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THE STUDY OF ASSOCIATION OF DYSLIPIDEMIA AND SERUM PARAOXONASE -1 ACTIVITY

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ABSTRACT

Introduction: In the past few decades, dyslipidemia has become a greater social burden in both industrialized and emerging nations, including our own. Dyslipidemia is known to be a significant risk factor for a number of non-communicable diseases (NCDs).Numerous epidemiological studies, particularly those focusing on cardiovascular disease (CVD), have demonstrated the frequency of dyslipidemia coexisting with non- communicable disease.

Aims: To determine the relationship between serum paraoxonase-1 activity and lipoprotein concentration in dyslipidemia, as well as to estimate paraoxonase-1 activity in both dyslipidemic and non-dyslipidemic individuals.

Materials and Methods: This study is cross-sectional, analytical, and observational. It takes place between June 2020 and May 2021.Patients in the working age range of 20 to 60 years who visit the Department of Biochemistry for a serum lipid profile measurement will be part of the research. All of the studies on paraoxonase 1 that are currently available were conducted on subjects who were between the ages of 20 and 60.

Results: In Non-dyslipidemia, the mean Triglycerides mg/dl of patients was 97.58 ± 26.36.In Dyslipidemia, the mean Triglycerides mg/dl of patients was 211.03 ± 78.13.There was statistical significance in the distribution of mean triglycerides mg/dl with characteristics ($p<0.0001$).In Non-dyslipidemia, the mean HDL-Cholesterol mg/dl of patients was 52.55 ± 8.13.In Dyslipidemia, the mean HDL-Cholesterol mg/dl of patients was 46.20 ± 7.16.There was statistical significance in the distribution of mean HDL-Cholesterol mg/dl with characteristics ($p<0.0001$).

Conclusion: We conclude that dyslipidemia is linked with a considerably decreased PON1 activity, which is favorably correlated with serum HDL levels. The HDL-associated enzyme PON1 has the ability to stop LDL oxidation.These results suggest that decreased PON and ARE activity in dyslipidemia may operate as a stand-

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alone cardiovascular disease risk factor.However, additional research in a range of demographics is required for definitive validation.

Keywords: Dyslipidemia, Lipid profile,Cholesterol, Lipoproteins and Paraoxonase-1 (PON-1).

INTRODUCTION

In the past few decades, dyslipidemia has become a greater social burden in both industrialized and emerging nations, including our own. Dyslipidemia is known to be a significant risk factor for a number of non- communicable diseases (NCDs).Numerous epidemiological investigations have demonstrated the frequency of dyslipidemia and no communicable diseases, particularly cardiovascular disease (CVD), coexisting. About 25– 30% of urban and 15-20% of rural individuals in India have dyslipidemia [1]. Though it affects both sexes, men are more likely to experience it. Those between the ages of thirty and forty are more likely to experience it. The frequency is noticeably higher in those over 60.

An aberrant metabolic state that results in a persistently elevated plasma concentration of lipids is known as dyslipidemia. To diagnose dyslipidemia, four blood parameters are measured: cholesterol, triglycerides, high density lipoprotein, and low density lipoprotein.

Dyslipidemia can be defined according to National Cholesterol Education Programme (NCEP) hypercholesterolemia (serum cholesterol levels ≥ 200 mg/dl), hypertriglyceridemia (serum triglyceride levels ≥150 mg/dl)[1]. Dyslipidemia can be of hyperlipoprotenemia and combined hyperlipidemia type. Hyperlipoprotenemia is elevation of lipoprotein usually due to LDL (≥ 130 mg/dl) but it may be due to decreased serum concentration level of HDL (< 40 mg/dl for men &<50 mg/dl for women).Combined hyperlipidemia is due to elevation of both lipoprotein and triglycerides. Although dyslipidemia is typically asymptomatic, it can cause symptoms such as peripheral arterial disease, coronary artery disease (CAD), and stroke, among other cardiovascular disorders, which can significantly reduce morbidity and death.[2]

Acute pancreatitis, severe infections, Cushing's syndrome, inflammatory bowel disease, diabetes mellitus, hypothyroidism, and many other conditions can also have dyslipidemia as a secondary symptom.[3]

Because it is necessary for the movement of cholesterol from various parts of the body to the liver for breakdown and resynthesis, HDL is also known as scavenger lipoprotein.[2] Because HDL keeps away our bodies from cholesterol accumulation by reverse cholesterol transport mechanism. It also prevents plaque formation. It's known as good cholesterol as a result.

