Original Research Article

Effect of statins treatment on glycemic status and development of new onset diabetes mellitus in a tertiary care teaching hospital: a cross sectional study

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Received: 02 April 2019
Accepted: 08 April 2019

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ABSTRACT

Background: Several observational studies, well controlled randomized trials and meta-analyses reported that patients treated with statins has high risk of new onset diabetes mellitus (NODM), but the exact incidence and mechanism is still unclear and controversy. The present study was planned to find out the incidence of prediabetes and NODM and possible mechanism of action.

Methods: This was a prospective, cross-sectional study carried out at the Department of General Medicine for a period of one and half year between August 2017 and February 2019. Normoglycemic patients whose fasting blood glucose levels below 100 mg/dL and at least one year of treatment with statins were recruited in the study. Glycemic status, development of prediabetes and NODM and insulin resistance were the primary outcomes whereas lipid profile, adverse drug effects of statins were secondary outcomes. Collected data was analysed by suitable statistical methods.

Results: A total of 146 patients were recruited and 120 completed the entire study. Mean fasting blood glucose levels before initiation of statin therapy was 89.45±10.21. After one year of statin therapy, patients were separated as prediabetics and new onset diabetics and there mean fasting blood glucose levels were 116.24±12.86 (n=10) and 152.44±20.12 (n=12) respectively. A total of 12 (10.0%) patients were developed NODM and 10 (8.2%) patients developed prediabetes at the end of statin therapy. Atorvastatin 40mg was most frequency prescribed statin followed by Atorvastatin 20mg. A total of 70 (58.3%) study participants developed mild to moderate drug related adverse effects (ADRs), statin-induced myalgia (55.7%) was the most common ADR.

Conclusions: Patients treatment with statins had developed prediabetes and NODM. Atorvastatin 40mg and greater dose significantly induced NODM. Fasting blood glucose levels should be measured periodically with prescription contains higher doses of statins.

Keywords: Atorvastatin, Diabetes, Hyperglycaemia, HMG-CoA inhibitors, New onset diabetes, Prediabetes, Statins

INTRODUCTION

Look back to the disease burden since last decade in India, there has been a sudden shift from communicable diseases to non-communicable diseases. Diabetes is one of the most non-communicable, chronic metabolic disorders with an estimated rate of 8.7% of individuals are living in India in the age group of 20 and 70 years. This rising prevalence is mainly due to combinations factors which include secondary lifestyles, tobacco and...
alcohol use, lack of physical activity unhealthy diets and sometimes drug induced. Macro and micro vascular complications due to diabetes may decrease the quality of life of an individual.¹

By 2020, the non-communicable disease burden will account for 80% of the global disease burden. Premature mortality before 70 years of age is due to cardiovascular diseases (CVDs) and metabolic disorders in India have increased drastically.² Hypercholesterolemia is one of the risk factors for CVDs and responsible for life-threatening myocardial infarction in most of the patients.

Several groups of drugs are available to treat hypercholesterolemia, out of that 3-hydroxy-3-methylglutaryl-CoA reductase (HMG-CoA reductase) inhibitors (statins: atorvastatin, rosuvastatin, simvastatin) are most commonly used drugs. HMG-CoA reductase is a rate-limiting enzyme involved in the cholesterol biosynthetic pathway.³ A study conducted by IMS Health during the period of 2006 to 2010 and showed that monthly statin prescription was increased drastically from 45.8 to 84.1/1000 patients with coronary heart disease (CHD).⁴ Several studies shown that Indian population has lowest values of high-density lipoprotein-cholesterol (HDL-C) and higher levels of total cholesterol, LDL, VLDL and TC:HD ratio. Higher levels of those lipids are one of the major predictors for coronary artery disease.⁵⁻⁷

South Asian population suffering from hypercholesterolemia will be definitely recommended and intensively treated with statin therapy. Recent studies had shown the association of statin therapy with development of prediabetes and new onset diabetes (NODM). Only few studies showed the positive association as well as incidence of NODM with statins.⁸⁻⁹ With this background, the present study was undertaken to analyze the glycemic status and insulin resistance of patients on statins therapy.

METHODS

A prospective observational study conducted in the Department of General Medicine, Maharaja Institute of Medical Sciences (MIMS), Vizianagaram, Andhra Pradesh, India. Study was carried out for a period of one half year between August 2017 and February 2019.

