Original Article

Efficacy of Atorvastatin (40mg) in Reducing Proteinuria in Chronic Kidney Disease (CKD) Patients

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ABSTRACT

Objective: his study was planned to determine the efficacy of atorvastatin 40mg in reducing proteinuria in Chronic Kidney Disease patients, in our population at district Bannu and adjacent areas.

Study Design: Cross-Sectional, Descriptive

Place and Duration of Study: This study was conducted at the Department of Medicine/Nephrology, DHQ Teaching Hospital (DHDTH) Bannu, Khyber Pakhtunkhwa. Study was carried out for a period of 12 months, from July 2020 to June 2021.

Materials and Methods: The study was conducted on 246 patients presented to Department of Medicine/Nephrology, DHQ Teaching Hospital (DHDTH) Bannu, Khyber Pakhtunkhwa, who were having Hyperlipidemia (cholesterol>6mmol/L=232mg/dl, LDL-chol>2mmol/L=78mg/dl, TGs>1.9mmol/L=170mg/dl) and some CDK component (based on Proteinuria ie urinary protein excretion of > 150 mg per day). They were started on atorvastatin in the dose of 40mg once daily for hyperlipidemia for three months, and called for follow up after 3 months, to look for proteinuria.

Results: Treating dyslipidemia with atorvastatin 40mg/day not only reduced the risk of cardiovascular events but also aided in preventing the further deterioration of renal function in CKD cases. Our results revealed that atorvastatin in the dose of 40mg once daily for three months significantly reduced serum lipids and proteinuria in CKD patients.

Conclusion: In the light of above discussed evidences, it is concluded that atorvastatin 40mg once daily can be used in CKD patients to reduce hyperlipidemia and proteinuria. However, more detailed research is required in future to evaluate the dose dependent effect of atorvastatin in reducing proteinuria and to compare the efficacy of different statins in reducing the proteinuria in CKD patients.

Key Words: Atorvastatin, Proteinuria, Chronic Kidney Disease (CKD), Bannu

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INTRODUCTION

Chronic Kidney Disease (CKD) is considered as a silent global epidemic. It has been associated with cardiovascular events. Hyperlipidemia is also a main risk factor for cardiovascular diseases and development of proteinuria and impaired renal function. The patients of CKD should be evaluated for dyslipidemia.

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Treating dyslipidemia not only reduces the risk of cardiovascular events but also aids in preventing the further deterioration of renal function in CKD cases.

CKD (Chronic Kidney Disease) is a global health issue with growing incidence and prevalence, poor outcomes and high cost [1]. Globally the increasing cases of CKD are very alarming and are threatening to reach epidemic proportions over the up-coming decades [2]. The incidence of CKD is increasing globally with annual growth rate of 8%. The epidemiological studies have reported that incidence of CKD is much higher in developing countries than in developed nations. The incidence of CKD is about 6 to 10 times higher in elderly patients aged between 70 to 90 years as compared to adults aged between 30 to 50 years [3].

CKD (Chronic Kidney Disease) is defined as decreased GFR (Glomerular Filtration Rate), increased urinary excretion of albumin, or both [4]. According to KDIGO (Kidney Disease: Improving Global Outcomes), CKD is defined as "Structural or functional abnormalities (markers of renal damage) present for more than 3 months with implications for health and requires one of two criteria to be documented or inferred for more than

3 months; either GFR < 60ml/min/1.73m^2 or markers of kidney damage including albuminuria" [5]. CKD has been classified into 5 stages (stage 1 to 5) depending upon the urinary excretion of proteins and renal function assessed by GFR which is derived from age, gender, race and serum creatinine concentrations. ESRD (End-stage renal disease) is the last or stage-5 of CKD characterized by GFR of < 15ml/min/1.73m [6].

Patients of CKD experience various symptoms both due to the treatment and the disease itself. The most common symptoms of CKD include drowsiness, lack of energy or fatigue, pain, pruritus, bone or joint pain, sleep disturbances, dyspnoea, poor appetite, poor mobility and dry skin etc. [7][8]. Hypertension and Diabetes are the main risk factors that lead to CKD [9]. Unhealthy diet, sedentary life style, obesity, increase age, hyperlipidemia, hyperuricemia and high alcohol consumption increases the risk of CKD [10].

Proteinuria (increase urinary protein excretion of > 150 mg per day [11]) is a hallmark of kidney disease. Besides blood pressure, serum creatinine and urinalysis, estimation of urinary protein excretion plays significant role in diagnosis, monitoring and classification of kidney diseases [12]. Proteinuria in CKD patients, is not only a prognostic tool of progression of CKD, but also a mediator of this disorder, and has been associated with high mortality and morbidity and increase cardiovascular risk in CKD patients [13].

Hyperlipidemia not only increases the risk of cardio-vascular disease but also considered as an independent factor that worsens the CKD. HMG CoA reductase inhibitors (statins e.g.; Atorvastatin) are widely used for the treatment of hyperlipidemia and for prevention of CHD (coronary heart disease). Apart from its lipid lowering effect, it has a protective effect on kidneys, and aids in reducing proteinuria, inflammation and prevents histological alterations of inflammation and fibrosis in the kidney [14].