HDL cholesterol's ability to prevent plaque formation explains why dyslipidemia is associated with low levels of this lipid, which also raises the possibility of negative side effects.[2]

High-density lipoproteins (HDL) physically bind the esterase-active enzyme human serum paraoxonase 1 (PON1).It is essential to HDL's biological function because it keeps the lipoprotein safe from oxidative damage to the membrane that surrounds the HDL molecule. Additionally, PON1 may serve as a predictor of atherosclerosis and coronary artery disease risk.

Serum paraoxonase 1 (PON1) is a 45 kDa glycoprotein that has lactonase activity, which allows it to metabolize some medications and prod rugs. It can also catalyze the breakdown of several organophosphates and nerve

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poisons.[4] This enzyme also protects low density lipoprotein (LDL) against oxidation. Reduced PON1 activity has been studied in relation to a number of illnesses, including type I diabetes, obesity, renal failure, and coronary artery disease (CAD).[5]

Numerous factors, including age and gender, as well as pharmaceutical, lifestyle, and environmental influences, affect PON1 activity.[6]Dietary lipids have been proposed as a significant moderating element. Research has indicated that PON1 activity may be impacted by dietary fatty acids. While monoenoic acids, particularly oleic acid, shield PON1 from oxidative inactivation, polyenoic fatty acids have demonstrated a significant negative effect on PON1 activity. Additionally, it has been shown that in healthy individuals, there is a slight decrease in blood PON1 activity when Tran's fats are substituted for dietary saturated fats. [7]

MATERIALS AND METHODS

Study Type - Observational, Analytical Study
Design- Cross-sectional Study
Duration- June 2020 to May 2021
Study Population- Patients attending the Department of Biochemistry for measurement of Serum Lipid Profile belonging to the working age group of 20 - 60 years will be included in the study. According to available literatures all the study on paraoxonase 1 were performed in the age group of 20-60 years.
Study group will consist of patients of working age group 20-60 years having altered serum lipid profile.
Control group will consists of age and sex matched patients of working age group 20-60 years with normal lipid profile.

Exclusion Criteria –

1) Patients having diabetes or on anti -diabetic medicine or statin.
2) Patients belonging to the age group of below 20 years or above 60 years will be excluded from the study.

RESULTS

Table 1: Distribution of lipid profile characteristics of the study population, according to dyslipidemia and non-dyslipidemia

Characteristics (Mean ± SD)	Non-dyslipidemia	Dyslipidemia	P-value
Total cholesterol (TC) mg/dl	159. 17 ± 25.90	235 ± 29.10	<0.001
Triglycerides mg/dl	97.58 ± 26.36	211.03 ± 78.13	<0.001
HDL-Cholesterol mg/dl	52.55 ± 8.13	46.20 ± 7.16	<0.001
LDL- Cholesterol mg/dl	94.52 ± 19.06	157.74 ± 24.13	<0.001
TC/ HDL ratio	3.06 ± 0.54	5.19 ± 0.96	<0.001
Para-nitro phenyl acetate	174.97 ± 26.19	137.45 ± 32.31	<0.001
Phenyl acetate	187.00 ± 17.15	152.47 ± 12.24	<0.001

Table 2: Correlation between Paraoxonase1 (using Paranitrophenyl acetate and Phenylacetate) activity and lipid profile and BMI

