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Statins and its Effects on Lipids and Glycemic Status: A Quasi-Experimental Study

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ABSTRACT

***Objective*:** To measure changes in lipid and glucose parameters after initiating statin therapy.
***Study Design*:** Quasi-experimental study.
***Place and Duration of Study*:** Department of Pathology and Medicine, Naval Hospital, Islamabad Pakistan, from Nov 2018 to Oct 2020.
***Methodology*:** Thirty-nine male individuals participated in the study after a detailed explanation and consenting procedure. At the outset of the study, baseline testing of fasting plasma glucose and lipid parameters was done. Participants were then started with 10 mg of Atorvastatin/day for six weeks, with visits every two weeks for testing for lipids and glucose.
Results: The mean age of participants was 42.47+11.65 years. %Δ (change) in mean (X) from baseline to result of last reading at six weeks for various evaluated parameters were as: %ΔX Fasting plasma glucose = +91.45, %ΔX total cholesterol=-139.63, %ΔX fasting triglycerides=-1.04%ΔX LDLc= -150.49 and %ΔXHDLc= -105.25. For HDLC, 14/31 showed a rise in levels compared to 17/31, who demonstrated a downward trend after starting statin therapy, indicating a differential response among subjects taking statin therapy.
Conclusion: Mean glucose levels increased from baseline to six weeks, whereas the mean of all lipid indices (including HDLc) declined in subjects on statin therapy.

Keywords: HMG CoA reductase inhibitors, Statin, Triglycerides, Glycemic Status.

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INTRODUCTION

The history almost dates back to 50 years when Alfred Alberts and other colleagues working for Merck research laboratories discovered a product from a bacterium that could inhibit HMG CoA reductase(HMGCR).[1] Current data associating statins in patients with conventional medical wisdom with cardiovascular disease indicate the drug's effects on HMGCR inhibition usually elevate HDL-cholesterol (HDL-C) concentration.[2] The literature review suggests that statin effects on HDLc for cardiovascular disease risk protect both primary and secondary end-points.[3,4] Though statin advocators indicate increased HDL-C after starting therapy, evidence demonstrates variability in HDL-C response with certain statin types.[5]

In addition to variability in current data, regional and racial differences in genetic associations, as authors also believe, can affect statin response for elevating HDL-C in our population.[6,7] Furthermore, the literature review has also highlighted diabetogenic tendencies with statin use, especially among the South-Asian population.[8] In addition, the concept of "residual Risk" after initiating statin therapy stays even after optimal statin therapy with certain patient groups with associated co-morbid like diabetes mellitus, where low HDL-C associated with hypotriglyceridemia can be a contributing factor which may need pharmacological intervention.[9,10] We decided to study the effects of Atorvastatin 10 mg among male subjects and monitored them twice weekly for six weeks. Various end-points were monitored to address the above-highlighted controversies regarding the increase or decrease in lipid parameters glucose.

METHODOLOGY

The quasi-experimental study was conducted at the Department of Pathology and Medicine at Naval Hospital, Islamabad Pakistan, from November 2018 to October 2020 after formal approval from the Hospital Ethical Review Committee (PNS HAFEEZ letter dated 01-Jan-2018).

Inclusion Criteria: Male individuals who visited the hospital and were willing to participate were informed about the study requirements, including medication

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intake (Atorvastatin 10 mg) for six weeks with follow-up at two weekly intervals.

Exclusion Criteria: Patients who had diabetes, hypertension, ischemic heart disease, ages <18 years or >60 years or any other chronic or acute ailments, taking any routine medication or supplements were excluded.