MATERIALS AND METHODS

Study Design: Cross-Sectional, Descriptive.

Place and Duration of Study: Department of Medicine/Nephrology DHQ Teaching Hospital (DHDTH) Bannu, Khyber Pakhtunkhwa, for a period of 12 months, from July 2020 to June 2021.

Inclusion Criteria:

- Patients with known chronic kidney disease (GFR <60 >15ml/min) for at least three months.
- Patients of both genders and either race.
- Age between 18 to 75 years.
- Both diabetic and non-diabetic CKD patients.
- Patient with Proteinuria in the range of 0.5-3.5 grams protein per gram Creatinine on urinary protein-creatinin ratio (uPCR).

Sample Size: 246 patients, who were having Hyperlipidemia and some CDK component.

Sampling Technique: Consecutive, Non-probability Sampling.

Exclusion Criteria: Those patients who were not filling the inclusion criteria,patients terminally ill, and patients who were not willing to be included in study, on Statins/other drugs decreasing proteinuria, and patients mentally retarded were not included, because they would not benefit from future planned treatment or would give recall bias. If included in the study, these would act as confounders to introduce bias in the study results.

1. Patients already on statins.
2. Patients of acute liver disease. ALT >300 IU/L.
3. Hypersensitivity to statins.
4. Patients on renal replacement therapy.
5. Patients on ACE inhibitors or ARBs for the least 3months.

Data Collecting Procedure: The study was conducted after approval from hospitals ethical and research committee/ board.

All the patients who were meeting the inclusion criteria, as per operational definitions, presented to the Department of Medicine/Nephrology, DHQ Teaching Hospital Bannu, through emergency or OPD, were included in the study. All patients were first counseled by explaining them the study objectives and possible side effects of the drug i.e. atorvastatin. All the queries regarding the study were answered clearly and properly. The purpose and benefits of the study were explained to all patients, and a written informed consent was obtained from all who agreed to participate in the study. Participants were explained in detail how to collect clean catch midstream random urine sample. Participants were ensured that all the information obtained will be kept confidential and will be used for research purpose only.

For all these patients (study population), at first visit, Renal Function Tests, Fasting Lipid Profile (Total cholesterol, LDL-Chol and TGs), and spot urine for Urine protein/creatinine ratio were sent to hospital lab initially to note as base line references, and these were noted on flow sheet as data collection tool having all variables of interest. Then the same investigations repeated from same lab, after the usage of atorvastatin 40mg daily at bedtime for consecutive three months, under the supervision of researcher, and reports were collected by him personally. To ensure follow up after 3months, contact numbers of patients were also noted.

All the patients were categorized in various groups. All the information including name, age, gender, address and lab values (both initial and at 3 months) were recorded in that pre-designed Proforma. Only a complete Proforma was subjected to analysis. Strict exclusion criteria was applied to control confounders and bias in the study results.

Statistical Analysis: Data obtained was entered into SPSS version 23 and analyzed in analytical statistics.

Mean ± SD were calculated for numerical/ quantitative variables like age. Co-relation between proteinuria and other clinical variables was analysed using multiple linear regression. For the comparison of pre and post treatment data, we used paired t-test. P- values of < 0.05 were considered significant. These were stratified among age and gender to see the effect modifiers. All results were presented in the form of tables, charts.

RESULTS

This results are tabulated at table 1&2.

Table 1 represents the association between proteinuria and its determinants from pre-treatment data. Statistical analysis showed that before treatment, LDL and triglycerides were significantly raised along with proteinuria, whereas no association of SBP, DBP and eGFR with proteinuria was observed.

Table 2 represents the efficacy of atorvastatin 40mg/day in treating proteinuria and its determinants (comparison between pre and post treatment data). Statistical analysis showed that atorvastatin 40mg/day, after 3 months of continuous dosing, significantly reduced the proteinuria, total cholesterol, triglycerides and LDL whereas no effect was observed on SBP, DBP and eGFR.

Table No.1: Determinants of Proteinuria from pre-treatment data

	Beta-coefficient	SE	P-value
Systolic BP	.034	.001	.574
Diastolic BP	.113	.001	.077
eGFR	-.117	.002	.062
Total cholesterol	.039	.001	.519
LDL-cholestrol	-.124	.002	.042
HDL-cholestrol	-.296	.002	.000
Triglyceride	.175	.005	.004

Table No.2: Efficacy of Atorvastatin 40mg in treating proteinuria and its determinants

	Pre-treatment		Post-treatment		P-value
	Mean	SD	Mean	SD	
Systolic BP	129.68	9.804	128.456	17.234	0.3
Diastolic BP	84.41	16.96	84.41	16.96	0.16
eGFR	86.709	9.006	87.345	12.777	0.48
Total cholesterol	247.04	17.06	187.63	11.18	0.0001
LDL-cholestrol	174.98	8.52	112.77	11.77	0.0001
HDL-cholestrol	43.35	2.89	42.5	3.27	0.0003
Triglyceride	172.18	6.7	144.44	8	0.0001
Protienuria (g/day)	2	0.22	0.8	0.15	0.0001

Table1: represents the association between proteinuria and its determinants from pre-treatment data. Statistical analysis showed that before treatment, LDL and triglycerides were significantly raised along with proteinuria, whereas no association of SBP, DBP and eGFR with proteinuria was observed.