Lipid profile	Paranitrophenyl acetate	p-value#	Phenylacetate	p-value
Total cholesterol	r = -0.441	**<0.001**	r = -0.630	**<0.001**
Triglycerides,	r = -0.427	**<0.001**	r = -0.591	**<0.001**
HDL-Cholesterol	r = 0.152	**0.02**	r = 0.383	**<0.001**

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LDL- Cholesterol	r = -0.427	**<0.001**	r = -0.645	**<0.001**
TC/ HDL ratio	r = -0.398	**<0.001**	r = -0.657	**<0.001**
BMI	r = -0.404	**<0.001**	r = -0.550	**<0.001**

Table 3: Comparison of dyslipidemia (according to different lipid profile criteria) and Paroxonase1activity using paranitrophenyl acetate

Parameters (n)		**Paranitrophenyl acetate (Mean ± SD)**	**Statistics (t-value, df, p-value)**
Total cholesterol (TC)	≥ 200 mg/dl (67)	138.01 ± 32.22	**-6.98, 134, <0.001**
	< 200 mg/dl (69)	173.87 ± 27.52	
Triglycerides (TG)	≥ 150 mg/dl (49)	132.04 ± 30.19	**-7.09, 134, <0.001**
	< 150 mg/dl (87)	169.82 ± 29.58	
HDL-Cholesterol	< 40 mg/dl (50)	135.89 ± 32.98	**-5.77, 134, <0.001**
	≥ 40 mg/dl (86)	168.03 ± 30.25	
LDL- Cholesterol	≥ 130 mg/dl (67)	138.01 ± 32.28	**-6.98, 134, <0.001**
	< 130 mg/dl (69)	173.88 ± 27.52	
TC/ HDL ratio	>4.5 (55)	135.16 ± 31.13	**-6.68, 134, <0.001**
	≤ 4.5 (81)	170.50 ± 29.69	

Table 4: Comparison of dyslipidemia (according to different lipid profile criteria) and Paroxonase1 activity using Phenylacetate

Parameters (n)		**Phenyl acetate (Mean ± SD)**	**Statistics (t-value, df, p-value)**
Total cholesterol (TC)	≥ 200 mg/dl (67)	148.53 ± 10.96	**-16.01, 134, <0.001**
	< 200 mg/dl (69)	193.16 ± 20.08	
Triglycerides (TG)	≥ 150 mg/dl (49)	147.35 ± 10.52	**-9.89, 134, <0.001**
	< 150 mg/dl (87)	184.59 ± 25.11	
HDL-Cholesterol	< 40 mg/dl (50)	148.34 ± 11.01	**-9.45, 134, <0.001**
	≥ 40 mg/dl (86)	186.45 ± 25.63	
LDL- Cholesterol	≥ 130 mg/dl (67)	148.54 ± 10.95	**-16.01, 134, <0.001**
	< 130 mg/dl (69)	193.16 ± 20.08	
TC/ HDL ratio	>4.5 (55)	148.07 ± 11.03	**-11.08, 134, <0.001**
	≤ 4.5 (81)	186.86 ± 24.28	

In Non-dyslipidemia, the mean Total cholesterol (TC) mg/dl (mean± s.d.) of patients was 159. 17 ± 25.90. In Dyslipidemia, the mean Total cholesterol (TC) mg/dl (mean± s.d.) of patients was 235 ± 29.10.There was statistical significance in the distribution of mean total cholesterol (TC) mg/dl with characteristics (p<0.0001). In Non-dyslipidemia, the mean Triglycerides mg/dl (mean± s.d.) of patients was 97.58 ± 26.36. In Dyslipidemia, the

