e-ISSN: 0976-822X, p-ISSN:2861-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2023; 15(6); 231-238

Original Research Article

A Prospective Observational Study Assessing Glycemic Status in Diabetes-Naïve Patients on Statins

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Received: 13-02-2023 / Revised: 22-03-2023 / Accepted: 25-04-2023
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Conflict of interest: Nil

Abstract

Aim: The aim of the present study to explore the possible diabetogenic effect of statins, the mechanism of this effect, and various comorbidities associated with this causation.

Material & methods: It was a prospective observational study carried out for a period of one year in the Department of Pharmacology, DMCH, Laheriasarai, Darbhanga, Bihar, India. A total of 132 patients were recruited and 100 completed the entire study.

Results: Male patients were nearly twice higher than females (65/35%). Majority of the patients were in between the age group of 60-65 years. Hyperlipidemia (94%) was the main etiology for prescribing statins followed by ischemic heart disease (55%). Nearly 72% of patients had hypertension as a concomitant disease. A total of 72% patients received ACEIs/ARBs as concomitant drugs followed by low dose aspirin (65%). Different strengths of HMG-COA inhibitors were prescribed, out of which Atorvastatin 40 mg was most frequency prescribed statin followed by atorvastatin 20 mg. Statin treatment on insulin resistance was interpreted by using homeostatic model assessment and quantitative insulin sensitivity check index (HOMA) value of greater than 2.27 was considered as insulin resistance. All patients who developed NODM had >2.27 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 who developed NODM had severe insulin resistance in the present study. A total of 55 (55%) study participants developed mild to moderate drug related adverse effects (ADRs). Statin-induced myalgia (54.54%) was the most common ADR, followed by headache (36.36%), GI complaints (25.45%). ADRs associated with statin treatment were classified according to the WHO-UMC causality assessment scale.

Conclusion: Statins have a mild-to-moderate risk of developing NODM. The dose of statins is an important factor that increases the risk of diabetes in statin users.

Keywords: Hyperglycemia, new onset diabetes, statins, type 2 diabetes

Introduction

Diabetes is one of the fastest-growing global health emergencies of the 21st century that has reached alarming levels. [1] 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. Type 2 diabetes (T2D) is a progressive illness associated with decreasing insulin secretion over time, [2] and poorly controlled diabetes leads to multiple organ damage that can increase the overall risk of premature death. [3] 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. [4] By 2020 non-communicable diseases will account for 80% of the global disease burden, causing a seven out of ten deaths in the developing country and half of them being premature deaths below the age of 70. [5] Hypercholesterolemia is one of the risk factors for CVDs and responsible for life-threating 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. [6] An observational study conducted by IMS Health from 2006 to 2010 revealed the monthly statin prescription increased from 45.8 to 84.1/1000 patients with coronary heart disease (CHD). [7] 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:HDL ratio. Higher levels of those lipids are one of the major predictors for coronary artery disease. [8] South Asian population suffering from hypercholesterolemia will be definitely recommended and intensively treated with statin therapy. [9]

Recent studies had shown the association of statin therapy with development of prediabetes and new onset diabetes (NODM). With this background, the present study was undertaken to analyze the glycemic status and insulin resistance of patients on statins therapy.

Material & Methods

It was a prospective observational study carried out for a period of one year in the Department of Pharmacology, DMCH, Laheriasarai, Darbhanga, Bihar, India. A total of 132 patients were recruited and 100 completed the entire study.

Patients of either sex, above 30 years of age and on statins for at least 1 year with a fasting blood glucose level <100 mg/dl at the time of initiation of statin were included in the study. Diabetics, patients on any concomitant medications that may raise blood glucose levels such as fluoroquinolones, beta-blockers, atypical antipsychotics, glucocorticoids, thiazide diuretics, protease inhibitors, and pregnant women and lactating women were excluded from the study. Patient's detailed history focusing on risk factors if any for metabolic syndrome and family history was taken. Demographic, clinical characteristics and drug history were recorded as per the proforma.

