significant

## RESULTS

**Table 1: Mean and Standard deviation of measured parameters in diabetic ESRD patients undergoing maintenance haemodialysis**

SN	Parameters	Mean $\pm$ S.D
1	TC (mg/dl)	168.88 $\pm$ 11.23
2	HDLc (mg/dl)	36.25 $\pm$ 3.24

3	LDLc (mg/dl)	106.73 ± 14.74
4	TG (mg/dl)	129 ± 13.98
5	VLDLc (mg/dl)	25.80 ± 2.79
6	Fasting plasma glucose (mg/dl)	164.16 ± 46.92
7	Fibrinogen (mg/dl)	510.81 ± 113.32
8	Atherogenic index (TC/HDLc)	4.70 ± 0.67

**Table 2: Mean and Standard deviation of measured parameters in non diabetic ESRD patients undergoing maintenance haemodialysis**

SN	Parameters	Mean ± S.D.
1	TC (mg/dl)	145.04 ± 23.14
2	HDLc (mg/dl)	48.35 ± 8.14
3	LDLc (mg/dl)	80.91 ± 26.29
4	TG (mg/dl)	78.94 ± 19.54
5	VLDLc (mg/dl)	15.79 ± 3.90
6	Fasting plasma glucose (mg/dl)	101.87 ± 6.61
7	Fibrinogen (mg/dl)	257.71 ± 15.53
8	Atherogenic index (TC/HDLc)	3.09 ± 0.71

**Table 3: Comparative analysis of various parameters between diabetic and non - diabetic ESRD patients undergoing maintenance haemodialysis using Student's t test**

SN	Parameters	t value	p value
1	TC	5.24	.000
2	HDLc	-7.80	.000
3	LDLc	4.84	.000
4	TG	11.784	.000
5	VLDLc	11.782	.000
6	Fibrinogen	12.517	.000
7	Atherogenic index (TC/HDLc)	9.316	.000

## DISCUSSION

In the present study, the comparison of lipid profile and plasma fibrinogen level as inflammatory markers for assessing cardiovascular risk between 32 diabetic and 32 non diabetic ESRD patients undergoing maintenance haemodialysis was done. In this study, atherogenic index (TC/HDLc) had also been determined and compared between control group and diabetes mellitus ESRD patients.

### A. Plasma fibrinogen level determination in diabetic and non diabetic ESRD patients undergoing maintenance haemodialysis:

The comparison between the plasma fibrinogen levels of diabetic ESRD patients with (mean ± S.D 510.81 ± 113.32 mg/dl) was found to be significantly higher than non diabetic (mean ± S.D 257.71 ± 15.53 mg/dl) ESRD patients undergoing haemodialysis ( $P < 0.001$ ).

In Gothenburg study plasma fibrinogen was an independent risk factor for MI and stroke on univariate analysis. On multivariate analysis, plasma fibrinogen was still statistically significant risk for stroke [62].

In the Framingham Study, the risk of developing cardiovascular disease was significantly related to plasma fibrinogen levels [70]. The influence of plasma fibrinogen on cardiovascular risk was much more pronounced in younger men. The impact of plasma fibrinogen levels on cardiovascular disease was comparable with the major risk factors, such as blood pressure, haematocrit, adiposity, cigarette smoking and diabetes; and was still an independent predictor of coronary artery disease on multivariate analysis) [63].

Acevedo M et al found that patients with CAD tended to have higher fibrinogen levels than those without the disease.

The role of fibrinogen concentration in the development of complications in diabetics was also suggested by Wilhelmsen et al, as a risk factor for stroke and myocardial infarction.

Fibrinogen may increase cardiovascular risk in several ways. It plays an important role in platelet aggregation, plasma viscosity, and fibrin formation. It is an acute phase reactant that is increased in inflammatory states and thus, its high level could simply be a reflection of underlying arterial plaque formation [64]. High plasma fibrinogen levels may cause a hypercoagulable state, platelet aggregation, and important rheological alterations. Red blood cell aggregation and disaggregation shear stress are profoundly altered by the level of fibrinogen. Enhanced red blood cell aggregability leads to increased blood viscosity, which in turn might induce a further slowing of the circulation, which may play a key role in the extent of arterial damage.

