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Original Article

Assessment of Action of Statins in End Stage Renal Disease

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ABSTRACT

Background and Aim: Chronic kidney disease (CKD) is one among the highest cause of morbidity globally. Statins are the top list of drugs used for them. It has been shown that the action of statins in severe CKD is paradoxical because lipid management cannot increase their survival. **Methods:** Sixteen CKD patients on dialysis for not less than 6 months who were receiving low dose of atorvastatin were recruited into the study. Blood investigations were performed and their results were compared with another group of non-user of lipid lowering agents. **Results:** Lipid profile, uric acid, calcium, phosphorous, parathyroid hormone, Vitamin D increased but these changes were significant in uric acid and Vitamin D level in the dialysis patients who receive low dose atorvastatin when compared to non-users of atorvastatin. **Conclusion:** Our results showed that atorvastatin in low dose can increase serum vitamin D and serum uric acid in ESRD patients. This side effect can be the herald of accelerated cardiovascular disease and metabolic bone disease. In contrary to popular belief, statins effect on CKD patients is deleterious by increase serum uric acid in an unknown mechanism.

Key words: Chronic kidney disease, Atorvastatin, End stage renal disease, Cardiovascular disease, Lipid profile.

INTRODUCTION

Chronic kidney disease (CKD) is one among the highest cause of morbidity globally. Statins are considered the best among the most commonly prescribed drugs for patients with CKD, but effectiveness of statins decreases significantly with the progression of CKD as end stage renal disease (ESRD) and increases mortality rate by promoting vascular calcification.[1] It is because serum triglyceride (TG) to high density lipoprotein cholesterol (HDL-C) ratio is elevated in patients with ESRD which increases cardiovascular (CV) mortality.[2]

For the occurrence of vascular calcification, one independent and important factor is uric acid which is also the main reason for cardiovascular fatal events. Unfortunately, studies done to reveal the role of uric acid in cardiovascular disease assessed the role of many drugs other than statins in coronary calcification and studies about statins' side effects mostly done in non-CKD patients. Few studies reported contradictory results about changes in uric acid levels following statins intake in cases with normal renal function.[1,3] The role of hyperuricemia in some morbidities such as hyperlipidemia, renal failure, diabetes and increasing age is well known, as uric acid is an independent factor for atherosclerosis by increasing platelet adhesiveness and increased thrombogenesis.

In the statins group of drugs, atorvastatin can reduce serum uric acid in normal renal function cases up to 12.5% by decreasing tubular reabsorption mechanism and this action of decreasing the serum uric acid level is not related to lipid-lowering effect of atorvastatin and such beneficiary effect decreases with renal dysfunction.[4]

MATERIALS AND METHODS

This cross-sectional study was conducted to evaluate the paradoxical actions of statins in ESRD patients receiving dialysis. It was conducted after the approval of research monitoring committee and Ethics committee. Written informed consent was obtained from the participants of the study.

In the present study, we recruited 16 CKD patients who were on hemodialysis for a minimum period of 6 months who were receiving low dose atorvastatin as a management for dyslipidemia. Blood sample was collected from all the subjects for the biochemical and haematological investigations. And their results were compared with another group of non-user of lipid lowering agents.

Statistical Analysis of Data

For comparison of the results of haematological and biochemical investigations across the group, Mann Whitney U test was used. *P* value less than 0.05 was considered as statistically significant.

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RESULTS

There was no significant difference in the age of the subjects between two groups. Our findings show 60% of patients under dialysis use atorvastatin in low dose 20-40 mg per day for hyperlipidemia while over 70% of users had normal lipid level (LDL<100 mg/dl). Serum uric acid in atorvastatin users was higher compared to non-user group which is statistically significant (P=0.03). Though calcium, phosphorous, parathyroid hormone, were increased in dialysis patients who were in statins compared to non-users of statins, it was not statistically significant. HbA_{1c} was lower in atorvastatin users group but it was not significant. Serum 25-hydroxy Vitamin D in the atorvastatin treated group was significantly higher compared to non-users of statins, despite all cases received a maintenance dose of calcitriol therapy as a part of management for secondary hyperparathyroidism. And statins users had also a higher level of serum parathyroid hormone (PTH) despite their higher serum Vitamin D level (Table 1).

