Impact of Enhanced Lipid Peroxidation on Carotid Artery Intima Media Thickness Ratio in Patients Receiving Maintenance Hemodialysis

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ABSTRACT

Objective: To determine the impact of increased lipid peroxidation on carotid intima media thickness ratio in patients receiving maintenance hemodialysis.

Study Design: Comparative prospective study.

Place and Duration of Study: Jinnah Post Graduate Medical Center Karachi in collaboration with University of Karachi, Pakistan, from Jan to Dec 2018.

Methodology: The hemodialysis patients were selected from the dialysis center where as the controls were recruited from normal healthy population. The cases taken were receiving maintenance hemodialysis thrice a week. Doppler ultrasonography technique was employed to detect the intima media thickness (IMT) ratio of common carotid artery of study subjects as well as controls. Lipid peroxidation was detected by serum oxidized LDL (ox-LDL) levels.

Results: The mean of right common carotid artery of group A samples was 0.45 ± 0.04 mm, left common carotid artery was 0.42 ± 0.01mm, and mean intima thickness was 0.43 ± 0.02 mm, the mean of right common carotid artery in group B was 0.93 ± 0.09 mm and mean of left common carotid in group B was 1.07 ± 0.14 mm and mean intima thickness of group B samples was 1.0 ± 0.09 mm. In group A mean Ox-LDL was 24.87 ± 5.23 U/ml while in group C samples mean Ox-LDL was 73.77 ± 6.77 U/ml.

Conclusion: Lipid peroxidation is much enhanced in patients on maintenance hemodialysis and leads to an increased carotid artery intima media thickness ratio which is a sign of development of atherosclerosis. This study will help the nephrologists in determining the causes of increased lipid peroxidation and development of atherosclerosis in patients on maintenance hemodialysis.

Keywords: Hemodialysis, Intima-media thickness, Lipid peroxidation.

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INTRODUCTION

Atherosclerosis is the major cause of mortality and morbidity in hemodialysis treated end stage renal disease patients. As estimated by European Registry of patients on renal replacement therapy the chances of cardiovascular complications among patients on renal replacement therapy is 35-50 times higher as compared to the general population.[1] Several factors have been identified as being responsible for this morbidity and mortality in this group of patients. The traditional factors are hypertension, dyslipidemia, diabetes, smoking etc, and complications arising from the underlying renal disease and the dialysis procedure itself.[2] The correlation between these factors and atherosclerotic changes is not clear. Oxidative stress is a major underlying factor for endothelial dysfunction and atherosclerosis.[3] This pathway includes initiation of fatty streak, lesion formation and progression and ultimately rupture of the plaque.[4,5] As the half-lives of free radicals and other reactive oxygen species is very less therefore the estimation of oxidative stress is done by estimation of the levels of stable compounds formed by oxidation of lipids and proteins and derivatives of nucleic acid oxidation.[6] The antibodies that are formed against these compounds like anti-oxidized low-density lipoprotein antibodies can also be detected.[7] The inflammatory cells secrete phospholipase A2 which is an enzyme that catalyzes the oxidative changes in LDL molecule.[8] These oxidative and inflammatory changes result in the generation of oxidized LDL (ox LDL). The initiating event in the development of atherosclerosis is the transport of oxidized low-density lipoprotein across the vascular endothelium and into the arterial wall.[9] The oxidized LDL accumulates in the intima layer of the blood vessels early in atherosclerosis and promotes the assembly of inflammatory cells at the site of the

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vascular damage.[9] Hence elevated levels of Ox-LDL are associated with accelerated atherogenesis.[10] To estimate the risk of atherosclerotic disease, detection of the levels of Ox-LDL can serve as an important biomarker.

High resolution B-mode ultrasonography is utilized as a noninvasive tool to detect the atherosclerotic process in the carotid artery. The atherosclerotic changes in the carotid artery are similar to the changes occurring in general atherosclerosis.[1] The atherosclerotic changes begin in the inner most layer i.e., the intima layer of the blood vessel. The carotid intima media thickness usually means the maximum thickness of the carotid bulb.[10] Normal upper range of intima/media thickness is 0.49-0.85 mm in men and from 0.50-0.89 mm in women.[10] This study will help the nephrologists in early detection and treatment of atherosclerotic changes in hemodialysis patients and hence improve the morbidity and mortality in these patients.

METHODOLOGY

This comparative prospective, hospital based study was carried out in Nephrology Department and Radiology Department of Jinnah Post Graduate Medical Centre Karachi, from January to December 2018. Open EPI website calculator was used for calculation of sample size. Sample size was calculated from open EPI website calculator using a reference study carried out in Shanghai China with a sample size of 84 subjects.[11] A sample size of 120 subjects was calculated which was further divided two groups. Group A included 60 normal controls from healthy population and group B included 60 patients receiving maintenance hemodialysis for more than 2 years duration.

