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Research Article

DOSE- AND TIME-DEPENDENT EFFECTS OF STATINS ON GLYCEMIC STATUS AND THEIR ASSOCIATION WITH NEW ONSET DIABETES MELLITUS

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ABSTRACT

Objectives: To compare the dose- and time-dependent effects of various statins on the glycemic status and to find their association in the development of new-onset diabetes mellitus (NODM).

Methods: The study was conducted for a period of 2 months from July 2014 to August 2014. In this cross-sectional observational study, non-diabetic subjects, who were on statin therapy for more than 2 months were recruited. Participants having previous records of results of diagnostic tests for blood glucose levels (before starting statin therapy) such as random blood sugar (RBS), fasting blood sugar, and glycated hemoglobin (HbA1c) values within normal range were included in the study and that values were taken as baseline value. Then another measurement of the same tests repeated when they enrolled into the study.

Results and Discussion: Of 22 subjects, 3 subjects were on rosuvastatin and the remaining 19 were on atorvastatin. Among the 22 subjects, 17 had symptoms of hyperglycemia such as polyuria, polydipsia, polyphagia, etc. after starting treatment with statins. It has been found that treatment with statins increases the risk of new NODM (27%) and there was a significant rise in the mean red blue and green (RBG) levels after therapy. Furthermore, there was a statistically significant rise in HbA1c values as the doses were increased. The duration of treatment and the body mass index and the type of statin have not significantly influenced the HbA1c values.

Conclusion: The values of statins in cardiovascular disorders have been clearly established and accepted. Their benefit is undeniable; however, they need to be taken with caution and care. Physicians should be aware of this adverse drug reaction due to statin therapy and they should monitor the glycemic control status of the patients during their regular follow-up period.

Keywords: Drug-induced diabetes, Statins, New-onset diabetes mellitus.

INTRODUCTION

Statins play a vital role in the primary and secondary prevention of cardiovascular (CV) disease by inhibiting HMG Co-A reductase enzyme thereby lowering blood cholesterol levels [1]. Substantial evidence suggests that the beneficial effects of statins may not only be due to their cholesterol lowering effects, but also due to their improvement in endothelial dysfunction, increased nitric oxide bioavailability, antioxidant properties, inhibition of inflammatory responses, and stabilization of atherosclerotic plaques which are collectively known as pleiotropic effects [2]. In spite of the beneficial effects, it also has few well-known adverse effects such as myalgia, liver enzyme elevation, and muscle weakness [3]. Recently, US- Food and Drug Administration (USFDA) has proposed a new safety warning concerning the association between dose-dependent statin therapy and the greater risk of new-onset diabetes mellitus (NODM) especially in those individuals predisposed to development of diabetes (the obese, insulin resistant and older patients) based on the data of clinical trial meta-analysis and epidemiological data from the published literature. This warning regarding their effects on glycemic control was approved by USFDA in February 2012 [4].

There are many proposed mechanism regarding the statins and development of DM. One among them is the downregulation of pancreatic beta cells function and impaired insulin release as a result of statin suppression of the ubiquinone biosynthesis. Another hypothesis states that it may promote beta cell apoptosis by enhancing the synthesis of nitric oxide. Furthermore, it has been suggested that it may cause DM by affecting insulin sensitivity of tissues. The inhibition of HMG-CoA reductase itself has a suppressing effect on isoprenoid synthesis, which in turn results in decreased GLUT-4 expression. A further proposed mechanism is modulation of adiponectin levels. It has been shown that lipophilic and hydrophilic statins have different effects on adiponectin and insulin resistance. Pravastatin being hydrophilic increases the adiponectin levels and thus has a reduced risk of developing DM. [5]

Although statin therapy reduces CV risk [1], its relationship with the development of diabetes is controversial. Moreover, the USFDA warning for statin therapy is based on the meta-analysis conducted on the US, UK, Middle East and African population. Most trials incorporated into the meta-analysis do not have a standardized method of diagnosis of diabetes also. To address these gaps, we conducted this study to find out the prevalence of NODM and to evaluate the dose and time-dependent effect of statin therapy on the development of NODM in Indian sub-population.

METHODS

After getting approval from Institutional Human Ethical Committee, subjects were enrolled into the study. A written informed consent form with a detailed explanation about the study was issued to all the subjects, who fulfilled the inclusion and exclusion criteria. Then explanation was also given to the subjects in their own language. Those who were willing and signed the consent form were enrolled into the study. This is an observational, cross-sectional study involving subjects who were on statin treatment for a period of 2 months or more. The study was conducted for a period of 2 months from July 2014 to August 2014 by the Department of Pharmacology in collaboration with the Cardiology department in a tertiary health care setup. The subjects enrolled in the study were selected based on the following inclusion and exclusion criteria. The inclusion criteria were:

1. Patients of age ≥18 years who were on statin therapy for ≥ 2 months, with or without concomitant drugs.
2. Patients with baseline* fasting blood glucose (FBG) ≤ 100 mg/dl or random blood glucose levels ≤140 mg/dl or HbA1c < 5.7% prior to statin therapy.

