Effects of Statins on the Serum Uric acid of Dyslipidemic Patients in the University of Port-Harcourt Teaching Hospital.

Egboh C. Stella-Maris[1], Iyeopu M. Siminialayi[2]

[1]Federal Medical Centre, Yenegoa
[2]University of Port-Harcourt.

Corresponding Author:
Egboh C. Stella-maris
E-mail: chinmastella@yahoo.com

Abstract

Introduction: *Uric acid, which is an end product of purine metabolism is associated with cardiovascular risk via its up regulation of inflammatory markers.*

Objectives: *To determine the effects of different statins on the serum uric acid level of dyslipidemic patients in the University of Port-Harcourt Teaching Hospital, as well as correlate the doses of the selected statins with these effects.*

Method: *This was a cohort study carried out over a period of 9 months from June 2017 to February 2018, in the University of Port-Harcourt Teaching Hospital. Dyslipidemic subjects who met the study criteria, had their baseline serum uric acid assayed and repeated at 3months.*

Results: *Three hundred and sixty six subjects were recruited, but forty-six were lost to follow-up. The subjects used for final analysis were 160 test subjects placed on statins and 160 control subjects who were statin- free. The mean age± SD of the test subjects was 57.02±12.45, while that of the control subjects was 51.86±13.27. Statins had a significant effect on the reduction of serum uric acid, although there was no significant correlation between the doses of statins used and the uric acid levels.*

Conclusions: *Statins were found to have hypouricemic effects, although there was no significant correlation between the dosages of statins and their effects on serum uric acid.*

Keywords: Uric acid, statins, Dyslipidemia, Port-Harcourt.

Introduction

Hyperuricemia is a health problem in industrialized nations with increasing prevalence world-wide. It has been associated with dyslipidemia and cardiovascular mortality.[1] In the United States, Rodriguez *et al*[2] *reported that* about 53% of adult population have dyslipidemia, predominantly hypertriglyceridemia (30%). In developing countries, the majority of the cardiovascular death is among the young adults and middle age group[3] and in the future, it will impact negatively on the economic growth and development as they belong to the working class. Uric acid has been found to have pro-inflammatory activity, which it exerts by the induction of nicotinamide adenine diphosphate oxidase(NADP-oxidase) in cultured adipocytes, thereby up-regulating C-reactive protein, a marker of inflammation in endothelium of the vascular smooth muscles.[4] Statins which are analogues of 3-hydroxy-3-methylglutaryl CoA (HMG CoA) and inhibitors of the rate limiting step of cholesterol synthesis have been reported to have other effects unrelated to its

cholesterol lowering activity,[5,6] of which hypouricemic effect is often associated. It is therefore necessary to determine if statins have effects on the reduction of uric acid level of dyslipidemic patients to encourage its use in the reduction of cardiovascular risk.

The aim of the study is therefore to determine the effects of statins on the serum uric acid of dyslipidemic patients in the University of Port-Harcourt Teaching Hospital and to also correlate the doses of different statins with these effects.

Materials and Methods

The study was carried out in the University of Port-Harcourt Teaching Hospital (UPTH), Port-Harcourt, a tertiary hospital in Port-Harcourt, Rivers State. The test subjects were diabetic, hypertensive and stroke patients who were about to be commenced on statins, presenting with dyslipidemia, defined as total cholesterol ≥ 5.17 mmol/l (200mg/dl), low density lipoprotein cholesterol (LDL-C) ≥ 3.36 mmol/l (130 mg/dl), high density lipoprotein cholesterol (HDL-C) ≤ 1.03 mmol/l (40mg/dl) for males, ≤1.3 mmol/l (50mg/dl) for females and Serum triglycerides(TG) ≥ 1.7 mmmol/l (150mg/dl) using ATP III criteria.[7] Subjects who had evidence of an inflammatory disorder or on anti-inflammatory drug were excluded. Dyslipidemic patients with similar illness as the case subjects who have given informed written consent, but are to be on life style modification were recruited as control subjects. Ethical approval was obtained from the Research Ethics Committee of the University of Port Harcourt Teaching Hospital and University of Port-Harcourt.