Inclusion Criteria: Inclusion criteria included subjects both male and female with age between 18-50 years, receiving hemodialysis therapy for more than 2 years and not taking supplementary antioxidants.

Exclusion Criteria: Exclusion criteria was patients suffering from malignancy, patients receiving hemodialysis due to acute renal failure, subjects having history of any previous cardiac disease or event and all subjects not willing to participate in the study.

Non probability consecutive sampling technique was used for the recruitment of study subjects. Biochemical parameters were measured in both the study groups. Ethical approval was obtained from the ethical review board of JPMC Karachi. Data obtained from the study subjects was kept confidential.

High resolution B mode ultrasonography was used for detection of the thickness of tunica media and tunica intima of common carotid artery. Serum Ox-LDL levels were analyzed using CEA527Hu Human oxidized low density lipoprotein, Ox-LDL ELISA Kit.

BMI was calculated by using the formula for BMI i.e weight (kg)/height (m^2). Data obtained was analyzed using SPSS version 23. The mean and standard deviation for the variables age, BMI, BP and Lipid profiles were reported in both the study groups. Linear regression analysis was utilized to detect relationship of carotid intima media thickness with lipid peroxidation. Independent sample t-test was utilized for the comparison of mean levels between the study groups. A *p*-value ≤0.05 was considered significant. Scatter plot was used for the graphical representation of data.

RESULTS

Table-I gives the mean comparison of anthropometric measurements of studied samples across three study groups using independent group t-test. Results showed mean age of group A samples was 34.67 ± 7.73 years, mean BMI was 23.47 ± 3.26 kg/m^2, mean systolic blood pressure was 107.33 ± 9.80 mmHg, mean diastolic blood pressure was 66.33 ± 8.09 mmHg, mean weight was 66.10 ± 7.75 Kg, and mean height was 1.69 ± 0.12 meters whereas group C patients had mean age 43.20 ± 4.66 years, mean BMI was 22.21 ± 4.21 Kg/m^2, mean systolic blood pressure was 159.0 ± 12.42 mmHg, mean diastolic blood pressure was 93.67 ± 10.66 mm Hg, mean weight was 64.67 ± 6.13 Kg and mean height was 1.63 ± 0.12 meters (*p*-value <0.01). A *p*-value of <0.05 was considered significant.

Table-I: Comparison of anthropometric measurements among study groups.

Characteristics	Group A (controls) (n=60)	Group B (hemodialysis) (n=60)	*p*-value
	Mean ± SD	Mean ± SD	
Age (years)	34.67 ± 7.73	43.20 ± 4.66	0.20
Body Mass Index (kg/m^2)	23.47 ± 3.26	20.21 ± 4.21	<0.01*
Systolic Blood Pressure (mmHg)	107.33 ± 9.80	159.00 ± 12.42	<0.01*
Diastolic Blood Pressure (mmHg)	66.33 ± 8.09	93.67 ± 10.66	<0.01*
Weight (kg)	66.10 ± 7.75	59.19 ± 6.13	<0.01*
Height (m)	1.69 ± 0.12	1.63 ± 0.12	0.20

**p-value <0.05 was considered significant using independent group t-test*

Table-II reports the mean comparison of serum Ox-LDL across studied groups, in group A mean Ox-LDL was 24.87 ± 5.23 U/ml while in group B samples mean Ox-LDL was 63.77 ± 6.77 U/ml (*p*-value <0.01).

Table-II: Serum oxidized LDL levels in both groups.

Serum Parameter	Group A (controls) (n=60)	Group B (hemodialysis) (n=60)	*p*-value
	Mean ± SD	Mean ± SD	
x-LDL(U/ml)	24.87 ± 5.23	63.77 ± 6.77	<0.01

**p-value <0.05 was considered significant using independent group t-test.*

Table-III, reports the mean and standard deviation of intima media thickness across selected patients of from the two groups, the mean of right common carotid artery of group A samples was 0.45 ± 0.04 mm, left common carotid artery was 0.42 ± 0.01 mm, and mean intima thickness was 0.43 ± 0.02 mm, the mean of right common carotid artery in group B was 0.93 ± 0.09 mm and mean of left common carotid artery was 1.07 ± 0.14 mm while the mean intima thickness of group B samples was 1.0 ± 0.09 mm (*p*-value <0.01). A *p*-value of <0.05 was considered significant.

Table-III: Mean comparison of intima media thickness across studied groups.