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mean Triglycerides mg/dl (mean± s.d.) of patients was 211.03 ± 78.13.There was statistical significance in the distribution of mean triglycerides mg/dl with characteristics (p<0.0001). In Non-dyslipidemia, the mean HDL-Cholesterol mg/dl (mean± s.d.) of patients was 52.55 ± 8.13. In Dyslipidemia, the mean HDL-Cholesterol mg/dl (mean± s.d.) of patients was 46.20 ± 7.16.There was statistical significance in the distribution of mean HDL-Cholesterol mg/dl with characteristics (p<0.0001). In Non-dyslipidemia, the mean LDL- Cholesterol mg/dl (mean± s.d.) of patients was 94.52 ± 19.06. In Dyslipidemia, the mean LDL- Cholesterol mg/dl (mean± s.d.) of patients was 157.74 ± 24.13.There was statistical significance in the distribution of mean LDL-cholesterol mg/dl with characteristics(p<0.0001). In Non-dyslipidemia, the mean TC/ HDL ratio (mean± s.d.) of patients was 3.06 ± 0.54. In Dyslipidemia, the mean TC/ HDL ratio (mean± s.d.) of patients was 5.19 ± 0.96.The mean TC/HDL ratio distribution with characteristics showed statistical significance (p<0.0001). In Non-dyslipidemia, the mean Para-nitro phenyl acetate (mean± s.d.) of patients was 174.97 ± 26.19. In Dyslipidemia, the mean Para-nitro phenyl acetate (mean± s.d.) of patients was 137.45 ± 32.31.There was statistical significance in the distribution of the mean Para-nitro phenyl acetate with characteristics (p<0.0001). In Non-dyslipidemia, the mean Phenyl acetate (mean± s.d.) of patients was 187.00 ± 17.15. In Dyslipidemia, the mean Phenyl acetate (mean± s.d.) of patients was 152.47 ± 12.24.The mean phenol acetate distribution with characteristics showed statistical significance (p<0.0001).

Paranitrophenyl acetate

The value of Pearson Correlation Coefficient (r) was -0.441. The Negative correlation was found between Paranitrophenyl acetate vsTotal cholesterol inLipid profile. The P-Value was <0.001. The result was statistically significant. The value of Pearson Correlation Coefficient (r) was -0.427. The Negative correlation was found between Paranitrophenyl acetate vs Triglycerides inLipid profile. The P-Value was <0.001. The result was statistically significant. The value of Pearson Correlation Coefficient (r) was 0.152. The positive correlation was found between Paranitrophenyl acetate vs HDL-Cholesterol inLipid profile. The P-Value was 0.02. The result was statistically significant. The value of Pearson Correlation Coefficient (r) was -0.427. The Negative correlation was found between Paranitrophenyl acetate vsLDL- Cholesterol inLipid profile. The P-Value was <0.001. The result was statistically significant. The value of Pearson Correlation Coefficient (r) was -0.398. The Negative correlation was found between Paranitrophenyl acetate vsTC/ HDL ratio inLipid profile. The P-Value was <0.001. The result was statistically significant. The value of Pearson Correlation Coefficient (r) was -0.404. The Negative correlation was found between Paranitrophenyl acetate vsBMI inLipid profile. The P-Value was <0.001. The result was statistically significant.

Phenylacetate

The value of Pearson Correlation Coefficient (r) was -0.630. The Negative correlation was found between Paranitrophenyl acetate vsTotal cholesterol inLipid profile. The P-Value was <0.001. The result was statistically significant. The value of Pearson Correlation Coefficient (r) was -0.591. The Negative correlation was found between Paranitrophenyl acetate vs Triglycerides inLipid profile. The P-Value was <0.001. The result was statistically significant. The value of Pearson Correlation Coefficient (r) was 0.383. The positive correlation was found between Paranitrophenyl acetate vs HDL-Cholesterol inLipid profile. The P-Value was 0.02. The result was statistically significant. The value of Pearson Correlation Coefficient (r) was -0.645. The Negative correlation was found between Paranitrophenyl acetate vsLDL- Cholesterol inLipid profile. The P-Value was <0.001. The result was statistically significant. The value of Pearson Correlation Coefficient (r) was -0.657. The Negative correlation was found between Paranitrophenyl acetate vsTC/ HDL ratio inLipid profile. The P-Value was <0.001. The result was statistically significant. The value of Pearson Correlation Coefficient (r) was -0.550. The Negative correlation

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was found between Paranitrophenyl acetate vsBMI inLipid profile. The P-Value was <0.001. The result was statistically significant.

