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THE PLEOTROPIC EFFECT OF STATIN THERAPY ON BLOOD PRESSURE IN DYSLIPIDEMIC PATIENTS IN UNIVERSITY OF PORTHARCOURT TEACHING HOSPITAL (UPTH)

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Abstract

Background: The rising incidence of People with cardiovascular disease (CVD's) in developing countries, stems from its growing ageing population, urbanization and westernization of their cultures and values. People with CVD's and at-risk benefit from early detection and management. Management includes counselling on life style modifications and the use of appropriate medication. Both have been shown to lead to an acceptable reduction in serum lipid level and a reduction in the incidence of atherosclerotic cardiovascular events. Statins are the most potent and most commonly prescribed hypolipidemic drugs worldwide, but are also reported to have pleiotropic effects, i.e. beneficial effects, other than their lipid lowering effects. This study aims to assess the pleotropic effects of statin therapy administered to dyslipidemic patient in UPTH on their blood pressure values.

Methods: This was a prospective cohort study carried out over a period of 9 months. 320 consecutives, consenting dyslipidemic subjects were recruited into the study. All subjects had a baseline fasting lipid profile and blood pressure measurement done. Test subjects had just commenced statins, while an equal number of age and sex matched control subjects were asked to make life style modifications (exercise and dietary) but were not exposed to statins. Both groups continued similar individualized drug therapies i.e. anti-hypertensive and oral hypoglycemic agents. They were all followed up for a period of 3 months, after which fasting lipid profile and blood pressure were re-assessed.

Results: This study's results indicated, a significant($p<0.05$) reduction in the levels of systolic blood pressure, and diastolic blood pressure, after 3 months of statin therapy in test cases, and amongst the control subjects asked to adopt exercise and make dietary modification for 3months. However, comparison of the absolute change in value of the mean for SBP and DBP, test cases relative to control cases revealed no statistically significant change ($p>0.05$) indicating statins do not show added control of systolic or diastolic blood pressure and so suggest no added clinical benefits after 3 months of therapy.

Conclusion: The results showed that statins in addition to their hypolipidemic actions in dyslipidemic patients in UPTH, do not have a significant effect ($p>0.05$) after 3 months of therapy on SBP and DBP level/control.

Keywords: hypolipidemic, dyslipidemic patients, systolic blood pressure, cardiovascular disease (CVD's).

Introduction

At the beginning of the 20th century, cardiovascular disease (CVD) was responsible for less than 10 percent of all deaths worldwide, but by 2001 that figure was 30 percent. About 80 percent of the global burden of CVD death occurs in low- and middle-income countries. Murray and Lopez (1996) predicted that CVD will be the leading cause of death and disability worldwide by 2020, mainly because it will increase in low- and middle-income countries. By 2001, CVD had become the leading cause of death in the developing world, as it has been in the developed world since the mid-1900s (Mathers et al., 2001). People with cardiovascular disease or who are at high risk of cardiovascular disease, (such as uncontrolled hypertension, uncontrolled diabetes, dyslipidaemia, tobacco use, unhealthy diet and obesity, physical inactivity and harmful use of alcohol) need early detection and management using counselling and medicines, as appropriate, to prevent increased morbidity and mortality (Chobanian et al., 2003). Statins are analogs of 3-Hydroxy-3-methylglutaryl co-enzyme A (HMG-COA) and inhibitors of the rate limiting step of cholesterol synthesis (HMG-COA reductase inhibitor). They are the most potent and most commonly prescribed hypolipidemic drugs worldwide (Clark, et al., 2012), but have been reported to also have pleiotropic effects, i.e. beneficial effects, other than their lipid lowering effects. They result from statin inhibition of isoprenoid metabolites, which are signalling protein that control cell shape, motility, differentiation, and proliferation. This role of statin is responsible for the non-cholesterol lowering effects referred to as the pleiotropic effects of statins. These effects include improvement of endothelial function, inhibition of vascular inflammation, reduction of oxidative stress, stabilization of atherosclerotic plaque and anti-cancer effects. This effects has not been evaluated in Nigerians and so this study sought to establish, if Nigerian adults on statin therapy for dyslipidaemia at the University of Port-Harcourt Teaching Hospital (UPTH) experience a significant lowering in their blood pressure, compared to an equal number of age and sex matched cohorts on similar individualized drug therapies, as in the test group (i.e. .oral hypoglycaemic and oral anti-hypertensive) managed by counselling, encouraging exercise and dietary modifications (not exposed to statins).

Materials and Methods

Description of study area:

The study was carried out in the University of Port-Harcourt Teaching Hospital (UPTH), Port-Harcourt, a main referral centre for Rivers State.