Parameters	Group A (controls) (n=60)	Group B (hemodialysis) (n=60)	*p*-value
	Mean ± SD	Mean ± SD	
Right common carotid artery (intima media thickness mm)	0.45 ± 0.04	0.93 ± 0.09	<0.01*
left common carotid artery (intima media thickness) (mm)	0.42 ± 0.01	1.07 ± 0.14	<0.01*
Mean intima media thickness (mm)	0.43 ± 0.02	1.00 ± 0.09	<0.01*

**p-value <0.05 was considered significant using independent group t-test*

DISCUSSION

The mortality rate in dialysis patients due to cardiovascular complications is approximately 30 times higher than the general population. The oxidative stress induced by the dialytic procedure is the most important factor leading to development of cardiac complications.

No significant difference in the mean ages among the two groups was found. A significant decrease in the weight and BMI was seen between the hemodialysis patients. This is similar to the findings of Rysz *et al*.[12] The decreases in BMI may be due to protein energy wasting and restricted diet in hemodialysis patients.

We found a significant increase in the mean systolic BP and diastolic BP of the hemodialysis patients as compared to the control group. This increase in BP which can be due to fluid overload, over activity of renin angiotensin system, erythropoietin administration and enhanced stimulation of the sympathetic nervous system. Our results are similar to the findings of Wang *et al*,[13] who reported a mean SBP of 143.2 ± 32.7mmHg and mean DBP of 79.0 ± 15.9 mmHg among hemodialysis patients.

Our study shows an increase in levels of serum oxidized LDL in subjects on maintenance hemodialysis (63.77 ± 6.77) as compared to controls (24.87 ± 5.23). Wagner *et al*,[14] in his study reported a mean level of Ox-LDL in hemodialysis patients as 74.6 ± 28.1 U/L. Hou *et al*,[15] also reported increased levels of Ox-LDL (89.15± 12.3 U/L) in hemodialysis treated patients. This increase in levels of oxidized LDL is due to increased oxidative stress after multiple cycles of hemodialysis resulting in increased lipid peroxidation.[16]

Significant results were obtained on Doppler ultrasonography. There was significant mean difference obtained across the two studied groups for mean intima media thickness, and right, left common carotid artery outcomes with *p*-value less than 0.01.

The mean of intima thickness in group A was 0.43 ± 0.02 while the mean of intima media thickness in group B was 1.0 ± 0.09. This signifies that patients receiving dialysis are at greater risk of developing atherosclerosis. This is in accordance with the published work of Manabe *et al*,[17] who reported a maximum IMT of ≥1.5 mm in hemodialysis patients.

Our results are also similar to Mahmoud *et al*[18] who also showed increased carotid artery IMT (1.0 ± 0.7) in hemodialysis patients. These findings suggest that patients on hemodialysis are subjected to oxidative stress that leads to the formation of oxidized LDL and generation of inflammatory mediators that lead to development of atherosclerotic heart disease. The carotid artery intima media thickness ratio is a non-invasive indicator and predictor of atherosclerotic heart disease and has been discussed in many previous studies.

Oxidative Stress is a universal challenge in hemodialysis patients. The enhanced Oxidative stress in hemodialysis patients is caused due to poor intake of exogenous antioxidants in diet, formation of oxidative products, and loss of antioxidants during hemodialysis.[19] These factors are linked to the development of atherosclerosis and chronic inflammation and lead to cardiovascular complications in these patients.[20] The administration of antioxidants plays a protective role against oxidative stress by neutralizing the harmful

effects of oxidative molecules however it has still not been adopted as a regular treatment protocol in clinical practice.[21] More prospective studies are required to elaborate the protective role of antioxidant administration in oxidative stress that can improve the cardiovascular mortality rate in hemodialysis treated end-stage renal disease. More over the oxidative stress parameters in these patients need to be monitored to avoid the possible outcomes of oxidative stress. Dietary guidelines should also be developed to ensure the intake of adequate vitamins and minerals in these patients.

CONCLUSION

Changes in serum ox-LDL levels and CCA IMT are much evident in hemodialysis treated end stage renal disease patients. High level of Ox LDL and the CCA IMT depict an enhanced lipid peroxidation status in these patients which leads to development of atherosclerosis and other cardiac complications in these patients. This study will help the nephrologists to identify the causes of cardiac morbidities and mortalities in these patients and to adopt measures for prompt detection and treatment of these outcomes.

Conflict of Interest: None.

Authors' Contribution

SR: Conception, design of study and manuscript writing, TM: Final analysis and approval of work, SK: Data collection and analysis, SHA: Drafting of manuscript, MTK: Literature review, SR: Statistical analysis.

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