In ≥ 200 mg/dl (67), the mean Total cholesterol (TC)(mean± s.d.) of patients was 138.01 ± 32.22. In < 200 mg/dl (69), the mean Total cholesterol (TC)(mean± s.d.) of patients was 173.87 ± 27.52. Distribution of mean Total cholesterol (TC)with Paranitrophenyl acetatewas statistically significant (p<0.0001). In ≥ 150 mg/dl (49), themean Triglycerides (TG)(mean± s.d.) of patients was 132.04 ± 30.19. In < 150 mg/dl (87), the mean Triglycerides(TG) (mean± s.d.) of patients was 169.82 ± 29.58. Distribution of mean Triglycerides (TG) with Paranitrophenyl acetatewas statistically significant (p<0.0001). In < 40 mg/dl (50), the mean HDL-Cholesterol (mean± s.d.) of patients was 135.89 ± 32.98. In ≥ 40 mg/dl (86), the mean HDL-Cholesterol (mean± s.d.) of patients was 168.03 ± 30.25. Distribution of mean HDL-Cholesterol with Paranitrophenyl acetatewas statistically significant (p<0.0001). In ≥ 130 mg/dl (67), the mean LDL- Cholesterol (mean± s.d.) of patients was 138.01 ± 32.28. In < 130 mg/dl (69), the mean LDL- Cholesterol (mean± s.d.) of patients was 173.88 ± 27.52. Distribution of mean LDL- Cholesterol with Paranitrophenyl acetatewas statistically significant (p<0.0001). In >4.5 (55), the mean TC/HDL ratio (mean± s.d.) of patients was 135.16 ± 31.13. In ≤ 4.5 (81), the mean TC/ HDL ratio (mean± s.d.) of patients was 170.50 ± 29.69. Distribution of mean TC/ HDL ratio with Paranitrophenyl acetatewas statistically significant (p<0.0001).

DISCUSSION

The current investigation was carried out to determine the relationship between serum paraoxonase-1 activity and lipoprotein concentration in dyslipidemia, as well as to estimate the paraoxonase-1 activity of the study population, which included both non-dyslipidemic and dyslipidemic individuals.

The research was carried out in the Department of Biochemistry from June 2020 to May 2021.This study comprised 136 participants in the working age group of 20–60 years who visited the Department of Biochemistry for a Serum Lipid Profile measurement.Patients in the 20–60 year old working age group with changed serumlipid profiles made up the study group.Patients in the working age range (20–60 years old) who were matched for age and sex and had normal lipid profiles made up the control group.

The results of this study indicate that there is no statistically significant variation in the distribution of sexes or in the age categories of the two study groups (p-value 0.110) [Table no-5.1 & Fig -5.1 (1-2)].Body mass index and waist circumference are significantly higher in patients with dyslipidemia as compared to the healthy controls [Table -5.2 & Fig -5.2(1)]. The dyslipidemic group of the study population have significantly higher fasting Cholesterol, LDL-c, TG, and Cholesterol to HDL ratio and significantly lower fasting HDL level. The most relevant finding of this study is significant decrease in paroxonase and arylesterase activities in dyslipidemicgroup[Table no-5.3 & Fig -5.3(1)]. It shows that HDL is positively correlated with both para-nitrophenyl acetate and phenylacetate whereas other parameters are negatively correlated [Table no -5.4 & Fig -5.4 (1-12)]. We have found that mean difference of paroxonase activity using paranitrophenyl acetate as substrateamong dyslipidemic and non-dyslipidemic group is statistically significant (Table no -5). There is also presence of statistically significant mean difference of paroxonase activity (phenylacetate as substrate) among dyslipidemic and non- dyslipidemic group(Table no -6).