All participants were explained regarding study requirements, including adherence to the Atorvastatin regimen, Following the regular dietary pattern and physical activity routine, information regarding side effects as available in drug pack insert, the importance of planned visits and use of data for onward publication with patient confidentiality, being addressed. Signing written consent was a mandatory step for participation. Those who initially consented verbally were requested to come to the Pathology Department in "exact medical fasting status". Based upon non-probability convenience sampling, only one case based upon first come, first volunteer was allowed entry into the study process on a given day. At the time of presentation, subjects were interviewed per formatted questionnaire, clinically examined for any acute or chronic ailment, and measured and measured vital signs, including blood pressure, height and weight, as per standard protocol. Ten ml of blood was collected in plain and Na-Fluoride bottles for lipid profile and fasting plasma glucose. After the laboratory visits, the patients were started with 10 mg of atorvastatin to be taken at night for the next six weeks till the completion of the study. Visits were allowed a relaxation based upon holidays of -2 days to +2 days or personal commitments. All the above samples were collected using the "exact medical fasting status" at each visit. Samples from all participants had their serum separated after appropriate labelling and were frozen till the completion of the study. Provided complete explanation to patients we lost multiple patients due to various reasons, including inconvenience to visit (n=54), non-adherence to timely sampling time points (n=9), muscle pains (n=17), loss of contact (n=9), and reasons not mentioned (n=32). We did have to exclude 2 cases of HDLc in the initial phase of the workup due to QC issues related to the kit. We used Selctra-ProM (Elitech Group, France) to measure glucose (GPO-PAP method), cholesterol by CHOD PAP, and triglycerides by GOD PAP method. Low-density lipoproteins (LDLc) and high-density lipoproteins (HDLc) were measured using detergent-based direct enzymatic method on random access clinical chemistry (Selectra ProM). The lab had a robust internal quality control program in terms of conformance to Westgard's rule and participation in the "National External QA program". All tests were run in duplicate, and the mean of two readings was taken as the true final value.

Data was entered into SPSS version 24 and MS Excel 2016 software. Mean±SD was calculated for continuous variables and for categorical variables, frequency and percentages were calculated. Group-wise differences from baseline to every two weeks till the end of six weeks were evaluated by one-way ANOVA analysis. Δ (change) in mean (X) from baseline to result of the last reading was also measured to see if the positive or negative drop was described for the analyzed parameters. Furthermore, we measured the total number of cases with percentages where HDL-C was increased over time and vice versa.

RESULTS

Individuals who participated appeared for 3-4 visits. The mean age of the participants was 42.47+1.65 years. %Δ (change) in mean (X) from baseline to result of last reading for various evaluated parameters were as: %ΔX Fasting plasma glucose = +91.45,%ΔX total cholesterol=-139.63,%ΔX fasting triglycerides=-1.04,%ΔX LDLc= -150.49 and %ΔXHDLc= -105.25. 14 out of 31 subjects showed a rise in HDL-C levels, while the other 17 demonstrated a downward trend after starting statin therapy, indicating a differential response among subjects taking statin therapy.Table-I to V show differences between FPG, TG, TC, HDL-C and LDL-C from baseline till the sixth week at two weekly intervals.

DISCUSSION

Our study highlighted that fasting glycemia increases after starting statin therapy. Literature on this subject indicates mixed trends. Statin therapy with atorvastatin in a minimal dosage, i.e., 10 mg/day, seems like alarming findings supporting the previous research relating hyperglycemia with statin strategy.[11] Wang et al. indicate the diabetogenic potential of statin therapy is minimal, i.e., 1/1000 and usually among susceptible patients with insulin resistance or impaired fasting glucose.[12] However, the literature suggests differences in the association among various statins with 10-20% of new-onset diabetes cases.[13,14] We believe post-statin hyperglycemia may be the byproduct of inhibiting HMG-CoA reductase

Table-I: One way ANOVA Results From Baseline to Final Testing Around Six Weeks for Fasting Plasma Glucose Monitored at 2 Weekly Intervals (n=39)

Parameters		Group-1 (n=38)	Group-2 (n=39)	Group-3 (n=35)	Group-4 (n=33)	*p*-value
Fasting Blood Glucose(mmol/L)		5.57±1.18	5.50±1.47	5.74±1.35	6.09±2.09	0.390
Inter-group Comparison (Post Hoc analysis) (Fasting Plasma Glucose in mmol/L)						
Group Comparison	Baseline to week-2	Baseline Vs. Week-4	Baseline Vs. Week-6	Week-2 Vs. Week-4	Week-2 Vs. Week-6	Week-4 Vs. Week-6
Fasting Blood Glucose (mmol/L)	*p*-value= 0.997	*p*-value= 0.971	*p*-value= 0.471	*p*-value= 0.917	*p*-value= 0.372	*p*-value= 0.774

Table-II: One way ANOVA Results from Baseline to Final Testing Around 6 Weeks for Total Cholesterol Monitored at 2 Weekly Intervals (n=39)

