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Efficacy of Atorvastatin on Proteinuria in Chronic Kidney Disease Patients of District Mardan, Pakistan

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ABSTRACT

Chronic kidney disease (CKD) is a major health problem world wise and is associated with increased risk for cardiovascular disease and end stage renal diseases. The prevalence of CKD is increasing rapidly in urbanizing country like Pakistan, where a significant population of 180 million is predisposed to diabetes and hypertension. Atorvastatin a lipid-regulating drug, used mostly for the treatment of CKD patients. The aim of the current study was to find out the prevalence of chronic kidney disease in district Mardan and to compare the efficacy of atorvastatin on proteinuria in CKD patients. Samples were collected from 3000 patients in the Mardan Medical Complex (MMC) using inclusion/exclusion criteria. The patients were classified into three groups on the bases of atorvastatin dose; Group I patient were treated with 20mg atorvastatin, group II with 40mg and group III with 60mg daily for three months. In the blood, serum creatinine and cholesterol level while in urine, Urine Protein to Creatinine ratio (UPCR) level was determined before and after use of atorvastatin. The results showed that the prevalence of CKD patients was 8.2% in district Mardan. The average level of proteinuria in CKD was 1.5 gram protein/gram creatinine. After atorvastatin treatment, proteinuria level was reduced to>1.5 in group I, ≤ 1.5 in group II,<1.5 in group III. From the current study it was concluded that40mg of atorvastatin (Group II) is effective and optimal dose for reducing of proteinuria in CKD patients, and may be atorvastatin become an important supportive therapy for renal damage in future.
KEYWORDS: Kidney, Atorvastatin, Proteinuria, Mardan, cardiovascular disorder.

INTRODUCTION

Kidneys are the most important organ of human body which perform different functions such as removal of waste products, water homeostasis, regulation of blood pressure and electrolyte balance [1]. Kidney disease usually affects both kidney and can also cause damage to other part of the body, especially heart. There are different types of kidney disease such as alport syndrome, diabetic nephropathy, glomerulonephritis, Berger's disease, kidney stones, nephrotic syndrome and polycystic kidney disease. But among all these disorder, CKD is the most end-stage renal disorder which usually leads to renal failure [2].Chronic kidney disease (CKD) is a major health problem resulting in a considerable increase of morbidity and mortality, decreased quality of life, and substantial health care costs. CDK occurs when kidney shrunk due to fibrosis or Glomerular Filtration Rate (GFR) value decreased below 60ml/min [3]. Diabetes and hypertension are also found to be the major causes of chronic kidney disease, together contributing to about 70% of cases. Hyperlipidemia has been hypothesized to play an important role in the progression of kidney disease[4].Extensive knowledge about abnormal lipid patterns among patients with advanced CKD and elevated total cholesterol, high non-HDL cholesterol, a high ratio of total cholesterol/HDL, and low HDL in particular was significantly associated with an increased risk of developing renal dysfunction [5].About 30% of CKD patients are progress to end-stage renal disease (ESRD) and some form of renal transplant therapy is required [6]. Chronic kidney disease progresses over time by transitions through advanced stages of CKD. This progression may occur due to the continuous effect of the disease responsible for inciting the damage and other multiple factors independent of the initial disease. These progression factors include hypertension, proteinuria, and smoking [7]. Normal kidneys don't allow serum proteins like albumin, globulins and other low molecular weight proteins to filter across its filtration barriers but once CKD develop these filters are damaged and protein leakage started in urine and lead to proteinuria[8].

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In CKD patient's proteinuria has been associated with high mortality and morbidity and also increases cardiovascular risk. Proteinuria is not only a biomarker of progression of chronic kidney disease but also a mediator of this devastating disorder. Micro albuminuria and cardiovascular risk in these patients has been reduced by using angiotensin-converting enzyme inhibitors (ACE) and statins [9]. In CKD patient's cardiovascular disease is the main cause of morbidity and mortality. By far a great majority of the patients will succumb to cardiovascular diseases or other complications of CKD prior to ESRD [10].For irreversible CKD, transplantation was the most effective modality of renal replacement therapy (RRT); however, this therapy have some limitation such as immunologic rejection, adverse effects of immune suppressant agents, and a relative shortage of organ availability. After implementation of Medicare funding for RRT in 1972, long-term dialysis rapidly evolved as first-line treatment but can be considered only a temporary respite from the basic form of treatment [11,12]. Therefore, strong evidence reported that transplantation is most successful when implemented before onset of long-term dialysis, only 2.5% of patients with end-stage renal disease undergo transplantation as initial RRT [13,14].