Fibrinogen and fibrin not only play a key role in coagulation but are also involved in cellular interactions, wound healing, and neoplasia. High plasma fibrinogen levels are associated with an increased risk of cardiovascular disease in healthy as much as in high-risk individuals.

In this study, it has been found that CAD occurs frequently in haemodialysis patients, with an even higher prevalence in diabetic patients in comparison to non diabetic ESRD patients undergoing haemodialysis.

## B. Serum lipid profile determination in diabetic and non diabetic ESRD patients undergoing maintenance haemodialysis:

The comparison between serum TC of diabetic with (mean  $\pm$  S.D  $168.88 \pm 11.23$  mg/dl ), serum LDLc (mean  $\pm$  S.D  $106.73 \pm 14.74$  mg/dl ), serum TG (mean  $\pm$  S.D  $129 \pm 13.98$  mg/dl) and serum VLDLc (mean  $\pm$  S.D  $25.80 \pm 2.79$  mg/dl) was found to be significantly higher than serum TC of non diabetic ESRD patients with (mean  $\pm$  S.D  $145.04 \pm 23.14$  mg/dl), serum LDLc (mean  $\pm$  S.D  $80.91 \pm 26.29$  mg/dl), serum TG (mean  $\pm$  S.D  $78.94 \pm 19.54$  mg/dl) and serum VLDLc (mean  $\pm$  S.D  $15.79 \pm 3.90$  mg/dl) undergoing maintenance haemodialysis ( $P < 0.001$ ).

Gerstein HC, Mann JF, Yi Q, Zinman B, Dinneen SF, Hoogwerf B, Halle JP, Young J, Rashkow A, Joyce C, Nawaz S, Yusuf S: HOPE Study showed that the mild renal insufficiency confers a risk for cardiovascular events even higher than that observed in patients with a coronary heart disease and a normal renal function. Although several factors may explain this association between renal and cardiovascular disease, there is growing evidence that hyperlipidemia contributes not only to cardiovascular disease but also to renal disease progression.

Samuelsson *et al.* demonstrated a strong correlation between triglyceride-rich apoB-containing lipoproteins and the rate of progression in non-diabetic patients with chronic kidney disease.

In Vaziri ND study: progressive renal failure especially that associated with proteinuria is accompanied by abnormalities of lipoprotein transport. Typically, the dyslipidemia is reflected predominantly in increased serum levels of triglycerides with high levels of VLDL, apoB and pre- $\beta$  HDL, and low levels of HDL and of apoA. Cholesterol levels may be very high in proteinuric patients [52].

Chronic renal disease is accompanied by characteristic abnormalities of lipid metabolism, which may appear as a consequence of nephrotic syndrome or renal insufficiency and are reflected in an elevated plasma lipid levels. Experimental and clinical studies have suggested a correlation between the progression of renal disease and dyslipidemia. High cholesterol and triglyceride plasma levels have been demonstrated to be independent risk factors for progression of renal disease in humans. The underlying pathophysiologic mechanisms for the relationship between lipid levels and progression of renal disease are not yet fully understood, although there are data that oxidative stress and insulin resistance may mediate the lipid-induced renal damage [50].

In this study, it has been found that serum HDLc of diabetic ESRD patients with (mean S.D  $36.25 \pm 3.24$  mg/dl) was found to be significantly less than non diabetic (mean  $\pm$  S.D

$48.35 \pm 8.14$  mg/dl) ESRD patients undergoing maintenance haemodialysis.

Muntner *et al.* showed that people with low HDL cholesterol and hypertriglyceridemia at baseline have a higher risk for having a loss of renal function.

In Kontush A, Chapman MJ study moreover, HDL serves as a potent endogenous inhibitor of inflammation, platelet adhesion and LDL oxidation, because of a number of HDL associated apolipoproteins (mainly apolipoprotein AI) and enzymes (paraoxonase-1, platelet-activating factor acetylhydrolase and lecithin-cholesterol acyltransferase (LCAT) [66].