The present study was approved by scientific committee as well as institutional ethics committee and informed consent was obtained from all of the study participants. Study was conducted according to the Declaration of Helsinki.

South Indian patients of both genders, above 35 years of age and treatment on statins at least for one year with evidence of fasting blood glucose level <100 mg/dL at the time of recruitment were included in the study.

Known case of diabetics and treatment with any one or combination of the beta-blockers, thiazide diuretics, fluoroquinolones, glucocorticoids, protease inhibitors were excluded from the study because those drugs may increase the blood glucose concentration. Pregnant women and lactating mother were also excluded.

Patient’s demographic and clinical characteristics which focusing the risk factors, metabolic syndromes and family history was recorded in pre designed data collection sheet. Study participants had received different strengths of statins over a period of one year and data was collected prospectively. Glycemic status, development of prediabetes and NODM were the primary outcomes whereas lipid profile, adverse drug effects of statins were secondary outcomes.

Blood glucose levels were analyzed immediately after recruiting the patients as well as end of the treatment. After separating the Prediabetes and NODM patients, their blood samples were sent for insulin levels and computerized model homeostatic model assessment (HOMA) which is a method to quantify the insulin resistance and beta-cell function and is calculated using the following equation.⁹

HOMA insulin resistance=

\[
\frac{\text{Fasting glucose X fasting insulin}}{22.5}
\]

Quantitative insulin sensitivity check index (QUICKI) was calculated by using the following formula.¹⁰⁻¹¹

\[
\text{QUICKI} = \frac{1}{\log (\text{fasting insulin } \mu\text{U/mL}) + \log (\text{fasting glucose } \text{mg/dL})}
\]

Adverse drug effects were recorded periodically throughout the study and causality assessment was performed by Micromedex 2.0 software (Truven Health Analytics, IBM, USA). Data analysis was performed using graph pad prism 8 (GraphPad, San Diego, California) and Excel application (Microsoft office 2016, USA). Discrete variables of demographic and clinical characteristics, treatment with statins, adverse drug reactions were showed in frequencies, percentages and interquartile range. Continuous variables of blood glucose levels, lipid profile, HOMA insulin resistance were expressed as mean ± standard deviation if normally distributed. Due to low sample size, survival analysis and Cox regression model for hazards ratio could not be performed.

RESULTS

A total of 146 patients were recruited and 120 completed the entire study. Baseline demographic details were showed in (Table 1).
Male patients were nearly twice higher than females (62.5/37.5%). Majority of the patients were in between the age group of 60-65 years. Hyperlipidemia (95.0%) was the main etiology for prescribing statins followed by ischemic heart disease (56.6%).

Nearly 71.0% of patients had hypertension as a concomitant disease. A total of 73.3% patients received ACEIs/ARBs as concomitant drugs followed by low dose aspirin (66.6%). Frequency with percentage use of various statins prescribed in the present study was shown in (Figure 1).

Different strengths of HMG-COA inhibitors were prescribed, out of which Atorvastatin 40 mg was most frequency prescribed statin followed by atorvastatin 20 mg.

Body mass index (BMI) of 61 (50.8%) study patients was within the normal category, 42 (35.0% patients were in the overweight category and 17 (14.2%) were fall in obese category. Percentage of study participants had clinical history of alcoholics (45.8%), smokers (42.5%), first-degree relative as diabetes (66.6%), and family history of cardiovascular disorder (40.0%). Lack of physical activity was seen in 28.3% of patients and 71.6% of patients regularly followed mild-to-moderate exercises. Other conditions which influence the insulin resistance were polycystic ovary diseases (23.3%), acanthosis nigricans (6.6%). The mean waist circumferences of males were 80.18 cms and females 90.48 cms.

Blood lipid levels and fasting blood glucose levels were showed in (Table 2). High levels of total cholesterol (220.18±62.95), triglycerides, LDL and low levels of HDL (34.21±10.42) were calculated. Fasting blood glucose levels before initiation of statin therapy was 89.45±10.21. After one year of statin therapy, patients were separated as prediabetics and new onset diabetics and their fasting blood glucose levels were 116.24±12.86 (n=10) and 152.44±20.12 (n=12) respectively.