The primary outcome of the study was the development of NOD mellitus (NODM) and development of prediabetes. Blood glucose levels were estimated in all patients included in the study. In all the patients who had developed diabetes, their blood samples were sent for fasting blood glucose and insulin levels. Possible mechanism of the development of diabetes was elucidated using a 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: [10]

Statistical Analysis

Data analysis was performed using SPSS version 23 (IBM Corp., Armonk, NY) and Excel software (Microsoft Windows

Operating system, version 2016. Licensce: Trialware). For baseline and demographic characteristics, the descriptive analysis was used. Continuous variables are expressed as mean ± standard deviation if normally distributed. Categorical variables were expressed as number of patients and percentages (n, %). Skewed data were expressed as a median and interquartile range (quartile 1 and quartile 3). Risk factors were analyzed as frequencies and percentages. Adverse drug reactions (ADRs) were analyzed using descriptive statistics. Survival analysis and Cox regression model for hazards ratio could not be done in the present study as the sample size was too small to make a definite conclusion regarding the same. Hence, descriptive statistics had to be followed.

Results

Table 1: Baseline demographic and clinical parameters of study population

Patient characteristics		**Value**
N		**100**
Male/female, N (%)		65/35 (65/35)
Age in years, Mean±SD		55.15±12.08
	Normal (n=50)	24.14±1.32
BMI (kg/m^2), Mean±SD	Overweight (n=35)	24.40±2.16
	Obese (n=15)	34.60±3.06
	Hyperlipidemia	94 (94)
Etiology or	Hypertension	72 (72)
diagnosis, n (%)	Ischemic heartdisease	55 (55)
	Overweight/obese	42 (42)
Waist	Males	82.24±8.12
Circumference (cm) Mean±SD	Females	92.56±10.28
	ACEIs/ARBs	72 (72)
Concomitant	Antiplatelet drugs:low dose aspirin	65 (65)
medications, N (%)	Clopidogrel	42 (42)
	Diuretics	20 (20)
	Antianginal drugs	12 (13)
Others		10 (10)
	Smokers	40 (40)
	Alcoholics	46 (46)
Clinical history,N (%)	First-degree relative as diabetes	65 (65)
	Family history of cardiovascular disorder	42 (42)
Physical	Not seen	30 (30)
activity, N (%)	Mild to moderate	70 (70)
Diseases whichinfluence the	Polycystic ovarydiseases	24 (24)
Insulin resistance, N(%)	Acanthosisnigricans	5 (5)

Male patients were nearly twice higher than females (65/35%). Majority of the patients were in between the age group of 60-65 years. Hyperlipidemia (94%) was the main etiology for prescribing statins followed by ischemic heart disease (55%). Nearly 72% of patients had hypertension as a concomitant disease. A total of 72% patients received ACEIs/ARBs as concomitant drugs followed by low dose

aspirin (65%). Body mass index (BMI) of 50 (50%) study patients was within the normal category, 35 (35% patients were in the overweight category and 15 (15%) were fall in obese category. Percentage of study participants had clinical history of alcoholics (46%), smokers (40%), first-degree relative as diabetes (65%), and family history of cardiovascular disorder (42%). Lack of physical activity was seen in 30% of patients and 70% of patients regularly followed mild-to-moderate exercises. Other conditions which influence the insulin resistance were polycystic ovary diseases (24%), acanthosis nigricans (5%). The mean waist circumferences of males were 82.24 cms and females were 92.56 cms.

Table 2: Percentage of patients received different types of statins

Stains	**N%**
Rosuvastatin 20 mg	15 (15)
Atorvastatin 80 mg	12 (12)
Atorvastatin 40 mg	45 (45)
Atorvastatin 20 mg	28 (28)

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

Table 3: 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)		224.16±65.35
Triglycerides (mg/dl)		144.06±48.42
LDL (mg/dl)		132.08±28.12
HDL (mg/dl)		36.22±10.12
Fasting blood glucose levels (mg/dl)		
Before statin therapy		88.42±10.22
After oneyear of statin therapy	Normal individuals(n=75)	88.14±10.64
	Prediabetes patients(n=10)	118.22±12.48
	NODM patients (n=15)	150.40±20.32
Inter-drug analysis Vs prediabetes (A) and NODM (B) (n=25)	Atorvastatin 20mg, n	A=3
		B=2
	Atorvastatin 40 mg, n	A=3
		B=7
	Atorvastatin 80 mg, n	A=3
		B=5
	Rosuvastatin 20mg, n	A=2
		B=0
HOMA value		
Prediabetes patients		1.45±0.55
NODM patients		3.02±0.72
QUICKI score		
Prediabetes patients		0.18±0.02
NODM patients		0.32±0.08

