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## Do Cholesterol Lowering Drugs Affect Electrolyte Balance In - Hypertensive Patients?

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### ABSTRACT

Coronary arterial disease is principal cause for death. Atherosclerotic changes due to dyslipidaemia have been the principal target for reducing the incidence of mortality due to coronary arterial diseases. Statins (HMG CoA reductase inhibitors) are the widely prescribed treatment for treating dyslipidaemia. However the effects of long term treatment with high dose statins may have several effects which were not desirable. A careful study of literature in the database did not reveal much on the effects of statin therapy on blood electrolyte levels. Hypertensive patients (n=60) who were on statin treatment (Atorvastatin n=29 & Rosuvastatin n=21) for at least one year at the time of recruitment were included. Their BP was recorded, fasting blood samples were collected for analysing Lipid profile and electrolyte (Na<sup>+</sup>, K<sup>+</sup>, Cl<sup>-</sup>). Mean of two samples (different days) were accepted and tabulated. Age matched controls (n=21), who were hypertensive patients but not on cholesterol lowering drugs, were also recruited. Blood pressure were high in both the groups. All parameters of Lipid profile were moderately elevated range in the Statin groups. The Potassium levels in the subjects was significantly elevated (p<0.05). The chloride level was also decreased (p<0.05) in the statin treated groups. We state that the electrolyte balance could be affected by the statins. Elevated Potassium levels observed indicated of marginal derangement of balance, could result from moderate decline in cortocosteroids. However our subjects were in low dosage, compared to standards in other countries. In higher dosage, the variations could be more evident. Therefore this aspect of statins must be kept in mind while treating hypertension.

**Keywords:** Atorvastatin, Rosuvastatin, Hypertension, Potassium, Sodium, Chloride

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## INTRODUCTION

Cholesterol is an integral molecule of all cells of the body. It also forms the principal molecule for formation of several hormones, so much important as to say, without cholesterol life is not possible. Hormones such as sex steroids, cortisol and aldosterone are formed from cholesterol. Death will occur in very short time if aldosterone is not produced. Sex steroid deficiency will cause impotency and infertility. However dyslipidaemia has been implicated in the causation of Coronary arterial disorders (CAD), which is one of the leading causes of death among elderly people. Among the risk factors such as diabetes mellitus, tobacco use, alcohol abuse and life style; dyslipidaemia also considered an important contributor to develop CAD. It was estimated that about 17.5 million people died of heart diseases in 2012, representing 31% of all deaths globally.[1] Recent statistics suggested higher mortality among age group of above 65 years from heart diseases.[2] HMG Co A reductase inhibitors commercially known as 'Statins', are being widely used in prevention and treatment of CAD. Since the Scandinavian Simvastatin survival study (S4) showed that use of statins in patients with coronary artery disease, reduced major cardiovascular events, mortality and dyslipidaemia, the interest in statin got a boost.[3] Series of studies subsequently reported usefulness of statins in coronary care and reducing LDL levels.[4,5] Further, the Heart Protection study in large group of subjects in high risk group, suggested lowering of major Cardiovascular events.[6] A series of such studies suggested that statins could be the breakthrough drug for preventing mortality due to cardiovascular disorders thus paving the way for wide use of statins. Apart from these primary effects, statins have been shown to have a number of pleiotropic actions, some desirable, but others not so. Some reports suggested an increase in cancer risk.[7] An increase of 25% more incidence of cancer in treatment group was reported by PROSPER study group also.[8] But in wider age groups, there was no significant increase in incidence of cancer.[9] Unfavourable effects on glucose metabolism were also reported.[10,11] Common adverse effect reported following use of statins is muscle weakness, myopathy and rhabdomyolysis.[12] Worldwide withdrawal of cerivastatin in 2001, following reports of fatal rhabdomyolysis, the long term effects of treatment cannot be wished away.[13,14] It has also been suggested that the statins are metabolised by the cytochrome oxidase system in liver, which also detoxify several other drugs, which therefore may cause hepatotoxicity when used with along other drugs in patients being treated with multiple drugs.[15] Adrenal gland is totally dependent on plasma cholesterol for the synthesis of steroid hormones. A decline in response to stimulation has been shown depletion of lipids, output adrenal hormones, after reduction in cholesterol levels following aggressive statin therapy.[16]

Recent guidelines on the use of statins by US FDA (<http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm293330.htm>) has clarified several issues regarding the use of statins to those who are prescribed with these drugs for prevention of CAD. In the article they mention the possibility of statins precipitating Type II diabetes mellitus and cognitive disorders. It also highlighted the muscle weakness as other complication of use of statins.(2016).[17] Fourteenth of March 2016, US FDA withdrew the permission to two of the cholesterol lowering drugs, citing that the benefit may not outweigh the side effects since cholesterol is no longer in the dietary watch list.