A total of 12 (10.0%) patients were developed NODM and 10 (8.2%) patients developed prediabetes at the end of statin therapy, further inter drug analysis was analyzed and showed in Table 2. Out of twelve patients, 6 (5.0%) patients developed NODM with atorvastatin 40mg treatment followed by Atorvastatin 80 mg (4 patients (3.3%), atorvastatin 20 mg (2 patients (1.6%) and none of the patients developed NODM with rosuvastatin 20 mg.

A total of 10 patients were developed prediabetes, out of these 4 (3.3%) patients developed with atorvastatin 40 mg treatment followed by atorvastatin 20 mg (3 patients (2.5%), atorvastatin 80 mg (2 patients (1.6%)) and one patient with rosuvastatin 20 mg.

Statin treatment on insulin resistance was interpreted by using homeostatic model assessment and quantitative

### Table 1: Baseline demographic and clinical parameters of study population.

| Patient characteristics                      | Value |
|-----------------------------------------------|-------|
| N                                             | 120   |
| Male/female, N (%)                            | 75/45 | (62.5/37.5) |
| Age in years, Mean±SD                         | 58.24±12.08 |
| BMI (kg/m²), Mean±SD                          |       |
| Normal (n=61)                                 | 20.12±1.26 |
| Overweight (n=42)                             | 26.30±2.10 |
| Obese (n=17)                                  | 33.90±3.08 |
| Etiology or diagnosis, n (%)                  |       |
| Hyperlipidemia                                | 114 (95.0) |
| Hypertension                                  | 85 (70.8) |
| Ischemic heart disease                        | 68 (56.6) |
| Overweight/obese                             | 48 (40.0) |
| Waist circumference (cm) Mean±SD              |       |
| Males                                         | 80.18±8.10 |
| Females                                       | 90.48±10.92 |
| Concomitant medications, N (%)                |       |
| ACEIs/ARBs                                    | 88 (73.3) |
| Antiplatelet drugs: low dose aspirin           | 80 (66.6) |
| Clopidogrel                                    | 48 (40.0) |
| Diuretics                                      | 24 (20.0) |
| Antianginal drugs                             | 16 (13.0) |
| Others                                        |       |
| Smokers                                       | 51 (42.5) |
| Alcoholics                                     | 55 (45.8) |
| First-degree relative as diabetes             | 80 (66.6) |
| Family history of cardiovascular disorder      | 48 (40.0) |
| Physical activity, N (%)                      |       |
| Not seen                                      | 34 (28.3) |
| Mild to moderate                              | 86 (71.6) |
| Diseases which influence the insulin resistance, N (%) |       |
| Polycystic ovary diseases                     | 28 (23.3) |
| Acanthosis nigricans                          | 08 (6.6) |

Male patients were nearly twice higher than females (62.5/37.5%). Majority of the patients were in between the age group of 60-65 years. Hyperlipidemia (95.0%) was the main etiology for prescribing statins followed by ischemic heart disease (56.6%).

Nearly 71.0% of patients had hypertension as a concomitant disease. A total of 73.3% patients received ACEIs/ARBs as concomitant drugs followed by low dose aspirin (66.6%). Frequency with percentage use of various statins prescribed in the present study was showed in (Figure 1).
insulin sensitivity check index (HOMA) value of greater than 2.27 was considered as insulin resistance. All patients who developed NODM had >2.27 (Table 2) which could be indicate that statin users developed insulin resistance is might be a probable mechanism. QUICKI score of <0.357 was considered as severe insulin resistance; again, all patients (Table 2) who developed NODM had severe insulin resistance in the present study.

Table 2: Mean distribution of lipid profile, blood glucose levels, homeostatic model assessment (HOMA) value and QUICKI score of study population.

| Parameter | Mean±SD |
|-----------|---------|
| Total cholesterol (mg/dl) | 220.18±62.95 |
| Triglycerides (mg/dl) | 142.04±48.82 |
| LDL (mg/dl) | 130.01±29.11 |
| HDL (mg/dl) | 34.21±10.42 |
| Fasting blood glucose levels (mg/dl) | |
| Before statin therapy | 89.45±10.21 |
| After one year of statin therapy | |
| Normal individuals (n=98) | 89.10±10.64 |
| Prediabetes patients (n=10) | 116.24±12.86 |
| NODM patients (n=12) | 152.44±20.12 |
| Inter-drug analysis Vs prediabetes (A) and NODM (B) (n=22) | |
| Atorvastatin 20mg, n (%) | A=3 (2.5%), B=2 (1.6%) |
| Atorvastatin 40 mg, n (%) | A=4 (3.3%), B=6 (5.0%) |
| Atorvastatin 80 mg, n (%) | A=2 (1.6%), B=4 (3.3%) |
| Rosuvastatin 20mg, n (%) | A=1 (0.8%), B=0 (0.0%) |
| HOMA value | |
| Prediabetes patients | 1.60±0.58 |
| NODM patients | 3.02±0.74 |
| QUICKI score | |
| Prediabetes patients | 0.19±0.04 |
| NODM patients | 0.28±0.06 |