Despres JP, Lemieux I, Dagenais GR, Cantin B, Lamarche B. studies have demonstrated that HDL cholesterol is a negative risk factor for atherosclerosis. Attman PO, Samuelsson O, Alaupovic P studied that diabetic ESRD patients have, generally, reduced plasma HDL-cholesterol levels compared to non diabetic ESRD patients .

Vaziri ND, Deng G, Liang K and Guarnieri GF, Moracchiello M, Campanacci L, et al. have been shown that patients with impaired renal function usually exhibit decreased levels of apolipoproteins AI and AII (the main protein constituents of HDL) , diminished activity of LCAT (the enzyme responsible for the esterification of free cholesterol in HDL particles), as well as increased activity of cholesteryl ester transfer protein (CETP) that facilitates the transfer of cholesterol esters from HDL to triglyceride-rich lipoproteins thus reducing the serum concentrations of HDL-cholesterol [53].

Dirican M, Akca R, Sarandol E, Dilek K and Liberopoulos EN, Papavasiliou E, Miltiadous GA, et al. studied that in addition to their reduced efficiency as cholesterol acceptors, HDL particles from individuals with impaired renal function have less effective antioxidative and anti-inflammatory function. This impairment can, at least in part, be attributed to the reduction in the activities of HDL-associated enzymes, such as paraoxonase (an enzyme that inhibits the LDL oxidation).

Attman PO, Samuelsson O, Johansson AC, Moberly JB, Alaupovic P studied that hemodialysis procedure may also have a contributory role in the reduced HDL cholesterol levels of dialysis patients. Thus, in dialysis patients the type of membrane and dialysate used in HD procedure may influence the HDL-cholesterol levels.

Blankstijn PJ, Vos PF, Rabelink TJ, van Rijn HJ, Jansen H, Koomans HA have been shown that the use of high-flux instead of low flux membranes is associated with an increase in apolipoprotein AI and HDL-cholesterol values.

Jung K, Scheifler A, Schulze BD, Scholz M has shown that, the type of dialysate may also significantly affect the serum levels of lipoproteins in HD patients. Indeed, it has been shown that the use of bicarbonate dialysate may result in

higher HDL-cholesterol concentrations than the use of acetate dialysate. The main function of HDL is the transport of surplus cholesterol from the arterial wall to the liver for excretion. This process, which is commonly called 'reverse cholesterol transport', is critical for cellular cholesterol homeostasis and protection against atherosclerosis [66].

### C. Atherogenic index determination in diabetic and non diabetic ESRD patients undergoing maintenance haemodialysis:

Framingham's study had suggested that as the TC/HDLc (atherogenic index or cardiac risk ratio) increases, so there is increased risk of coronary heart disease (CHD) [65, 66].

In this study, it has been found that, this ratio was significantly ( $p < 0.001$ ) elevated in diabetic ESRD patients, as compared to non diabetic ESRD patients undergoing maintenance haemodialysis which indicates higher risk of adverse cardiac and renal events in diabetic ESRD patients. These parameters may thus be used for analyzing the risk of atherosclerosis in ESRD patients.

## CONCLUSION

Thus, it can be concluded that plasma fibrinogen, lipid profile and atherogenic index are known risk factors for atherosclerosis in the general population. Fibrinogen concentration and lipid profile is significantly elevated in diabetic ESRD patients undergoing maintenance haemodialysis [68, 69]. Increase in lipid profile causes platelet adhesion and lipid oxidation and increase in plasma fibrinogen levels promote hypercoagulability. Both in combination have synergistic effect to accelerate the rate of atherosclerosis. Identification of high risk patients permits the focusing of treatment to optimize efforts to reduce mortality.

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## LIST OF ABBREVIATIONS

CAD    Coronary artery disease  
CHD    Coronary heart disease

CHOD    Cholesterol oxidase  
ESRD    End Stage Renal Disease  
GPO    Glycerol phosphate oxidase  
DAP    Dihydroxy acetone phosphate  
HD    Haemodialysis  
PAI-1    Plasminogen activator inhibitor-1  
tPA    Tissue plasminogen activator  
GOD    Glucose Oxidase  
POD    Peroxidase  
FBS    Fasting Blood Sugar

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