Plasma aldosterone has been reportedly reduced following treatment with Simvastatin.[18] Hypotension has been reported in some patients who received Simvastatin therapy.[19] A random search of Pubmed and several other internet and library sources, we could not find any recent article directly related to the electrolyte balance in the patients treated with Statins. All studies were done in early days of discovery of effect of statins.[16] However statins have been reportedly produced hyperkalemia[20] and rhabdomyolysis[21] in patients. Since wide use of statins has been observed in last few years in clinical practice in prevention and management of CAD, even to those who are not showing any cardiovascular disorders[22, 23] we carried out this work to relook into the effects of statins on plasma electrolyte parameters. In this study we proposed that since cholesterol is integral ingredient of steroid hormone biosynthesis, there could be some influence on the electrolyte levels of the patients, which could be useful for the clinicians at the time of deciding the treatment strategy. The results of this study in a small sample of patients are presented here.

## MATERIALS AND METHODS

Male and female subjects (n= 60) who were under treatment with statins for more than one year were recruited who have been either on Atorvastatin (n=29) or Rosuvastatin (n=21). Ten patients who were

short listed had to be omitted from the study because of incomplete data. Therefore data from 50 patients were included for statistical analysis. Their fasting blood samples were collected on two different days. Sodium, Potassium, Chloride levels were determined in the clinical laboratory (Ion Selective Electrode (ISE) indirect method; Roche-Hitachi Auto analyser). Mean values (meq  $\pm$  SD) were taken and compared with similar data from the age matched controls (n=20; 11 male & 10 females) who were hypertensive but not on statin therapy. On the first sample of blood, their lipid profile was also analysed. Systolic and diastolic blood pressure (mmHg) was meticulously recorded using a standard Sphygmomanometer and stethoscope and noted.

Clearance from Institutional ethical committee was obtained before the data collection started. An informed consent was obtained from each subject after explaining them the implications of this study. All the data will be kept in strict confidentiality. No more than 5 ml of blood was collected from each subject for tests.

Inclusion criteria:

1. Adult Subjects who are on statin therapy for at least for One year (Atorvastatin OR Rosuvastatin, 20 mg/day)
2. Consenting persons
3. Age matched hypertensive patients who are not taking any stains as controls

Exclusion Criteria:

1. Patients with any other endocrine disorders namely kidney diseases, thyroid, diabetes mellitus or any other disease which may affect electrolyte balance.
2. Patients who are on diuretic treatment
3. Pregnant women
4. Subjects below the age of 18

The Data obtained was be analysed by suitable statistical methods using SPSS 18 by applying Student's 't' test.

### RESULTS

The lipid profile of the patients were as follows: Cholesterol (210 $\pm$ 15 mg/dl); Triglycerides (160 $\pm$ 25 mg/dl); HDL (40 $\pm$ 6 mg/dl); LDL (140 $\pm$ 15); Cholesterol/HDL ratio (5.1). All these values are high normal and below high risk levels in whole of the group.

**Table 1: Blood pressure (mmHg), Na<sup>+</sup> level (meq/L), K<sup>+</sup> level (meq/L) & Cl<sup>-</sup> (meq/L) levels in the atorvastatin and Rosuvastatin treated patients. SBP = Systolic Blood Pressure; DBP + Diastolic Blood Pressure; Values Mean  $\pm$ SD. \* = p<0.05; \*\* = p<0.01**