Subjects were recruited into the study using a systematic sampling technique. After adjusting for 10% attrition, 366 subjects were recruited, but 46 were lost to follow-up. 160 test and 160 control subjects were used for the final analysis. It was a cohort study carried out over a period of 9 months from June 2017 to February 2018. Patients who met the study criteria were recruited and followed up for 3 months. Patients were counseled to fast for at least 8 hours prior to the determination of fasting lipid profile. Patients had fasting lipid profile and serum uric acid done at baseline and repeated 3 months later. Total-cholesterol was measured using the enzymatic method (cholesterol oxidase method), which the principle is based on the hydrolysis of cholesteryl esters and oxidation of the 3-OH group of cholesterol. The very low density lipoproteins and low density lipoproteins were precipitated with a polyanionic reagent and the HDL-cholesterol was then determined with colorimetric enzymatic method at an absorbance of 510nm.[8] Triglycerides were measured enzymatically in serum using a series of coupled reactions in which triglyceride was hydrolyzed to produce glycerol. Glycerol was then oxidized using glycerol oxidase, and H_2O_2, which was measured at an absorbance of 546nm.[9] LDL-c values was calculated using the Friedewald equation. LDL-c = TC – (HDL-c + TG /2.2). Uricase method was used for uric acid estimation, whereby uric acid is transformed by uricase to hydrogen peroxide which reacts with 4-aminoantipyridine in the presence of peroxidase to produce a colored complex which is directly proportional to the uric acid levels in the sample.[10]

Statistical Package for Social Sciences 22 (SPSS-22) was used for data analysis. Results were presented as mean±standard deviation for continuous variables. Continuous variables were compared with the students T-test, while proportions or categorical parameters were compared with chi-square test. A p value of less than 0.05 was considered statistically significant.

Results.

Table 1: Socio-demographic characteristics of the study population.

Socio-demographics	Test Group N=160(%)	Control Group N=160(%)	Total N=320(%)
Age(years): group			
21-30	0(0.00)	24(15.00)	24(7.50)
31-40	22(13.75)	22(13.75)	44(13.75)
41-50	17(10.63)	16(10.00)	33(10.31)
51-60	58(36.25)	42(26.25)	100(31.25)
61-70	43(26.88)	56(35.00)	99(30.94)
>70	20(12.50)	0(0.00)	20(6.25)
Mean ± SD	57.02 ±12.45	51.86±13.27	-
Sex:			
Female	98(61.25)	94(58.75)	192(60.00)
Male	62(38.75)	66(41.25)	128(40.00)

The mean age± SD of the test subjects was 57.02±12.45 and that of the control was 51.86±13.27. Among the test subjects, 61.25% were females while 38.75% were males, however, 58.75% of the recruited control subjects were females compared to 41.25% who were males.

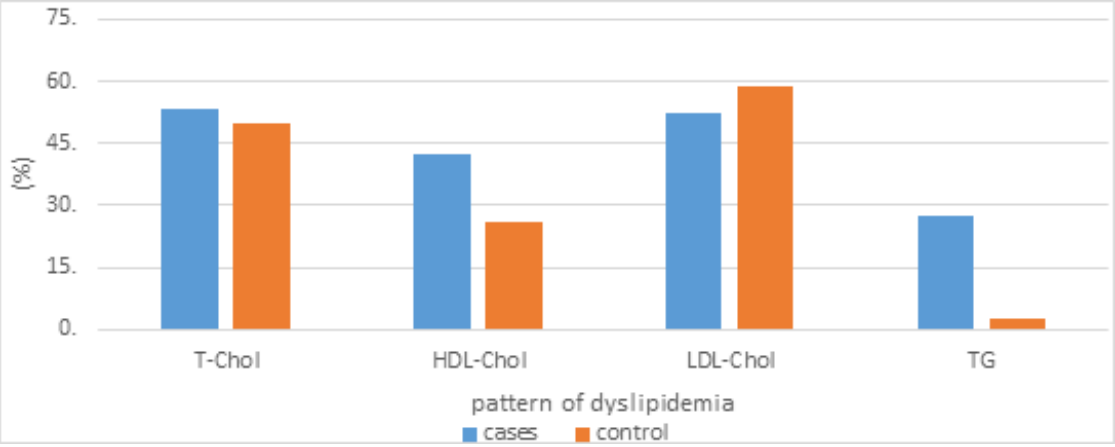

Figure 1: Pattern of dyslipidemia among the test subjects and control

Among the test subjects, the commonest form of dyslipidemia was high T-cholesterol reported in 53.1% of the recruited subjects, while hypertriglyceridemia (27.5%) was the least pattern of dyslipidemia. However, high LDL-Cholesterol was the most prevalent pattern of dyslipidemia seen in 58.7% of the control subjects, while low-HDL cholesterol found in 26.2%, represented the least type of dyslipidemia among the control subjects.

Table 2 : Comparison of the mean serum uric acid of the test and control subjects at the start and after 3 months of statins therapy.