Use of statins is beneficial for most patients with CKD who are at high cardiovascular risk [15], although research is needed to ascertain how to best prevent kidney injury. Currently, it has been recommended that statins have the ability to slow down kidney function decline in patients with renal diseases. Statins competitively inhibit HMG-CoA reductase which catalyzes the biosynthesis of cholesterol. Statins can also reduce the rate of very low density lipoprotein synthesis and increasing its clearance and thus decrease TG in some patients [16,17].Present study assessed the efficacy of different doses of atorvastatin on proteinuria in chronic kidney disease patients which would help to sensitize the treating physicians regarding the use of these drugs in slowing the progression of chronic kidney disease. This present comparative study would help to evaluate optimize dose of atorvastatin in reducing proteinuria and can be addressed to the health authority to plan future strategy for the problem.

MATERIALS AND METHODS

Sample and Data Collection

This study was carried out at Mardan Medical Complex; Mardan (MMC Mardan) & AWKUM. Patients with CKD were selected from MMC Mardan. The name of patient, their age and hospital ID number was written in the Performa of those patients from which the sample was collected. Sample was collected from the blood serum and urine of CKD patients, using Inclusion/Exclusion criteria.

Ethical approval

All the experimental procedures were approved from the bioethics committee from the department of Biochemistry Abdul Wali Khan University Mardan Pakistan. To ensure their voluntary participation, inform consent was obtained from all the participants.

Inclusion criteria

Patients having documented CKD by ultrasound or GFR calculation (less than 60 ml/min), both gender having age above 18 years and Patient having proteinuria in the range of 0.5-3.5 grams protein per gram creatinine on UPCR was included in this study.

Exclusion criteria

In exclusion criteria include those patients with renal replacement therapy and acute liver disease was excluded from this study because atorvastatin can further damage liver. Those patients were also excluded from the study who already used atorvastatin or show hypersensitivity to atorvastatin.

Classification of patients

In this study all the patients were classified into three different groups, on the basis of atorvastatin dose used daily for three months. These group were named as; Group I (treated with 20mg atorvastatin daily), Group II (treated with 40mg atorvastatin daily), Group III (treated with 60mg atorvastatin daily). Each group contain equal number of patients.

Serum creatinine and cholesterol analysis

The serum sample of proteinuria patients were analyzed for the estimation of blood serum creatinine and cholesterol level, before and after use of different doses of atorvastatin treatment. The creatinine assay kit (SIGMA-ALDRICH)

was used for serum creatinine determination quantitatively while cholesterol assay kit (CELL BIOLAB, INC) was used to measure total cholesterol level in the blood serum of CKD patients with proteinuria.

Determination of UPCR level

UPCR assay kit (IDXXX) is used to measure the amount of protein in a random urine sample along with urine creatinine and reported as the ratio of urine protein to creatinine (UPCR). UPCR initially was determined as a base line reference and then after the use of atorvastatin. The result was compare with previous result of UPCR patient to determine the efficacy of atorvastatin with different doses on proteinuria. For the estimation of UPCR test, catalyst one chemistry analyzer was used.

Data analysis

All collected data was put in SPSS version 17. For quantitative variables like age of the patient, pre and post treatment proteinuria descriptive statistics such as mean and standard deviation was calculated. Finally to see the effect modification, efficacy was stratified between age and gender.

RESULTS

Prevalence of CKD in district Mardan

In this study out of 3000, 246 patients was found that having proteinuria in the range of 0.5-3.5 gram/gram creatinine. From this study it was concluded that the prevalence of proteinuria in CKD patients in district Mardan was 8.2%, as shown in Table1.

Table 1: Prevalence of CKD in district Mardan

Total number of observed patients	Total number of CKD patients	Prevalence of CKD in district Mardan
3000	246	8.2%

Classification of CKD patients on the basis of age

On the basis of age, CKD patients was classified into three classes which showed that 89 (36%) patients were in age range 20-40 years, 145 (59%) patients were in age range 41-60 years, 12 (5%) patients were in age range >60 years (Table 2). This result showed that patients in the range 41-60 years presenting high suspected clinical feature of CKD.

Table 2: Age wise distribution of CKD patients

AGE	FREQUENCY	PERCENTAGE
20-40 years	89	36%
41-60 years	145	59%
> 60 years	12	5%
Total	246	100%

Classification of patients based socioeconomic value

In this study the patients are classified into three classes, based on socioeconomic value. This classification is based on income, occupation and education facilities. Additionally, education and low income are also significant predictors of physical and mental health problems due malnutrition, lack of health facilities and heavy and stressful jobs. This result showed lower class people have high risk to CKD as compared to middle and upper class (Table 3).