Parameters		Group-1 (n=38)	Group-2 (n=39)	Group-3 (n=35)	Group-4 (n=33)	*p*-value
Total cholesterol (mmol/L)		5.23±1.16	3.60±0.66	3.61±0.66	3.77±0.73	<0.001
Inter-Group Comparison (Post Hoc Analysis) Total Cholesterol in mmol/L)						
Group Comparison	Baseline to week-2	Baseline Vs. Week-4	Baseline Vs. Week-6	Week-2 Vs. Week-4	Week-2 Vs. Week-6	Week-4 Vs. Week-6
Total cholesterol (mmol/L)	*p*-value= <0.001	*p*-value= <0.001	*p*-value= <0.001	*p*-value= 1.00	*p*-value= 0.861	*p*-value= 0.861

Table-III: One way ANOVA results from baseline to Final Testing Around 6 weeks for Fasting Triglycerides monitored at 2 weekly intervals (n=39)

Parameters		Group-1 (n=39)	Group-2 (n=39)	Group-3 (n=35)	Group-4 (n=33)	*p*-value
Total cholesterol (mmol/L)		1.77±0.83	1.52±0.972	1.52±0.69	1.67±0.81	0.494
Inter-group comparison (Post Hoc analysis) (Fasting triglycerides in mmol/L)						
Group Comparison	Baseline to week-2	Baseline Vs. Week-4	Baseline Vs. Week-6	Week-2 Vs. Week-4	Week-2 Vs. Week-6	Week-4 Vs. Week-6
Fasting triglycerides (mmol/L)	*p*-value= 0.553	*p*-value= 0.590	*p*-value= 0.965	*p*-value= 1.00	*p*-value= 0.858	*p*-value= 0.878

Table-IV: One way ANOVA Results From Baseline to Final Testing Around 6 weeks for LDL-Cholesterol (LDLc) Monitored at 2 Weekly Intervals (n=39)

Parameters		Group-1 (n=39)	Group-2 (n=39)	Group-3 (n=35)	Group-4 (n=33)	*p*-value
LDL cholesterol (mmol/L)		3.032±0.96	1.95±0.584	1.975±0.54	2.039±0.49	<0.001
Inter-Group Comparison (Post Hoc analysis) LDL-Cholesterol in mmol/L)						
Group Comparison	Baseline to week-2	Baseline Vs. Week-4	Baseline Vs. Week-6	Week-2 Vs. Week-4	Week-2 Vs. Week-6	Week-4 Vs. Week-6
Fasting triglycerides (mmol/L)	*p*-value= <0.001	*p*-value= <0.001	*p*-value= <0.001	*p*-value= 0.998	*p*-value= 0.944	*p*-value= 0.980

Table-V: One way ANOVA Results from Baseline to Final Testing Around 6 Weeks for HDL-Cholesterol (HDLc) Monitored at 2 Weekly Intervals (n=39)

Parameters		Group-1 (n=39)	Group-2 (n=39)	Group-3 (n=35)	Group-4 (n=33)	*p*-value
HDL cholesterol (mmol/L)		3.032±0.96	1.95±0.584	1.975±0.54	2.039±0.49	0.690
Inter-group comparison (Post Hoc analysis) HDL-Cholesterol in mmol/L						
Group Comparison	Baseline to week-2	Baseline Vs. Week-4	Baseline Vs. Week-6	Week-2 Vs. Week-4	Week-2 Vs. Week-6	Week-4 Vs. Week-6
HDL-cholesterol (HDLc) (mmol/L)	*p*-value= 0.9551	*p*-value= 0.675	*p*-value= 0.812	*p*-value= 0.926	*p*-value= 0.978	*p*-value= 0.998

inhibitors shifting metabolic pathways towards gluconeogenic processes by inhibiting the mevalonate within the body and thus adding to insulin resistance. Impaired insulin secretion and compromised β cell function via enhanced intracellular cholesterol uptake due to inhibiting intracellular cholesterol synthesis by

statins has also been postulated.[15] Another aspect which has been highlighted by Laakso *et al*. is the pharmacological dose of statin, and statin use highlights higher diabetogenic tendencies among Asians.[16] In addition, we utilized atorvastatin, a lipophilic statin that has also shown higher hyperglycemic tendency than hydrophilic ones. Anyhow, statin diabetogenic tendency in the light of our local data and shared evidence must be taken cautiously to avoid drug-induced diabetes to avoid unnecessary diabetes medications.[17]