Study population: The case group included all subjects presenting to the medical out-patient clinic, general out-patient department or medical wards with dyslipidaemia and were just being commenced on statins. An equal number of age and sex matched dyslipidemic patients who had similar illnesses, and were on similar drug regimens, but had not being commenced on statins but were counselled to adopt lifestyle changes include diet and exercise modifications were recruited as control subjects.

Inclusion criteria for test subjects:

Patients, aged 18years and above. Patients who gave informed written consent. Dyslipidemic diabetic, hypertensive patients, chronic kidney disease, stroke, nephrotic syndrome, obese and sickle cell disease patients, about to be commenced on statins were eligible.

Exclusion criteria for test subjects:

Patients who did not given an informed written consent. Evidence of sepsis, autoimmune disorders or other inflammatory conditions. Patients who are also on anti-inflammatory drugs like corticosteroids or Non-steroidal anti-inflammatory drugs. Pregnant women and breast-feeding mothers. Patients with active liver disease were excluded.

Inclusion criteria for control subjects:

Patients who gave informed written consent. Age and sex matched patients on similar individualized drug therapies and Patients who had not been commenced on statins were included.

Exclusion criteria for control subjects:

Unwillingness to give an informed, written consent. Patients who were on statins, pregnant women and breastfeeding mothers were excluded

Ethical consideration / Consent Process:

Consent was sort and given by the Ethics Committee of the University of Port-Harcourt, Graduate School, and the Research Ethics Committee of the University of Port Harcourt Teaching Hospital to recruit patients and obtain data in line with their stipulations. Consent was also obtained from participants, after details of the investigations were explained and, they were assured they could withdraw at any time during the study and this would not deny them of medical attention/benefits in this hospital. The cost of the investigations done in this study was borne by the investigator.

Sampling technique:

Consecutive sampling method used was most practical in this hospital-based study. All consecutive consenting subjects who met the study criteria were recruited, either into the test group or the control group.

Sample size determination:

Sample size determination was done using the Kish method. 320, age and sex matched respondents were equally recruited into both groups, i.e. 160 participants in each group.

Study design:

The study was a prospective cohort study carried out over a period of 9 months from June 2017 to February 2018, where dyslipidemic patients who had just been placed on statins and met other study criteria, were recruited consecutively as test subjects. They had baseline blood pressure (BP) measurements recorded, and a fasting lipid profile (FLP) assay. Age and sex matched patients who were dyslipidemic but had not been commenced on statins were recruited as control subjects and both sets of subjects were followed-up and the above-mentioned test repeated at 3 months.

Statistical analysis:

Data was analysed using a commercially available statistical data management software statistical package for social sciences 20 (SPSS-20). Results are presented as mean ± standard deviation for continuous variables. Charts and tables were used to illustrate results where appropriate. Continuous variables were compared with the students T-test, while proportions or categorical parameters were compared with chi-square test. The independent t-test was used to compare absolute change values for the variables between test cases and control subjects. Pearson's correlation test was used to draw associations/correlations, p-value of less than 0.05 was considered statistically significant.

Results

This was a prospective cohort study involving 320 subjects, 160 test subjects and 160 control subjects. Respondents who met the study criteria were recruited and followed up over a 3 months period.

Pattern of medical illnesses in this study:

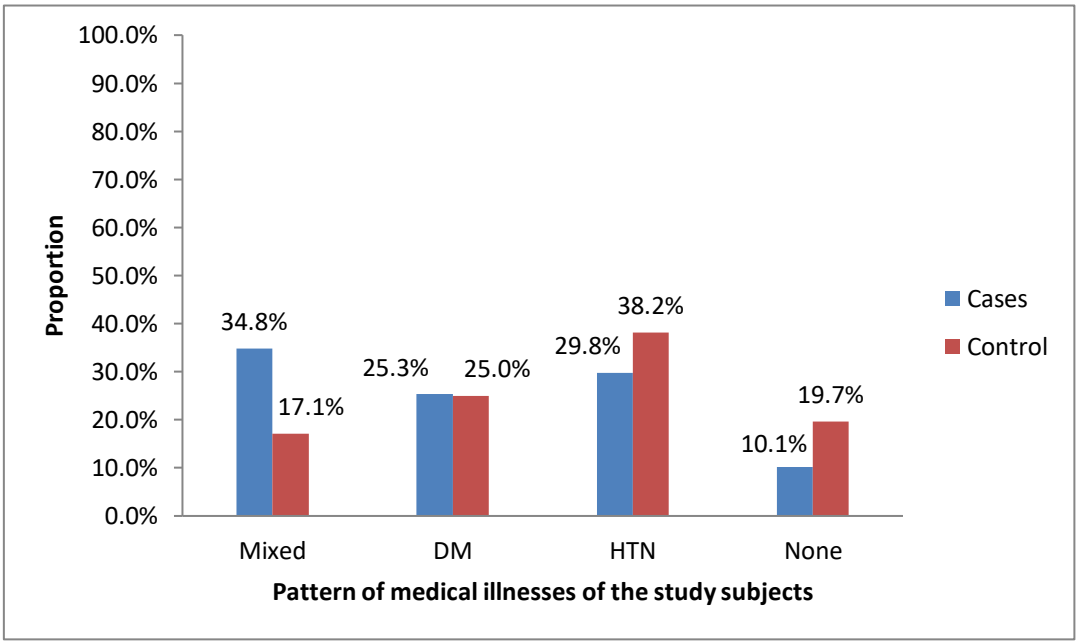

Figure 1.0: A bar chart showing Pattern of medical illnesses of the study subjects

The study recruited, higher proportions of hypertensive patients in the control group compared to the cases,38.2% (61) vs 29.8% (48). Respondents with diabetes mellitis, DM [25.3%(41) test cases vs 25.0% (40)control cases] .Majority of the respondents had more than one illness ,mixed conditions ,diabetic-hypertensive patients,[34.8%(56) test cases vs 17.1%(27)control cases].None, represents chronic renal disease and other conditions associated with dyslipidaemia that met recruitment criteria (10.1%(15) test cases vs 19.7%(32) control cases)

Statin regimen and doses used in the test group

Table 1: Statin regimen and doses used in the test group

Type of statin	**Cases(n) Freq (%)**	**Total n Freq (%)**	X^2	**P**
Rosuvastatin				
5mg	5(4.3)	117(73.13)	68.45	0.001[x]
10mg	97(82.9)			
20mg	15(12.8)			
Atorvastatin				
10mg	22(51.2)	43(26.88)		
20mg	16(37.2)			
40mg	5(11.6)			
Mean dose±SD				
Rosuvastatin	11.06±3.59		5.91	0.001[x]
Atorvastatin	17.21±9.59			

There was a statistically significant higher number of prescriptions for rosuvastatin over atorvastatin (73.13% vs. 26.88%) (X2=68.45; p=0.001); although more significant mean dosages for atorvastatin over rosuvastatin were observed to be used (11.06 vs. 17.21) (t=5.91; p=0.001).

Association between doses of Statins and changes in FLP and BP level in the test cases using Pearson's correlational coefficient (r)

Table 2: Association between doses of Statins and changes in FLP and BP level in the test cases using Pearson's correlational coefficient (r)

Characteristics	**R**	**95% CI**	**p-value**
TC	0.065	-0.399, 0.966	0.414
LDL-C	0.034	-0.322, 0.664	0.494
SBP	0.023	-0.048, 0.065	0.776
DBP	-0.002	-0.109, 0.106	0.978

**Statistically significant (p<0.05)*

There is no statistically significant association observed between dosages of statin and 3-month value of TC, LDL-C, SBP, and DBP (p<0.05).

Table 3: Comparison of the mean FLP and BP values of the case group and control group at commencement of statin and 3 months later (Comparison of the absolute change in mean, case vs control)

Group	Baseline (Mean ± SD)	3 Months later (Mean ± SD)	Absolute Change (Mean ± SD) + (increase) -(decrease)	Paired t-test (p-value)
	TCHOL-1	**TCHOL-2**		
Cases	5.25 ± 1.94	4.36 ± 1.49	-0.9 (1.47)	10.87 (0.001) *
Control	5.24 ± 2.21	4.66 ± 1.45	-0.6 (1.39)	5.20 (0.001) *
Independent t-test (p-value)	***4.35 (0.962)***	***1.89 (0.06)***	***2.20 (0.03) ****	
	LDLCHOL-1	**LDLCHOL-2**		
Cases	3.40 ± 1.71	2.21 ± 1.83	-1.2 (1.85)	11.54 (0.001) *
Control	3.38 ± 1.72	2.73 ± 1.42	-0.7 (1.39)	5.90 (0.001) *
Independent t-test (p-value)	***0.1 (0.917)***	***2.69 (0.01) ****	***12.35 (0.001) ****	
	SBP-1	**SBP-2**		
Cases	131.33 ± 21.08	121.03 ± 17.48	-10.30 (11.76)	15.67 (0.001) *
Control	127.63 ± 21.73	118.30 ± 16.71	-9.32 (8.45)	13.19 (0.001) *
Independent t-test (p-value)	***1.59 (0.112)***	***1.41 (0.159)***	***0.76 (0.448)***	
	DBP-1	**DPB-2**		
Cases	79.28 ± 10.63	73.75 ± 8.15	-5.5 (11.01)	8.98 (0.001) *
Control	79.73 ± 11.21	73.83 ± 6.71	-5.9 (13.23)	5.64 (0.001) *
Independent t-test (p-value)	***0.37 (0.705)***	***0.10 (0.930)***	***0.52 (0.602)***	