A total of 70 (58.3%) study participants developed mild to moderate drug related adverse effects (ADRs) showed in Table 3. Statin-induced myalgia (55.7%) was the most common ADR, followed by headache (40.0%), GI complaints (28.5%). ADRs associated with statin treatment were classified according to the WHO-UMC causality assessment scale and showed in (Table 3).

**DISCUSSION**

Development of statin induced prediabetes and NODM are the primary outcomes of the present study, we observed that 8.2% (n=10) of patients developed prediabetes and 9.9% (n=12) patients were developed NODM within a median time interval of 4.2 years. Treatment with Atorvastatin 40 mg had developed higher incidence of prediabetes as well as NODM in the present study. Fasting blood glucose levels before initiation of statin therapy was 89.45±10.21. After one year of statin therapy, patients were divided into prediabetics and new onset diabetics and their fasting blood glucose levels were above the normal levels (pre-diabetics: 116.24±12.86, n=10) and diabetics: 152.44±20.12, n=12).

Prosper trial has reported that 6.6% incidence of NODM was developed by Pravastatin 40 mg compared to control group with a median follow-up of 3.2 years.12 The diabetogenic potential of statin was shown to be dose-dependent and it was also confirmed by meta-analysis conducted by Presss D et al, the results shows that higher dose of statins developed 12% risk of NODM compared to low dose statins with 4.9 years of median follow-up.13 Another meta-analysis by Navarese EP et al, concluded that the incidence of NODM with rosuvastatin 20 mg, atorvastatin 80 mg, and pravastatin 40 mg was 25%, 15%, and 7% respectively.14 A HOMA score of >2.27 is considered as insulin resistance, all NODM patients had more than normal score (3.02±0.74) and prediabetes patients showed borderline (1.60±0.58) in the present study.15 QUICKI score of <0.357 is considered as severe insulin resistance, all NODM patients had more than normal score (0.28±0.06) and prediabetes patients showed borderline (0.19±0.04) in the present study.16 This might be indicating that the mechanism of statin-induced diabetes could be insulin resistance. This proposed mechanism can be one of the multiple mechanisms by which statins increase the risk of diabetes.