Table 2: represents the efficacy of atorvastatin 40mg in treating proteinuria and its determinants (comparison between pre and post treatment data). Statistical analysis showed that, atorvastatin 40mg/day, after 3 months of continuous dosing, significantly reduced the proteinuria, total cholesterol, triglycerides and LDL, whereas no effect was observed on SBP, DBP and eGFR.

DISCUSSION

Globally, Chronic Kidney Disease (CKD) is considered as 16th leading cause of death. Timely screening, proper diagnosis and early treatment by health care clinician is necessary to prevent CKD associated complications such as cardio-vascular events, end-stage renal disease and death [15]. Proteinuria is a typical and persistent sign of renal dysfunction in CKD patients. It has been considered as a therapeutic target in delaying the progression of CKD and preventing cardio-vascular mortality in CKD patients [16]. In this study, we have determined the efficacy of atorvastatin; a drug which belongs to HMG CoA reductase inhibitor (anti-hyperlipidemic agent) class, in reducing the proteinuria, in the dose of 40mg once daily, for three consecutive months. According to the results of our study, it has been established that, there is a strong relation between serum cholesterol, triglycerides, LDL and proteinuria. Statistical analysis by linear regression of pre-treatment data showed, increased serum lipids concentration along with proteinuria, in CKD patients. Our study findings also revealed that atorvastatin 40mg once daily for three months is very effective in reducing serum lipids concentration, as well as proteinuria (which is a classical symptom of CKD) in CKD patients.

Increase serum lipids concentration leads to impaired renal function [17]. Abnormal lipo-protein metabolism often accompanies renal disease, and is considered to be involved in the pathogenesis of kidney injury. Hyperlipidemia is a modulator for progression of primary renal diseases. Elevated serum lipoproteins along with proteinuria, increase the rate of loss of renal function by two-folds. One of the mechanism that supports the evidence of hyperlipidemia induced renal injury is that, the serum lipids directly acts on the resident cells of the kidney. The renal tubulo-interstitium and glomerulus is a preferred site for lipid deposition where they interact with the resident cells. Due to the absence of basement membrane that separates mesangium and the capillary stream, and the presence of fenestrated epithelium lining glomerular and peritubular capillaries, lipids easily access these areas and initiates local metabolism. Mesangial cells have been shown to bind and take up native and oxidized LDL cholesterol. Binding of LDL and other

lipids to mesangial cells initiates cellular proliferation, and stimulates the secretion of inflammatory mediators such as prostanoids, interleukin-6, platelet derived growth factor (PDGF), TGF- β 35, 36, 37, 38 leading to initiation of injury process [18].

Treating hyperlipidemia, not only reduces the proteinuria, but also slows down the progression of CKD and its associated complications [19]. Statins (HMG CoA reductase inhibitors) are used as a first line therapy in the management and treatment of dyslipidemia and prevention of atherosclerosis and cardio-vascular diseases. The use of statins in CKD population, not only helps in treating hyperlipidemia and reducing proteinuria, but also delays the progression of CKD and its adverse outcomes [20]. Hence these evidences strongly support our current study findings i.e. atorvastatin 40mg is very effective in reducing proteinuria in CKD patients.

CONCLUSION

In the light of above discussed evidences, it is concluded that atorvastatin 40mg once daily can be used in CKD patients to reduce hyperlipidemia and proteinuria. However, more detailed research is required in future to evaluate the dose dependent effect of atorvastatin in reducing proteinuria and to compare the efficacy of different statins in reducing the proteinuria in CKD patients.

Recommendations: In the view of the above study, we **recommend:** All the health care providers and physicians should be aware of the hidden burden of the hyperlipidemia and proteinuuria, where the patients have no or vague signs symptoms, but having positive lab findings, for early diagnosis and prompt treatment of these, to decrease the disease progression, its complications, burden and their misery.

Hyperlipidemia is a main risk factor for cardiovascular diseases and development of proteinuria and impaired renal function. The patients of CKD should be evaluated for dyslipidemia.

Author's Contribution:

Concept & Design of Study:	Nafidullah Khan, Raza Muhammad Khan
Drafting:	Nafidullah Khan, Raza Muhammad Khan
Data Analysis:	Muhammad Nadeen Khan
Revisiting Critically:	Raza Muhammad Khan, Haider Ali Khan
Final Approval of version:	Nafidullah Khan, Raza Muhammad Khan

Conflict of Interest: The study has no conflict of interest to declare by any author.

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