Table 3: Classification based on socioeconomic value

Total no of patients	Lower class	Middle class	Upper class
246	130	75	41

Gender wise distribution of CKD patients

Among 246 patients, it was analyzed that 114 (46.34%) patients were male and 132 (53.66%) patients were female (Table 4). In this study the female ratio was high due to increased risk of hypertension and diabetes.

Table 4: Gender wise distribution of CKD patients

GENDER	FREQUENCY	PERCENTAGE
MALE	114	46.34%
FEMALE	132	53.66%
Total	246	100%

Classification of patients based on GFR value

In this study, CKD patients with proteinuria were classified into four groups on the basis GFR (Table 5). The frequency of CKD patients having GFR value in the range 45-59 mL/min showed increased risk to CKD.

Table 5: Stages of CKD patients based on GFR value

Stages of CKD with GFR value	Frequency	Percentage
Moderate CKD (stage IIIA) with GFR = 45-59 mL/min	90	36.58%
Moderate CKD (stage IIIB) with GFR = 30-44 mL/min	81	32.93%
Severe CKD (stage IV) with GFR = 15-29 mL/min	52	21.14%
End stage CKD (stage V) with GFR = <15 mL/min	23	9.35%
Total	246	100%

Serum cholesterol and creatinine level before and after treatment

In the blood serum of CKD patient's cholesterol and creatinine level was shown in the table 6. The mean value of serum cholesterol and creatinine was high in CKD patients with proteinuria while a significant decrease was observed after atorvastatin treatment as compared to before treatment.

Table 6: Serum cholesterol and creatinine level in CKD before and after treatment

Serum biomarker	Pre-treatment	Post-treatment		
Total cholesterol (mg/dl)	253.26 ± 39.72	Group I (20mg)	Group II (40mg)	Group III (60mg)
		195.6 ± 23.8	183.6 ±23.8	174.6± 23.7
Creatinine (mg/dl)	1.97 ± 0.52	1.46 ± 0.2	1.31 ±0.24	1.2 ± 0.19

Proteinuria level before and after treatment

In CKD patients, proteinuria level was analyzed with mean and standard deviation (S.D) before atorvastatin treatment. The result showed that before atorvastatin treatment proteinuria level in CKD patients was high with mean and S.D, compared to normal control. After atorvastatin treatment with different doses the post-operative proteinuria level with mean and S.D was significantly reduced in all three groups as compared to pretreated results (Table 7).

Table 7: Pre and post-treatment proteinuria level

Proteinuria level	Pre-treatment	Post-treatment		
Gram protein/gram creatinine	1.5± 0.835	Group I (20mg)	Group II (40mg)	Group III (60mg)
		>1.5±0.835	≤1.5±0.675	<1.5±0.535

DISCUSSION

CKD is the main cause of earlier mortality and co morbidities. CKD patients have a greater risk of premature mortality associated with cardiovascular disease even during the initial stages of disorder. Oxidative stress, inflammation, platelet and endothelial dysfunction, electrolyte imbalances and proteinuria usually increase in renal dysfunction [18]. The prevalence of CKD has been evaluated based on proteinuria in different populations of Pakistan. The combined prevalence of CKD in all provinces in Pakistan was found to be 14%. Based on economic survey 2005-06, about 21 million people have CKD patients in the total population of Pakistan [19]. In present data

total 3000 patient were studied in MMC Mardan, in which 246 patients were found with CKD having proteinuria. Table 1 showed that the prevalence of CKD patients was found to be 8.2% in district Mardan.

It has been known that estimated GFR decline with age. In the diabetic population Diabetes-related ESRD incidence has decreased in all age-groups in the US due to the reduction in the prevalence of ESRD risk factors and improved treatment. The 15-year cumulative risks were 52% for ESRD and 11% for pre-ESRD death. The prevalence of CKD among females in the Chinese population is 7.4% with age 18-39 while the patients with age from 60-70 have 24.2% [15]. The present study determined that in young patients (age <40 years) the ratio of CKD is low(36%) while in elderly patients (40 to 60 years) CKD ratio was significantly high (59%) due to different risk factors such as hypertension and diabetes. The CKD ratio is very high in older individual (>60 years) due to decline renal functions, diabetes and hypertension but these patients usually die early (Table 2).The prevalence of CKD in Pakistan is probably high due to increased risk factors such as diabetes and hypertension. Most of the CKD patients cannot get optimized management due to many reasons such as lack of financial support by the government, high cost of management, absence of health insurance, complex management issues, less health care facilities, failure of health professionals to recognize the magnitude of this disease and the complications of CKD. Due to these factors the magnitude of complications of CKD patients in Pakistan is expected to be higher [20]. In this study out of three classes, lower class people have high risk to CKD due to low income and education, physical and mental health problems, malnutrition and lack of health facilities (Table 3).