DISCUSSION

Statins therapy may be harmful by promoting vascular calcification in patients with ESRD by changing serum uric acid level.[1,3] The effect of stains on uric acid in non-CKD patients show atorvastatin (but not simvastatin) significantly lowered serum uric acid levels.[4] Derosa G, *et al*. showed serum uric acid significantly decreases with atorvastatin and simvastatin, but not with pravastatin and rosuvastatin.[5] In another study, it has been shown that atorvastatin in high dose (80mg/day) instead of moderate dose (40mg/day) can reduce serum uric acid independent of patients' serum lipid profile.[6] On contrary, one study showed that blood uric acid level increased following the use of statins.[7]

Table 1: Comparison of laboratory tests between statin users and non-users.

	Low dose Atorvastatin (20-40mg)	No statins user	P
Age	58±12	58±8	0.8
Triglyceride	107±30	92±36	0.3
Cholesterol	143±35	125±26	0.3
HDL	38±11	35±6	0.5
LDL	81±31	68±20	0.4
AST	16±6	16±7	0.9
ALT	15±9	16±5	0.8
ALP	305±178	186±56	0.1
Uric acid	7.7±1.9	5.7±1.1	0.03*
Ca	8.3±0.6	7.6±0.9	0.1
Phosphor	5.2±1.8	4.9±1.7	0.7
Ca ×P	42±14	37±13	0.5
PTH	464±296	157±90	0.01
Serum Vitamin D	31±11	19±8	0.03*

*P value less than 0.05 was considered statistically significant.

Statins have close metabolic relations with Vitamin D level and low serum Vitamin D (<20ng/ml) can be associated with statins intolerance and some statins like as rosuvastatin can increase serum 25-hydroxy vitamin D level by undefined mechanisms.[8] In this study atorvastatin in low dose increased vitamin D level in patients under dialysis but such event is not preventive for severe secondary hyperparathyroidism (higher PTH level) that was seen in low-dose atorvastatin users, this phenomenon may be related to more associated metabolic and morbidity commonly seen in statins users and a strong association of hyperuricemia and hyperparathyroidism.[9]

A recent meta-analysis of 13 randomized controlled trials show in patients with CKD under statins therapy, major cardiovascular events occurred in 13% of stage 3, 10% of stage 4 and 22% of the stage 5 CKD groups, indicate the risk of cardiovascular events grows with the advanced stages of CKD. Our study presented that 10 out of 16 cases under dialysis use statins mainly as a cardioprotective in a routine way instead of lipid-lowering therapy because of patients' serum lipid profile in statins user showed there was not any case of hypertriglyceridemia (TG>200 mg/dl), hypercholesteremia (Cholesterol>200) and LDL level was lower than 70 mg/dl in 50% of cases that consider as the target level for starting dyslipidemia management (>190 mg/dl for non-diabetes and >70 mg/dl for diabetes).[10] Based on these paradoxical findings, authors suggest some underlying mechanisms such as the presence and burden of inflammation, oxidative stress, protein energy-wasting, renal replacement modality and genetic predisposition, but they ignored to evaluate statins as an influencing factor on serum uric acid, an independent factor for cardiovascular events.[11]

There is a bigoted belief to statins efficacy worldwide for CKD patients despite lacking criteria for dyslipidemia management. Atorvastatin in low doses can be associated with increase uric acid and Vitamin D level, hyperuricemia can be a promoter of vascular calcification, cardiovascular events and secondary hyperparathyroidism despite their higher Vitamin D level. Finding of such metabolic changes and cut off level of glomerular filtration rate for appear such paradoxical sign of statins in different types and doses are big questions that need to be replied in future in more comprehensive studies.

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I dedicate this article to Dr Mohammad Mosadegh, God bless his soul.

CONFLICT OF INTEREST

The author declares no Conflict of interest.

ABBREVIATIONS

CKD: Chronic Kidney Disease; **ESRD:** End Stage Renal Disease; **TG:** Triglyceride; **HDL-C:** High Density Lipoprotein Cholesterol; **LDL-C:** Low Density Lipoprotein Cholesterol **CV:** Cardiovascular; **PTH:** Parathyroid hormone.

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