Inflammatory marker	Baseline(mean±SD)	3months (mean±SD)	Mean ±SD (decrease-) or (increase+)	Paired t test	p-value
Uric acid(umol/l)					
Test subjects					
Control	297.38±69.16	284.91±86.28	-12.47±34.50	4.57	0.001*
Independent t-test(p-value)	320.31±63.08	317.74±65.21	-2.5±32.65	0.99	0.32
	1.55(0.123)	2.20(0.03)*	3.11(0.002)*		

**Statistically significant (p<0.05)*

There was a significant reduction of the mean serum uric acid of the subjects on statins by 12.47±34.5 after 3months of therapy as well as a significant difference between the mean serum uric acid of the test and control subjects after 3 months (p=0.002)

Table 3: The effects of different statins on serum uric acid

Type of statin	Baseline Uric acid	Uric acid at 3months	Mean decrease	p-value
Artovastatin	274.74±63.08	254.88±60.79	19.86±32.65	0.0001*
Rosuvastatin	305.70±68.00	295±67.78	9.76±23.53	0.006*

**Statistically significant (p<0.05)*

There was a significant reduction of the mean serum uric acid of patients on artovastatin and rosuvastatin by 19.86±32.65 and 9.76±9.76 respectively. The mean decrease among patients on artovastatin was found to be more than rosuvastatin.

Table 4: Comparison of the effects of the various doses of statins on the serum uric acid of the test subjects after 3months of therapy

Statins	n(% frequency)	Uric acid(umol/l) start	Uric acid(umol/l) 3 months	Mean decrease(-) or increase(+)	Paired t test
Rosuvastatin	117(73.13)				
5mg	5(4.3)	280.00±100.00	274.20±99.04	-5.80±10.20	1.27
10mg	97(82.9)	302.95±69.00	290.81±67.77	-12.13±39.02	3.06
20mg	15(12.8)	332.07±42.25	336.33±40.85	+4.27±30.47	0.54
Artovastatin	43(26.88)				
10mg	22(51.2)	266.64±72.60	250.77±62.93	-15.86±30.75	2.41
20mg	16(37.2)	265.50±43.75	243.38±41.84	-22.13±11.14	7.94
40mg	5(11.6)	340.00±87.38	309.80±84.03	-30.20±11.88	5.68

**Statistically significant (p<0.05).*

Among patients on rosuvastatin, 5mg and 10mg, serum uric acid was reduced by 5.80±10.20 and 12.13±39.02 respectively, while 20mg increased the mean serum uric acid by 4.27±30.47. However, 10mg, 20mg and 40mg of artovastatin reduced serum uric acid by 15.86±30.75, 22.13±11.14 and 30.20±11.88 respectively.

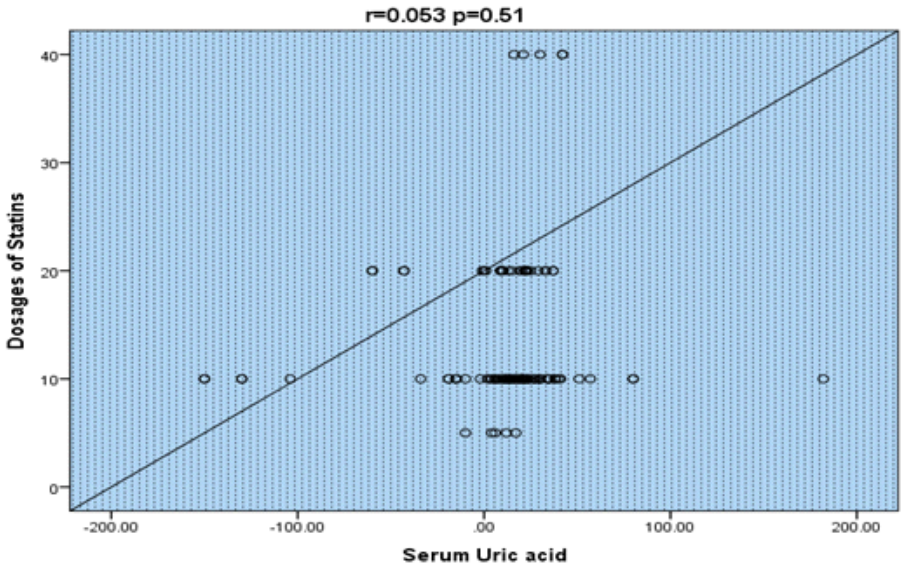

Figure 2: A scatter plot showing the Pearson correlational co-efficient between the doses of statins and the changes in the serum uric acid of the case subjects. There was no significant correlation between the doses of statins and their effects on serum uric acid.