Much effort has been made to identify the risk factors associated with CKD development, establish better prevention strategies and early detection of CKD patients, effect of gender on the prevalence, progression and characteristics of CKD. The life time risk of diabetes is greater in women than in men and has greater prevalence chronic kidney disease due to hypertension, hyperglycemia, dyslipidemia and obesity. In addition, female sex has been associated with higher risk of nephropathy [21]. The current study also found gender base differences in the prevalence of CKD risk factors. Females (53.66%) have a greater prevalence of CKD as compared to males (46.34%) (Table 4). Patients with increased levels of proteinuria have a high risk of severe CKD and as an indicators of future decreased in GFR, but limited therapeutic options are available to decrease proteinuria. Use of statins is beneficial for most patients with CKD who are at high cardiovascular risk [22]. The result showed that serum cholesterol and creatinine level was high in CKD patient with proteinuria before atorvastatin treatment but significantly reduced after atorvastatin treatment due to their high therapeutic efficacy in CKD patients as shown in the table 6 respectively.

Statin therapy may benefit CKD patients by improving renal function and reduced proteinuria [23].The PLANET I study showed that 40 mg rosuvastatin decreased the excretion of urinary protein, close to baseline, in patients with diabetes and proteinuria but the eGFR was significantly reduced from the baseline [24]. Therefore Reno protective effect of statins depends upon the dose and type of statin used. High-dose statin therapy improve the decrease in eGFR in CKD patients (eGFR <60 mL/min/1.73 m2) [25]. In this study atorvastatin was used with different doses for reducing proteinuria in CKD patients. Before treatment, the proteinuria level was found to be very high in CKD patients range between 0.5-3.5 gram protein/gram creatinine with mean 1.5± 0.83 while a significant reduction was observed in patients with atorvastatin treatment(Table 7). In group II (40mg dose) the proteinuria level was significantly reduced, as compared to group I, with less adverse effect. The patients with 60 mg atorvastatin (group III) treatment, was more significantly reduced proteinuria as compared to group I & II but having more adverse effect. Therefore, 40mg atorvastatin is a optimized dose for proteinuria in CKD patients.

Conclusion

The current results suggested that atorvastatin treatment is safe and reduces the risk of major cardiovascular events in patients with chronic kidney disease. These agents may have antiproteinuric effects in chronic kidney disease patients. Different doses of atorvastatin reduce the risk of CKD. High dose of atorvastatin reduces proteinuria significantly but due to adverse effect high dose prove unsuccessful. There are also additional benefits appear to occur by using 40mg of atorvastatin as compared to those patients whose treated with standard CKD management. In conclusion our results suggested that atorvastatin may have a dose-related effect on kidney function as only high-intensity atorvastatin significantly improved renal function assessed by estimated GFR and our results also added evidence that the use of 40mg of atorvastatin in CKD patients may delay progression of kidney disease. From the current study it was concluded that use of 40mg atorvastatin daily for three months is an optimized dose for patients with CKD by preventing progression end-stage renal disease.

Recommendations and Limitations of the current study

There are certain limitations of the current study which should be considered. The current study enrolled a small sample size from a single district of Pakistan; therefore large randomized trial should be conducted among different districts of Pakistan to confirm these finding. Second, other confounding factors such as type 2 diabetes and hypertension and change of metabolic parameters should also be considered.

As due to adverse side effect of atorvastatin in dialysis and renal transplant recipients and risk of myopathy, it is highly recommended, that the patients of diabetes mellitus and renal impairment should be monitored carefully. In our current study, no severe adverse effects such as persistent elevations in liver function enzymes and creatine values were observed in those patients whose using 40mg of atorvastatin. But still, It is also an important recommendation to keep in mind that the liver function enzymes and creatinine kinase levels must be monitored and guidelines should be strictly followed. The clinical significance of the results requires further studies for confirmation.

Competing Interest

All the authors declared that they have no competing interest.

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