In contrast to glycemia, we observed all lipids and lipoprotein categories to have a modest but variable rate of decline after statin therapy. As per convention, total cholesterol and LDL demonstrated a higher reduction after statin initiation. Likewise, serum fasting triglyceride levels decreased over six weeks of statin therapy from baseline. While the effect on triglycerides is less still, there are clear re-commendations to manage hypertriglyceridemia.[18]

The most concerning finding from our study was the reduction in HDLc after initiation of statin therapy, which implies that the positive effect of cholesterol and LDLc reduction is diffused by lowering good HDLc. This finding does not concord with Bergheanu et al.'s results, which demonstrated a rise in HDLc after rosuvastatin and atorvastatin.[19] However, our data demonstrated an overall reduction in HDLc in more than 50% of subjects, which may be pertinent and raises some question marks for statin therapy. Recent data, however, supports our results. Ambrosy *et al*. demonstrated lower HDLc levels in 80/209 subjects after statin use who were also considered to have higher chances of major adverse cardiovascular events (MACE).[20] An interesting study identified that rs717620 SNP of ABCC2 was specifically associated with low HDLc response with post-simvastatin therapy.[21] In summary, low HDLc response after any statin therapy must be appreciated with concern for any incoming ASCVD or pharmacogenomics studies, where possible, must be attempted to elucidate the cause of low HDLc.

LIMITATIONS OF STUDY

We utilized atorvastatin in our study, and specified off-shoot studies addressing the effect of statins on lipids and glucose may be conducted. Atorvastatin impacts glycemic control in a dose-dependent manner, so the effects of different doses must be elucidated further. Multiple patients either refused to be included in the study or later dropped out due to non-compliance, so a community outreach study could have been a better option for conducting the study.

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CONCLUSION

Atorvastatin therapy over six weeks in male participants, apart from demonstrating a significant reduction in atherogenic lipid parameters, including TC and LDL-C, also showed worsening tendencies for HDL-C and glycemia. More multi-central trials incorporating other statin categories must follow this study.

Conflict of Interest: None.

Authors Contribution

Following authors have made substantial contributions to the manuscript as under:

SHK & RS: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

AH & MG: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

ZAQ & JH: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Endo A. The discovery and development of HMG-CoA reductase inhibitors. J Lipid Res 1992; 33(11): 1569-1582.
2. O'Keeffe AG, Nazareth I, Petersen I. Time trends in the prescription of statins for the primary prevention of cardiovascular disease in the United Kingdom: a cohort study using The Health Improvement Network primary care data. Clin Epidemiol 2016; 8: 123-132. https://doi.org/10.2147/CLEP.S104258
3. Cho KI, Sakuma I, Sohn IS, Hayashi T, Shimada K, Koh KK. Best Treatment Strategies with Statins to Maximize the Cardiometabolic Benefits. Circ J2018; 82(4): 937-943. https://doi.org/10.1253/circj.CJ-17-1445
4. Zhang Y, Liang M, Sun C, Qu G, Shi T, Min M, et al. Statin Use and Risk of Pancreatic Cancer: An Updated Meta-analysis of 26 Studies. Pancreas 2019; 48(2): 142-150. https://doi.org/10.1097/MPA.0000000000001226
5. McTaggart F, Jones P. Effects of statins on high-density lipoproteins: a potential contribution to cardiovascular benefit. Cardiovasc Drugs Ther 2008;22(4):321-338. https://doi.org/10.1007/s10557-008-6113-z
6. Puri R, Nissen SE, Shao M, Kataoka Y, Uno K, Kapadia SR, et al. The beneficial effects of raising high-density lipoprotein cholesterol depends upon achieved levels of low-density lipoprotein cholesterol during statin therapy: Implications for coronary atheroma progression and cardiovascular events. Eur J Prev Cardiol 2016; 23(5): 474-485.