Discussion

The mean serum uric acid of the subjects on statins was significantly reduced when compared to the statin-free subjects and the reduction in uric acid was more among patients on artovastatin when compared to rosuvastatin. This implies that statins have significant hypouricemic effect on patients with dyslipidemia. This finding was similar to a retrospective study by Ogata and his colleague[11] who reported a significant reduction of serum uric acid of dyslipidemic patients on artovastatin and rosuvastatin by 6.5% and 3.6% respectively after 6 months of therapy. This suggests that artovastatin may have a better hypouricemic effect than rosuvastatin. Additionally, Millionis et al[12] reported that 40mg of artovastatin had a significant hypouricemic effect after 3 months of therapy, while, there was no change in uric acid level with the same dose of simvastatin after the same duration of therapy.

On the contrary, Derosa et al[13] reported a significant reduction in serum uric acid level among patients on artovastatin and simvastatin therapy and this effect was not evident on patients who were on pitavastatin and rosuvastatin therapy. This suggests that this pleiotrophic effect of statin is linked to the individual drugs rather than the class of drug. Moreover, artovastatin has also been found to be a more potent statin than simvastatin because of its additional binding interactions.[14] In this study, there was no significant correlation between doses of statins used and serum uric acid, a possible explanation could be due to the short duration of the medication. Moreover, most patients were on moderate intensity statins.

Conclusion

Statins were found to significantly reduce the serum uric acid of dyslipidemic patients, although there was no significant dose dependent effect of statins on serum uric acid.

References

1. Jin M, Yang F, Yang I, Yin Y, Luo JJ, Wang H, et al. Uric acid, hyperuricemia and vascular diseases. Frontiers in bioscience: *a journal and virtual library*. 2012;**17**: 656-659
2. Rodriguez C.J, Daviglus M.L, Swett K, González H.M, Gallo L.C., Wassertheil-Smoller, S et al. Dyslipidemia patterns among Hispanics/Latinos of diverse background in the United States. *The American journal of medicine*. 2014;***127***:1186-1194
3. Mukherji S, Ramakrishnan TS. World Heart Day: May the force be with your HEART. Medical journal, *Armed Forces India*. 2016;**4**:313.
4. Lu W, Xu Y, Shao X, Gao F, Li Y, Hu J. Uric acid produces an inflammatory response through activation of NF-κB in the hypothalamus: implications for the pathogenesis of metabolic disorders. *Scientific reports*. 2015;**16***:*121-144.
5. Rohilla A, Rohilla S, Kumar A, Khan MU, Deep A. Pleiotropic effects of statins: A boulevard to cardioprotection. *Arabian Journal of Chemistry*. 2016 ;**9**:S21-7
6. Shuhaili MF, Samsudin IN, Stanslas J, Hasan S, Thambiah SC. Effects of different types of statins on lipid profile: a perspective on Asians. *International journal of endocrinology and metabolism.* 2017;**15**(2).
7. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001;**285**:2486-2487.
8. Vassault A, Grafmeyer D, De Graeve J, Cohen R, Beaudonnet A, Bienvenu J. Quality specifications and allowable limits for validation of methods used in clinical biochemistry. In *Annales de biologie Clinique*.1999;**57**:685-695.
9. Fossati P, Prencipe L. Serum triglycerides determined colorimetrically with an enzyme that produces hydrogen peroxide. *Clinical chemistry*, 1982;***28***: 2077-2080.
10. Zhao Y, Yang X, Lu W, Liao H, Liao F. Uricase based methods for determination of uric acid in serum. *Microchimica Acta*. 2009;***164***: 1-6.
11. Ogata N, Fujimori S, Oka Y, Kaneko K. Effects of three strong statins (atorvastatin, pitavastatin, and rosuvastatin) on serum uric acid levels in dyslipidemic patients. *Nucleosides, nucleotides and nucleic acids*. 2010 ; ***29***: 321-324.
12. Milionis HJ, Kakafika AI, Tsouli SG, Athyros VG., Bairaktari ET, Seferiadis KI et al. Effects of statin treatment on uric acid homeostasis in patients with

primary hyperlipidemia. *American heart journal*. 2004;***148***:635-640.

13. Derosa G, Maffioli P, Reiner Ž, Simental-Mendía LE, Sahebkar A. Impact of statin therapy on plasma uric acid concentrations: a systematic review and meta-analysis. *Drugs*. 2016;**76**:947-56
14. Clark M., Finkel R., Rey J., Whalen K Lippincott's Illustrated Reviews: Pharmacology. *Lippincott Williams and Wilkins*, Baltimore. 2012; 5th Edition., pp 455-56