Baseline*: Participants having previous records of results of diagnostic tests for glycemic control (before starting statin therapy) within normal range will only be included in the study, and that values were taken as a baseline value.

The exclusion criteria were:
1. Known Diabetic patients.
2. Women with a history of gestational DM.
3. Subjects with the parental history of DM

The following parameters were assessed by standard methods

Body mass index (BMI) calculated and interpreted as per Quetelet's index [6]. Fasting or Random blood glucose levels (mg/dl) were estimated using Glucose Oxidase-Peroxidase method. HbA1c levels (%) were estimated using automated analyzer based on mini column HPLC method. Then the entire data obtained were entered in Excel sheet for analysis. American diabetes association (ADA) 2013 criteria [7] were used to diagnose NODM. The data were also analyzed for causality relationship between the drug and the NODM using Naranjo's causality assessment scale [8].

Statistical analysis was done using NCSS software. Descriptive analysis was done for demographic characteristics like age, gender, etc. To compare the means of RBG before and after therapy was done using paired t test. Subgroup analysis was done to find the association between the type of statins and HbA1c values with the help of Pearson's chi-square analysis. Multiple linear regression analysis was performed to predict the control variable HbA1c with the dependent variables like BMI, duration of treatment and dosage of statins. A p=0.05 was considered statistically significant.

RESULTS

The study was done for a period of 2 months from July 2014 to August 2014. Of the 29 subjects screened for eligibility assessment only 22 subjects were recruited to the study because 7 subjects had poor compliance to the treatment. 15 (68%) were males and 7 (32%) were females. The mean age of the subjects was 54.45 (9.08). 3 subjects were on rosuvastatin therapy and the remaining 19 were on atorvastatin. Among the subjects on atorvastatin therapy, 7 were on a daily dose of 40mg, 2 were on 10 mg and 10 were on 20 mg dosage schedule. The average dose of atorvastatin and rosuvastatin were 24.73 (11.23) and 10, respectively. The mean duration of treatment was 6.72 (3.23) months.

Based on the Quetelet's index, the BMI was calculated for all the subjects and we found that 8 subjects were within normal range of BMI, 11 were grouped as overweight, 2 were underweight and 1 was in the obese group. Among the 22 subjects, 17 had symptoms of hyperglycemia such as polyuria, polydipsia, polyphagia, etc., after starting treatment with statins.

After statin therapy 8 patients (36.4%) had impaired HbA1c level and 6 (27.2%) were diagnosed as diabetic based on the ADA 2013 diagnostic criteria. Remaining 8 (36.4%) were normal. The prevalence of diabetes in our study group was 27%. The RBG values before and after statin therapy of all the subjects irrespective of the duration of treatment is given below in Fig. 1. Mean random blood sugar obtained before therapy was 96.72±5.1. Mean RBS after therapy irrespective of the duration of therapy was 112.63±31.1. Paired t-test was done to compare the means of RBS before and after statin therapy. It was found that t (21) = −2.547, p<0.01 and it showed that there was a statistically significant increase in random blood sugar values from 96.72±5.1mg/dl to 112.63±31.1 mg/dl (p<0.01) after treatment with the mean increase

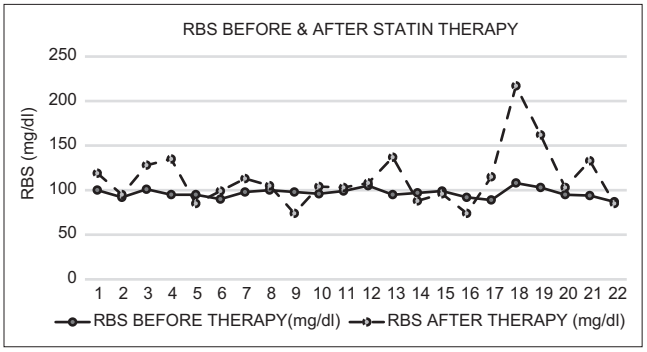

Fig. 1: Changes in red, blue, and green level before and after statin therapy irrespective of treatment duration

of 15.90±29.3 mg/dl. The 95% confidence interval for the difference is (−28.9, −2.91). Subgroup analysis of subjects was done to find out whether there was a correlation between individual statin types and HbA1c using Pearson's Chi-square analysis. This showed that there is no statistically significant correlation between these two variables (p=0.400)

A multiple regression analysis was done to predict whether HbA1C was affected by the dosage of statins, duration of therapy and BMI. Among these variables only dosage of statins significantly influenced HbA1c, with F (3, 18) = 3.507, p<0.05, R^2=0.369. This analysis showed that for every mg rise in dosage there was a 0.039 increase in HbA1c values. The others did not have a statistically significant effect on HbA1c values. Naranjo's causality assessment was done for the 6 subjects, who were diagnosed as diabetic after statin therapy and found that the ADR was of possible category.

