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THE PLEOTROPIC EFFECT OF STATIN THERAPY ON FASTING BLOOD SUGAR (FBS) LEVEL IN DYSLIPIDEMIC PATIENTS IN UNIVERSITY OF PORTHARCOURT TEACHING HOSPITAL (UPTH)

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Abstract

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 subjects in UPTH on their blood sugar level/control. 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 (FLP) and Fasting Blood Sugar (FBS). 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) and were not exposed to statins. Both groups continued similar individualized anti-hypertensive and oral hypoglycaemic medications. They were all followed up for a period of 3 months, after which fasting lipid profile and fasting blood sugar were re-assessed. The results showed a significant ($p<0.05$), 1.1-point decrease in the level of fasting blood sugar (FBS) as absolute change in mean value for the test cases at 3months from baseline and a significant ($p<0.05$), 0.76-point decrease in the level of FBS as absolute mean value for the control group 3months from baseline. Comparison of the values of absolute change in mean, test case relative to control cases revealed no statistically significant difference ($p >0.05$). This neither indicated better control of FBS level nor did it suggest an added clinical relevance 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 FBS level/control.

Keywords: Statin, Pleotropic, dyslipidemic, fasting blood sugar, Fasting lipid profile, individualized drug therapies, UPTH

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, 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 there, fasting blood sugar level 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 anti-hypertensive agents) managed by counselling, encouraging exercise and dietary life style 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 who had just being commenced on statins and gave consent. 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. (consent forms placed after refrences).

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 consenting dyslipidemic patients who had just been placed on statins and met other study criteria, were recruited consecutively as test subjects. They had a baseline fasting blood sugar (FBS) assay. Age and sex matched dyslipidemic patients who were on similar individualized drug therapies hypoglycemic and anti-hypertensive agents as their test cohorts but had not been commenced on statins were recruited as control subjects. They also had a baseline fasting blood sugar (FBS) assay. 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.

Declaration / Conflicts of Interest

There are no conflicts of interest associated with this manuscript and the editorial board is not responsible for the authenticity of the paper/article.

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.

Table 1: Comparison of the mean FLP and FBS 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) ****	
	FBS-1	**FBS-2**		
Cases	7.30 ± 4.59	6.18 ± 2.43	-1.1 (3.36)	5.94 (0.001) *
Control	6.30 ± 3.64	5.54 ± 1.70	-0.76 (3.04)	3.17 (0.002) *
Independent t-test (p-value)	***2.01 (0.003) ****	***2.45 (0.01) ****	***0.81 (0.421)***	***2.45 (0.01) ****

**Statistically significant (p<0.05)*

TCHOL¬ Total Cholesterol
LDLCHOL¬ Low Density Lipoprotein Cholesterol
FBS ¬ Fasting Blood Sugar
SD ¬ Standard Deviation

Result Interpretation of Table 1.
Effects of Statin Therapy on Fasting Blood Sugar Level of Both Groups: (Baseline and 3 Month Later)

FBS: FASTING BLOOD SUGAR
A baseline mean value of 7.30 ± 4.59 points was obtained for the test cases and following statin administration and an assessment 3months later, a value of 6.18 ± 2.43 points was recorded, indicating a statistically significant (p<0.05). 1.1-point decrease in mean value.
The control group had a mean baseline value of 6.30 ± 3.64 points, but, following exercise and dietary modifications for 3month, a value of 5.54 ± 1.70 points was recorded, indicating a statistically significant (p<0.05) 0.76-point decrease in mean value.
A statistically significant difference (p<0.05) in fasting blood sugar level between test cases and control group was noticed at 3month.

Comparison of the absolute change in value of the mean, (1.1 test case vs 0.76 control case) revealed no statistically significant (p>0.05) change in the test group which was exposed to statins.

Discussion

Reduction of Fasting Blood Sugar (FBS) in the Test Group

A significant reduction was seen comparing baseline to 3 month later values in both groups, more so, in the test group exposed to statins. This decrease, seen amongst test subject exposed to statins may be as a result of statins displacing oral hypoglycaemic drugs from plasma protein binding sites, thus potentiating their actions. This also may explain the weak negative linear association, comparing statin doses used to the 3months outcome for FBS level (r = -0.2, p< 0.05) which is like the results of a related Indian study in 2017 by Parida et al, which evidenced the effect of Atorvastatin on glycaemic status was dose

dependent. However, comparison of the absolute change in value of the mean of FBS level for test cases to that of control cases, revealed no statistical significance at 3 months and therefore suggests no added clinical relevance. This result also, corroborates the time course results of Parida et al., 2017 which reports, high dose of statin therapy showed significant increase in blood glucose parameters after 6 months of therapy whereas, low dose is associated with statistically significant increase in glycaemic parameters after 12 months of therapy. High dose statins (>80mg) are associated with increased occurrence of new onset type 2 diabetes mellitus. This occurs as statins cause hyperglycaemia by increasing calcium concentration in the islet cells leading to a reduction in insulin release (beta cell exhaustion) or by decreasing GLUT 4-mediated peripheral glucose uptake (Insulin unresponsiveness). Statin use is associated with a rise of FBS in patients with and without diabetes, (Sukhija et al., 2009).

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 FBS level and control.

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Abbreviations:	
CVD:	**Cardiovascular Diseases**
FLP:	**Fasting Lipid profile**
FBS:	**Fasting Blood Sugar**
HMG-CoA:	**3Hydroxy 3methyl ghitaryl Co-enzyme A**
LDL-CHOL:	**Low Density Lipoprotein Cholesterol**
SPSS-20:	**Statistical package for social sciences, version 20.**
TCHOL:	**Total Cholesterol**
UPTH:	**University of Port Harcourt Teaching Hospital.**
UPH:	**University of Port Harcourt**
WHO:	**World Health Organization?**