1	2	3	4	5	6	7	8	9
Parameters	Control values	Whole group (n=50)	Females control (n=10)	Female (n=14)	Male Control (n=11)	Male (n=36)	Atorvastatin (n=29)	Rosuvastatin (n=21)
Age (Years)	51.57	53	51.4	59.36	48.15	58.08	59.52	55.55
SD	8.1	13.8	7.9	12.18	8.6	12.55	11.32	14.55
SBP(mmHg)	124	128.2*	126.5	130.9*	122.5	130.09*	128.76	132.25
SD	9.5	8.45	8.6	9.6	8.5	9.35	8.64	10.42
DBP(mmHg)	84.5	84.9	84.8	86.8*	83.7	86.44*	85.38	88.38
SD	4	7.3	4.2	8.4	6.7	8.12	7.45	9.16
Na (meq/L)	144.28	140	144.4	142.8	144.18	141.67	142.66	139.88
SD	4.78	5.38	5.3	4.75	4.51	4.92	4.29	5.54
K (meq/L)	4.22	4.59	4.4	4.67	4.06	4.66*	4.54*	4.88**
SD	0.46	0.36	0.55	0.42	0.29	0.41	0.38	0.38
Cl (meq/L)	104.85	96.89**	104.3	101.22	105.36	100.36**	100.45*	100.19*
SD	5.49	2.2	6.48	0.42	4.70	3.43	3.56	3.37

There was significantly elevated Blood pressure in the group selected for this study (Table 1) ( $p < 0.01$ ). Sodium levels did not show significant changes compared to control group. Marginal decrease in Sodium was observed in the Rosuvastatin group. However it was not statistically significant. All the groups showed the values within the normal clinical range. Potassium level was elevated in all groups above the higher range of normal in the Statin treated group. In Rosuvastatin treated group, it was significantly increased. But these values were within normal clinical range. Chloride levels were lower in treated groups compared to the control group. Elevated  $K^+$  levels and lowered Chloride levels in chronically treated patient are the prominent findings of this study.

## DISCUSSION

In the present study we investigated the blood electrolyte levels among the hypertensive patients who were being treated with cholesterol lowering medication for more than one year in Mangalore, South India. The use of Statins as a therapeutic and preventive strategy for the coronary arterial disease has gained momentum. It has also been suggested that any person above the age of 50 years may be prescribed statins.<sup>22,23</sup> But pleotropic effects of statins have been a matter of debate for some time.<sup>[24,25]</sup> Recent studies on effect of statins on electrolyte levels is scarce in literature. The group of subjects recruited here were all on the statin therapy for more than one year and they showed a high normal levels of lipid profile. The effect of long term treatment with Atorvastatin or Rosuvastatin on electrolyte balance has not been studied recently and the related literature about this appears very scant. Use of statins in treating hypercholesterolemia must be done with caution, as recent reports showed evidence of statin induced myalgia and its range of symptoms underlying statin-associated side-effects.<sup>[26]</sup> Further there are also articles suggesting that statin treatment could lead to Insulin resistant diabetes mellitus.<sup>[27,28]</sup>

In our study we found that the Sodium levels comparable to normal values among the study group. The potassium level was found to be high normal. Elevated potassium levels more obvious in Rosuvastatin treated group. Edelman & Witztum, in 1989 reported hyperkalemia during treatment using statins.<sup>[29]</sup> However the elevation in potassium was not high enough to produce the clinical symptoms of hyperkalemia. Chloride level was significantly depressed among women. Though the reduction was marginal, in all groups the chloride level was lower than the control levels. Several articles have mentioned the Adrenal cortical morphology changes after treatment with HMG CoA reductase inhibitors.<sup>[30,31]</sup> In this study, a marginal variation was observed in the electrolyte levels after treatment with Atorvastatin or Rosuvastatin. But the values obtained in our study were well within normal range. The number of subjects included in this study was small and were all moderately hypertensive. They were under treatment for more than one year, without major cardiovascular complications. Therefore 20 mg dose of statin treatment was administered to them. However in present study patients who were using a relatively lower dose of statins compared to the western countries are recruited. Therefore, the effect of higher doses on the electrolyte balance needs to be assessed and more details will emerge only after assessing the same in larger group of patients. More studies are required to accurately predict the effects on electrolyte balance and other pleotropic effects of statins in the light of increasing adverse reports appearing on this subject in the literature.

## CONCLUSION

Electrolyte levels namely, Sodium, potassium and chloride levels, observed in the study group were all in normal range in both Atorvastatin and Rosuvastatin treated hypertensive patients. This dosage (20 mg/day) did not show abnormally high values in any of the parameters. But in other countries much higher dosages are prescribed. The potassium level was found to be higher level within the normal range, in all the study group individuals. So also there were moderately lowered Chloride levels. Therefore broader studies with different dosages are required to investigate if higher dosage and more aggressive treatment regimen for control of hyper triglyceridemia will lead to any changes in the electrolyte balance.

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