Effects of the of statin therapy on the test group (systolic Blood pressure/ diastolic blood pressure): Baseline and 3 month later result interpretation of table 3

SBP: Systolic Blood Pressure

The results showed a baseline mean value of (131.33 ± 21.08) points and following statin administration for 3months, an assessment showed a value of (121.03 ± 17.48) points, indicating a statistically significant ($p<0.05$) 10.30-point decrease in its mean value (absolute change in mean value). For the control group, a mean baseline value of (127.63 ± 21.73) points was recorded, following exercise and dietary modifications for 3months, a value of (118.30 ± 16.71) points was recorded, indicating a statistically significant ($p<0.05$), 9.32-point decrease in the absolute mean value. Comparison of the absolute change in mean value, (10.30 test case vs. 9.32 control), revealed a statistically insignificant ($p >0.05$) difference.

DBP: Diastolic Blood Pressure

The results indicated a baseline mean value of 79.28 ± 10.63 for the test cases and following statin administration for 3 months, an assessment showed a value of 73.75 ± 8.15, indicating a statistically significant ($p<0.05$) 5.5-point decrease in the mean value at baseline versus 3-month follow-up. For the control group, a mean baseline value of 79.73 ± 11.21 was recorded, and following exercise and dietary modifications, a 3month assessment value of 73.83 ± 6.71 was recorded, indicating a statistically significant ($p<0.05$), 5.9-point decrease in mean value. Comparison of the absolute change in mean value, (5.5 test case vs. 5.9 control) revealed no statistically significant ($p>0.05$) change in the absolute mean value of the test cases which were exposed to statins.

Discussion

Statins have other beneficial actions besides their lipid lowering effect known as pleiotropic effects. How these effects, alter blood pressure level and control in the Nigerian dyslipidemic patients in University of Port-Harcourt teaching hospital, is what this study investigated. This study results indicated, a significant reduction in the levels of systolic blood pressure and diastolic blood pressure after 3 months of statin therapy in the test cases exposed to statins and also amongst the control group not exposed to statins. However, comparison of the absolute change in value of the mean for SBP and DBP, test cases versus control cases revealed no significant change indicating, statins do not show added control of SBP or DBP, and so, suggest no added clinical relevance at 3 months.

Effect on Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) in the Test Group

Baseline values relative to 3 month later recordings, for both groups showed a significant decrease in systolic and diastolic mean blood pressure. Comparison of the absolute change in mean of the test group to the control group indicated no statistically significant change. This suggestive, non-significant reduction in blood pressure at 3 months of statin administration, corroborates the results from a randomised double-blind placebo controlled statin trial which reports, statins lower both SBP and DBP relative to placebo, and that the effect extends to persons with "prehypertension," those with lower-normal BP, and persons not receiving BP-lowering medications, (Chobanian et al., 2003) and Golomb (2008). Chobanian et al, used low dose, simvastatin and pravastatin (< 40mg) and addressed persons without diabetes mellitus, known cardiovascular disease, or dyslipidaemia. The findings, therefore, were not extend to these high-risk groups. Subjects with hypertension, most in need of BP reduction, were not strongly represented, as in this study (test group 64.6% vs control group 55.3% hypertensive). Chobanian et al revealed a time course of BP changes after statin initiation and the effect of stopping statins on BP. were examined. BP reductions with statins were suggestive and not significant in his sample at 1 month of treatment but were manifest and significant at 6 months. At 2 months after statins were discontinued, the difference in BP between the statin and placebo groups had dissipated. This study saw respondents in the test group, exposed to statin therapy for 3 months only. Perhaps, this was the reason the study didn't produce a significant effect on the systolic and diastolic blood pressure. A more recent meta-analysis of randomized controlled statin trials, reporting effects on BP, with an aggregate sample size of 828 subjects, reported significant reduction in systolic BP only, (Strazzullo et al., 2007). This modest reduction in BP induced by statins, could contribute to a reduction in the incidence of stroke reported with statin administration, as stroke incidence, although inconsistently related to LDL-C, is strongly related to BP. (Sirol et al., 2001). Mechanisms by which statins may reduce BP include up-regulation and/or activation of endothelial nitric oxide synthase (a potent vasodilator) and improvements in endothelial function and flow-mediated vasodilation, (Järvisalo., et al., 1999).

Conclusion

The results showed that statins in addition to their hypolipidemic actions do not have a significant pleiotropic effect after 3 months of therapy on SBP and DBP level and control.

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