Numerous studies have demonstrated that Asians are more likely than people in other parts of the world to have dyslipidemia. [8]Changes in lipid metabolism are linked to obesity [150], which increases the risk of

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cardiovascular illnesses. Reduced PON1 activity in obese persons is associated with a higher body mass index.[9] Thus the body mass index is an independent predictor of PON1 activity.[10]

Zakietal.hadfoundthesimilarfindings.Paragaetalhadalsofoundthesimilarresults.Ferrietti *et al*. demonstrated also low levels of paroxonase activity in obese individuals. However,Rector *et al*.[11] described lower serum PON1 activityin patients with reduced body weight. This finding is contradictory of our study. PON activity has been evaluated in several diseases associated with alterations of plasma lipid levels. The study of Arora et.al. had revealed that significantly higher levels of TC, TG, LDL and lower levels of HDL are found in dyslipidemic individuals than the healthy control. This corroborates with our study. There is similarity in the findings between the our study and the study done by **Suvarna *et al***.[12]**Singh *et al***,[13], **Saha *et al***[14] also described the same that statistically significantly positive correlations between HDL & PON1 activity and between HDL & ARE activitity in dyslipidemia. In the study done by **Abbott *et al***[15] reported no association between PON and the parameters of lipid profile of cases. This result is contradictory to us.

The enzyme Paroxonase has 3 isoforms: paraoxonase-1 (PON 1), paraoxonase-2(PON2) and paraoxonase-3 (PON 3). Among the three isoforms of paroxonase, paroxonase 1 is catalytically more active.PON1 is a 43 kDa calcium-dependent glycoprotein with 355 amino acid residues.PON2 was discovered first. Lateron PON3 and lastlythe PON 1 was discovered .[16] Paroxonase enzymes can perform three enzymatic actions by lactonase,arylesterase and paroxonase activity. All three isoforms, however, lack the ability to elicit any of these three actions. For instance, PON 2 only exhibits extremely modest arylesterase activity and only lactonase activity.PON 3 has very little paraoxonase activity, weak arylesterase activity, and significant lactonase activity. PON1 exhibits each of these three catalytic functions.[16]

The PON1 gene, which is found on the long arm of chromosome 7, encodes PON1 in humans.[17]The primary organ that produces serum PON1 is the liver. It circulates alongside high density lipoprotein and is discovered with it.However, PON 1 lacks catalytic activity in the absence of interaction with HDL [18].PON1's ability to defend against exposure to particular organophosphates (OP) is another crucial role.Through its ability to scavenge free radicals, the enzyme also contributes significantly to reducing oxidative stress in the human body.It is important in preventing low-density lipoprotein (LDL) and high-density lipoprotein (HDL) particles from oxidizing, as well as reducing inflammation.

It protects cell membrane by inhibiting lipid peroxidation,[19] Thus the PON1 has a protective role against atherosclerosis and cardiovascular disease. Recent years have seen the proposal of two distinct definitions for HDL: HDL quantity (plasma levels of circulating HDL) and HDL quality (HDL's atheroprotective qualities). Although HDL concentrations had been shown to be predictive for atherosclerotic cardiovascular events in population-based large-scale epidemiologic studies, it was insufficient for the evaluation of functional variationsof HDL particles and the determination of the association with atherosclerotic disease risk. The terms healthy HDL‘, functional HDL, or dysfunctional HDL‘ have been frequently used in place of HDL in recent studies.[20] The antioxidant activity of healthy HDL may be associated with potentialanti atherogenic activity.

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CONCLUSION

We conclude that dyslipidemia is linked with a considerably decreased PON1 activity, which is favorably correlated with serum HDL levels.The HDL-associated enzyme PON1 has the ability to stop LDL oxidation.These results suggest that decreased PON and ARE activity in dyslipidemia may operate as a stand- alone cardiovascular disease risk factor.Clear confirmation, however, requires more research in a wider range of populations.

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