CVDs are one of the main leading causes of morbidity and mortality in developing countries and in India.5 Statins are prescribed to patients which prevents the atherosclerosis thereby prevent the life-threatening myocardial infarction. But data emerging from randomized clinical trials showed that statins may increase in glycated hemoglobin and fasting glucose levels which prompted the drug authorities to add a safety label.17,18 Several meta-analyses showed the association between long-term statin therapies with increase glycemic levels as well as development of prediabetes and NODM was real, but mechanistic confirmation is still unclear with controversy.19 An observational study conducted by the Canadian network for drug observational studies concluded that incidence of NODM...
occurs more frequently in first 4 months after initiation of therapy. Statins are the most effective and prescribed drugs to treat hypercholesterolemia and have good effect in prevention of primary and secondary cardiovascular disorders. Large population in the worldwide affects by NODM induced by statins, but association, magnitude of incidence needs to be evaluated and studies are warranted in the Indian population. The present study mainly aimed to evaluate the glycemic status of patients treated with statins at least for 1 year. Furthermore, the present study also addresses the role of insulin sensitivity in statin-induced NODM. The JUPITER (Justification for the use of statin in prevention; an intervention trial evaluating rosvastatin) trial concluded that a total of 27% of patients developed NODM in the rosuvastatin group compared to placebo. A study conducted by Sattar et al. reported that non-diabetic individuals who received statins had 9.0% increased risk of NODM. Demographic parameters like obesity, old age, consumption of alcohol and metabolic syndrome can develop the NODM and these risk factors increase the atherosclerosis by 3-fold and 12-fold risk of NODM. Hence, statins therapy with other risk factors may unmask the NODM. Atorvastatin 40 mg was the most commonly prescribed statin out of various prescribed statins to the patients in the present study. A total of 43.3% (n=52) patients were on atorvastatin 40 mg, 31.0% (n=37) were on Atorvastatin 20 mg, 17.0% (n=19) were on rosuvastatin 20 mg and 10.0% (n=12) were on atorvastatin 80 mg. Hence, a total of 12 (10.0%) patients were developed NODM and 10 (8.2%) patients developed prediabetes at the end of statin therapy, further inter drug analysis showed that out of twelve patients, 6 (5.0%) patients developed NODM with atorvastatin 40mg treatment followed by atorvastatin 80 mg (4 patients (3.3%), atorvastatin 20 mg (2 patients (1.6%)) and none of the patients developed NODM with rosuvastatin 20 mg. A total of 10 patients were developed prediabetes, out of these 4 (3.3%) patients developed with atorvastatin 40 mg treatment followed by atorvastatin 20 mg (3 patients (2.5%)), atorvastatin 80 mg (2 patients (1.6%) and one patient with rosuvastatin 20 mg. These findings are inconsistent with Thomson SR et al, study conducted in Karnataka, India. In contrast to the present study, Koh et al., ASCOT-LLA, Lipid, and Prosper trials concluded that higher doses of atorvastatin 80 mg develops NODM compared to lower doses of atorvastatin 10 mg, 20 mg, 40 mg and rosuvastatin 5 mg. In the present study, different strengths of atorvastatin (20 mg, 40 mg and 80 mg) and one strength of rosuvastatin (20 mg) were prescribed. Various drug utilization and prescription pattern studies in India reported that atorvastatin was most frequently used statin followed by Rosuvastatin and Simvastatin. Hyperlipidemia (95.0%) and hypertension (70.8%) were the most commonly associated comorbidities in the present study. This observation was consistent with CARDS (collaborative atorvastatin diabetes study) trial which showed the 84% incidence of hypertension. Insulin resistance is defined as normal or elevated insulin level showing decreased biological response, it can be seen in patients with polycystic ovary diseases, fatty liver, acanthosis nigricans, atherosclerosis and skin tags. A total of 29.9% (n=36) patients showed insulin resistance in the present study. A total of 58.3% (n=70) patients had reported drug related adverse effects in the present study. Of these, myalgia (55.7%) was reported by half of the patients followed by headache (40.0%). Statin-induced hepatitis was observed by two patients. Causality assessment of adverse events was showed possible causality to statin use, two cases of statin-induced hepatitis of probable causality and drug was withdrawn due to the same. These findings were in consistent with several randomized clinical trial across the world. The strengths of present study are that authors observed the association of statins therapy with NODM with parameters of fasting blood glucose levels, HOMA and QUICKI score (only few studies were available in India), which clearly gives the possible mechanism of developing NODM in South Indian population. Authors separated the prediabetes and NODM group and analyzed the fast blood glucose levels and followed up prospectively over a period of one year. The limitations of the study were sample size and study design. Due to low sample size authors could not perform the survival analysis and logistic regression to find out the influence of risk factors to develop NODM. Cross-sectional study was conducted to prove the study objectives, this study design was not enough to find out the association between statins and NODM because exposure and outcomes were observed at single point of time. Randomized clinical studies with more sample size will be needed in future to draw the better conclusions. Statins are administered to the hyperlipidemic patients for reducing the blood lipid levels which in turn prevent the cardiovascular disorders. But statins should be prescribed with caution due to development of prediabetes and NODM. Fasting blood glucose levels should be measured with prescription contains higher doses of Atorvastatin (40mg above) periodically at least once in every 4 months for any worsening of glycemia. Physician must educate the patients about statins before initiation therapy and motivate towards non-pharmacological therapy which disable the patient for development of NODM. ACKNOWLEDGEMENTS

Authors would like to acknowledge staff of Department of general medicine, Maharaja’s Institute of Medical
Sciences, Nellimarla, Vizianagaram, Andhra Pradesh, India.

**Funding: No funding sources**

**Conflict of interest: None declared**

**Ethical approval: The study was approved by the Institutional Ethics Committee**

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Cite this article as: Rao CKNSV, Vankayala A, Sayana SB, Raju DSSK. Effect of statins treatment on glycemic status and development of new onset diabetes mellitus in a tertiary care teaching hospital: a cross sectional study. Int J Adv Med 2019;6:xxx-xx.