DISCUSSION

In this observational cross-sectional study conducted for a period of 2 months from July 2014 to August 2014 in Mahatma Gandhi Medical College and Research Institute, Pondicherry, it has been found that treatment with statins increases the risk of new ONDM (27%) and there was a significant rise in the random blood glucose levels after the statin therapy. Furthermore, there was a statistically significant rise in HbA1c values as the dosage of statins was increased. The duration of treatment and the BMI has not significantly influenced the HbA1c values. There was no significant association found between the types of statins prescribed and HbA1c values.

In our study, we found that out of 22 subjects, 8 (36.4%) had impaired HbA1c level and 6 (27.2%) developed NODM. This shows that there is an increased risk of NODM (27%) and impairment of glucose level with statin therapy. This is well correlated with the meta-analysis done by Rajpathak *et al*. in the year 2009 including 57,593 patients on statin therapy with a mean follow-up of 3.9 years and they found that 2082 cases developed incident diabetes. In that they have concluded that there is a small, but significant increase in risk of developing diabetes and the benefits of statins on CV diseases likely outweigh any potential detrimental effects on glucose metabolism and diabetes risk [9]. In another meta-analysis done by Sattar *et al*., which included 13 trials on statins with 91,140 participants of whom 4278 developed diabetes during a mean of 4 years and showed that there is a 9% increased risk for NODM but the risk is low when compared with the reduction in coronary events [10]. Navarese *et al.* in a meta-analysis showed that there was a 25% increased risk with rosuvastatin 20 mg/day when compared with a placebo [5].

In this study, we found that there was no significant association between the type of statins and increase in diabetic risk. This was controversial to the earlier research done by Carter AA, who compared the effect of different types of statins and development of NODM. In

that they concluded that there was no significant risk on treatment with pravastatin, fluvastatin, and lovastatin, but it was higher with rosuvastatin, atorvastatin and simvastatin, and pravastatin may be preferred in patients with high risk of developing DM [11]. Similarly Navarese in a meta-analysis showed that risk is lowest with pravastatin 40 mg/day and 25% increased risk with rosuvastatin 20 mg/day when compared with a placebo and intermediate risk with atorvastatin 80 mg/day. They opined that different types and doses of statins have different potential to increase the incidence of DM. The reason for this controversial opinion in our study might be the subjects were prescribed either atorvastatin or rosuvastatin [5].

We observed a statistically significant rise in RBG after statin therapy, which was analogous to the study of Sukhija *et al.* who analyzed the data of 345,417 patients from the Veterans Affairs VISN 16 database and noticed the change in fasting plasma glucose (FPG) over a mean time of 2 years. They resolved that statin use is associated with a rise of FPG in patients with or without diabetes independent of their age [12].

Our analysis showed that for every mg rise in dosage, there was a 0.039 increase in HbA1c values and it was statistically significant. This was identical to the research conducted by Dormuth *et al.,* who compared the effects of higher and lower potency statins on the risk of developing NODM. In that they have included 8 population-based cohort studies and one meta-analysis. They have concluded that the risk is more with higher potency statin used for secondary prevention of CV disease and clinicians should be aware of that when prescribing statins to the patients.[13] In another pooled analysis of 5 statin-related trials done by Preiss *et al.* including 32572 patients, they have compared intensive dose with moderate-dose statin therapy and concluded that intensive dose therapy is associated with an increased risk of NODM than moderate dose and thus showed a dose-dependent association [14]. Waters *et al*. has done an analysis based on 3 large RCT on atorvastatin and concluded that high-dose atorvastatin therapy increases the risk of NODM and it warrants careful monitoring [15].

There was no significant changes observed in HbA1c values with respect to duration of treatment which contradicted the findings of the research done by Dormuth *et al.,* who observed that there was a significant rise in risk of NODM in the first 2 years of therapy with higher potency statins and risk is higher in the first 4 months of use [13]. Similarly Kryzhanovski *et al.* studied in the short-term (12 weeks) and long-term effect (56 weeks) of pitavastatin with simvastatin on FBG in patients with primary or mixed dyslipidemia and concluded that pitavastatin has no significant effect on FBG, but Simvastatin has increased FBG significantly in patients on long-term treatment [16]. This controversy might be due to the study subjects included in our study were on shorter duration of treatment with an average of 6.72 (3.23) months.