https://doi.org/10.1177/2047487315572920
7. Bergheanu SC, Van Tol A, Dallinga-Thie GM, Liem A, Dunselman PH, Van der Bom JG, et al. Effect of rosuvastatin versus atorvastatin treatment on paraoxonase-1 activity in men with established cardiovascular disease and a low HDL-cholesterol. Curr Med Res Opin 2007; 23(9): 2235-2240. https://doi.org/10.1185/030079907X226104
8. Catapano AL. Pitavastatin and HDL: Effects on plasma levels and function(s). Atheroscler Suppl 2017; 27: e1-e9. https://doi.org/10.1016/j.atherosclerosissup.2017.05.001
9. Adams SP, Sekhon SS, Tsang M, Wright JM. Fluvastatin for lowering lipids. Cochrane Database Syst Rev 2018; 3(3): CD012282. https://doi.org/10.1002/14651858.CD012282.pub2
10. Sonal Sekhar M, Unnikrishnan MK. South-Asian population has a higher likelihood for diabetes risk for statins regardless of potency. Med Hypotheses 2015; 84(3): 283-284. https://doi.org/10.1016/j.mehy.2014.12.026
11. Woo HI, Kim SR, Huh W, Ko JW, Lee SY. Association of genetic variations with pharmacokinetics and lipid-lowering response to atorvastatin in healthy Korean subjects. Drug Des Devel Ther 2017; 11: 1135-1146. https://doi.org/10.2147/DDDT.S131487
12. Wang P. Statin dose in Asians: is pharmacogenetics relevant? Pharmacogenomics 2011; 12(11): 1605-1615. https://doi.org/10.2217/pgs.11.98
13. Reiner Z. Managing the residual cardiovascular disease risk associated with HDL-cholesterol and triglycerides in statin-treated patients: a clinical update. Nutr Metab Cardiovasc Dis 2013; 23(9): 799-807. https://doi.org/10.1016/j.numecd.2013.05.002
14. Mach F, Ray KK, Wiklund O, Corsini A, Catapano AL, Bruckert E, et al. European Atherosclerosis Society Consensus Panel. Adverse effects of statin therapy: perception vs. the evidence - focus on glucose homeostasis, cognitive, renal and hepatic function, haemorrhagic stroke and cataract. Eur Heart J 2018; 39(27): 2526-2539. https://doi.org/10.1093/eurheartj/ehy182
15. Carmena R, Betteridge DJ. Diabetogenic Action of Statins: Mechanisms. Curr Atheroscler Rep 2019; 21(6): 23. https://doi.org/10.1007/s11883-019-0780-z
16. Laakso M, Kuusisto J. Diabetes Secondary to Treatment with Statins. Curr Diab Rep 2017; 17(2):1 0. https://doi.org/10.1007/s11892-017-0837-8
17. Cederberg H, Stančáková A, Yaluri N, Modi S, Kuusisto J, Laakso M. Increased risk of diabetes with statin treatment is associated with impaired insulin sensitivity and insulin secretion: a 6 year follow-up study of the METSIM cohort. Diabetologia 2015; 58(5): 1109-1117. https://doi.org/10.1007/s00125-015-3528-5
18. Agouridis AP, Kostapanos MS, Elisaf MS. Statins and their increased risk of inducing diabetes. Expert Opin Drug Saf 2015; 14(12): 1835-1844. https://doi.org/10.1517/14740338.2015.1096343
19. Rochlani Y, Kattoor AJ, Pothineni NV, Palagiri RDR, Romeo F, Mehta JL. Balancing Primary Prevention and Statin-Induced Diabetes Mellitus Prevention. Am J Cardiol 2017; 120(7): 1122-1128. https://doi.org/10.1016/j.amjcard.2017.06.054
20. Ambrosy AP, Yang J, Sung SH, Allen AR, Fitzpatrick JK, Rana JS, et al. Triglyceride Levels and Residual Risk of Atherosclerotic Cardiovascular Disease Events and Death in Adults Receiving Statin Therapy for Primary or Secondary Prevention: Insights From the KP REACH Study. J Am Heart Assoc 2021; 10(20): e020377. https://doi.org/10.1161/JAHA.120.020377
21. Hirayama K, Ota T, Harada K, Shibata Y, Tatami Y, Harata S, et al. Impact of Paradoxical Decrease in High-density Lipoprotein Cholesterol Levels After Statin Therapy on Major Adverse Cardiovascular Events in Patients with Stable Angina Pectoris. Clin Ther 2017; 39(2): 279-287. https://doi.org/10.1016/j.clinthera.2016.12.006