Majority of the research work done so far to describe the association between statin therapy and NODM were completely based only on the meta-analysis of various statin trials. So far, no single study was designed and powered to address NODM as a primary endpoint. Furthermore, the definition of DM varied among the trials, often derived from non-standardized criteria, and new-ONDM was usually not effectively screened for. Hence, the strengths of our study was that we used ADA diagnostic criteria for diagnosing DM and primary outcome measure was NODM.

The limitations of this report were shorter duration of the study and since it was a cross-sectional study we can only find their association but cannot give a causal inference or rule out the other confounding factors.

CONCLUSION

In this observational cross-sectional study conducted for a period of 2 months from July 2014 to August 2014 in Mahatma Gandhi Medical College and Research Institute, Pondicherry, it has been found that treatment with statins increases the risk of new ONDM by 27% and there was a significant rise in the random blood glucose levels after the statin therapy. Furthermore, there was a statistically significant rise in HbA1c values as the dosage of statins was increased. The duration of treatment, type of statin used, and the BMI has not significantly influenced the HbA1c values.

The study participants who were diagnosed as diabetic were given proper treatment and people with pre-diabetic risk were given proper counseling about diet, exercises, and importance of regular glycemic control monitoring. Physicians should be aware of this adverse drug reaction due to statin therapy and they should monitor the glycemic control status of the patients during their regular follow-up period.

To overcome the limitations of our study, it is better to plan a cohort study or randomized control trial with the NODM as a primary outcome measure for a longer duration of time.

The values of statins in CV disorders have been clearly established and accepted. Their benefit is undeniable; however, they need to be taken with caution and care, which is why it is crucial in the role of the physician when it comes to comprehending the risks involved while prescribing these valuable yet deleterious drugs to the general population.

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REFERENCES

1. Feher MD, Foxton J, Banks D, Lant AF, Wray R. Long-term safety of statin-fibrate combination treatment in the management of hypercholesterolaemia in patients with coronary artery disease. Br Heart J 1995;74(1):14-7.
2. Liao JK, Laufs U. Pleiotropic effects of statins. Annu Rev Pharmacol Toxicol 2005;45:89-118.
3. Maji D, Shaikh S, Solanki D, Gaurav K. Safety of statins. Indian J Endocrinol Metab 2013;17:636-46.
4. Shah RV, Goldfine AB. Statins and risk of new-onset diabetes mellitus. Circulation 2012;126:e282-4.
5. Navarese EP, Szczesniak A, Kolodziejczak M, Gorny B, Kubica J, Suryapranata H. Statins and risk of new-onset diabetes mellitus: Is there a rationale for individualized statin therapy? Am J Cardiovasc Drugs 2014;14:79-87.
6. Garrow JS, Webster J. Quetelet's index (W/H2) as a measure of fatness. Int J Obes 1985;9:147-53.
7. American Diabetes Association. Standards of medical care in diabetes – 2013. Diabetes Care 2013;36 Suppl 1:S11-66.
8. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, *et al.* A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239-45.
9. Rajpathak SN, Kumbhani DJ, Crandall J, Barzilai N, Alderman M, Ridker PM. Statin therapy and risk of developing type 2 diabetes: A meta-analysis. Diabetes Care 2009;32:1924-9.
10. Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, de Craen AJ, *et al.* Statins and risk of incident diabetes: A collaborative meta-analysis of randomised statin trials. Lancet 2010;375:735-42.
11. Carter AA, Gomes T, Camacho X, Juurlink DN, Shah BR, Mamdani MM. Risk of incident diabetes among patients treated with statins: Population based study. BMJ 2013;346:f2610.
12. Sukhija R, Prayaga S, Marashdeh M, Bursac Z, Kakar P, Bansal D, *et al.* Effect of statins on fasting plasma glucose in diabetic and nondiabetic patients. J Investig Med 2009;57:495-9.
13. Dormuth CR, Filion KB, Paterson JM, James MT, Teare GF, Raymond CB, *et al.* Higher potency statins and the risk of new diabetes: Multicentre, observational study of administrative databases. BMJ 2014;348:g3244.
14. Preiss D, Seshasai SR, Welsh P, Murphy SA, Ho JE, Waters DD,

et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: A meta-analysis. JAMA 2011;305: 2556-64.

15. Waters DD, Ho JE, Boekholdt SM, DeMicco DA, Kastelein JJ, Messig M, *et al.* Cardiovascular event reduction versus new-onset diabetes during atorvastatin therapy: Effect of baseline risk factors for diabetes. J Am Coll Cardiol 2013;61:148-52.
16. Kryzhanovski V, Eriksson M, Hounslow N, Sponseller CA. Short-term and long-term effects of pitavastatin and simvastatin on fasting plasma glucose in patients with primary hyperlipidemia or mixed dyslipidemia and ≥2 risk factors for coronary heart disease. J Am Coll Cardiol 2012;59:e1659.