High levels of total cholesterol (224.16±65.35), triglycerides, LDL and low levels of HDL (36.22±10.12) were calculated. Fasting blood glucose levels before initiation of statin therapy was 88.42±10.22. After one year of statin therapy, patients were separated as prediabetics and new onset diabetics and their fasting blood glucose levels were 118.22±12.48 (n=10) and 150.40±20.32 (n=15) respectively. Out of 15 patients, 7 patients developed NODM with atorvastatin 40mg treatment followed by Atorvastatin 80 mg, atorvastatin 20 mg and none of the patients developed NODM with rosuvastatin 20 mg. A total of 10 patients were developed prediabetes, out of these 3 patients developed with atorvastatin 40 mg treatment followed by atorvastatin 20 mg, atorvastatin 80 mg and one patient with rosuvastatin 20 mg. Statin treatment on insulin resistance was interpreted by using homeostatic model assessment and quantitative insulin sensitivity check index (HOMA) value of greater than 2.27 was considered as insulin resistance. All patients who developed NODM had >2.27 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 who developed NODM had severe insulin resistance in the present study.

Table 4: Adverse drug effects profile of study patients on statins therapy

Type of ADR	Frequency (%) (N=55)
Myalgia	30 (54.54)
Headache	20 (36.36)
GI complaints	14 (25.45)
Tingling sensation	16 (29.09)
Dizziness	8 (14.54)
Loss of appetite	6 (10.90)
Hepatitis	2 (3.63)

A total of 55 (55%) study participants developed mild to moderate drug related adverse effects (ADRs). Statin-induced myalgia (54.54%) was the most common ADR, followed by headache (36.36%), GI complaints (25.45%). ADRs associated with statin treatment were classified according to the WHO-UMC causality assessment scale.

Discussion

Diabetes is one of the fastest-growing global health emergencies of the 21st century that has reached alarming levels. [11] Type 2 diabetes (T2D) is a progressive illness associated with decreasing insulin secretion over time [12], and poorly controlled diabetes leads to multiple organ damage that can increase the overall risk of premature death. [13] Evidence shows that optimal glycemic control is a goal for diabetes management. The general target of glucose control is glycated hemoglobin (HbA1c) ≤7% for non-pregnant adults, and a less stringent HbA1C goal of 8% (64 mmol/mol) is optional for patients with a risk of severe hypoglycemia and advanced microvascular or macrovascular complications. [14] However, HbA1c is expensive and unavailable in many places. Therefore, a fasting plasma glucose (FPG) level of 80–130 mg/dl without caloric intake for at least 8 h is one of the standard diagnostic criteria. [15] In India, Cardiovascular diseases (CVD) is projected to be the largest cause of death and disability by 2020 with 2.6 million. Indians are predicted to die due to coronary heart diseases, which constitutes 54.1% of all CVD deaths. It is estimated that, nearly half of these deaths are likely to occur among young and middle-aged individuals (30-79 years). This is because Indians experience CVD deaths at least a decade before their

counterparts in the developed countries. [16] Currently, lipid-lowering agents are widely used to reduce the risk of coronary events. However, there is wide variation in the selection and use of lipid-lowering agents. [17,18]

Male patients were nearly twice higher than females (65/35%). Majority of the patients were in between the age group of 60-65 years. Hyperlipidemia (94%) was the main etiology for prescribing statins followed by ischemic heart disease (55%). Nearly 72% of patients had hypertension as a concomitant disease. A total of 72% patients received ACEIs/ARBs as concomitant drugs followed by low dose aspirin (65%). Body mass index (BMI) of 50 (50%) study patients was within the normal category, 35 (35% patients were in the overweight category and 15 (15%) were fall in obese category. Percentage of study participants had clinical history of alcoholics (46%), smokers (40%), first-degree relative as diabetes (65%), and family history of cardiovascular disorder (42%). Lack of physical activity was seen in 30% of patients and 70% of patients regularly followed mild-to-moderate exercises. Other conditions which influence the insulin resistance were polycystic ovary diseases (24%), acanthosis nigricans (5%). The mean waist circumferences of males were 82.24 cms and females were 92.56 cms. The diabetogenic potential of statin was shown to be dose-dependent and it was also confirmed by meta-analysis conducted by Presiss 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. [19] 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. [20]

Statin treatment on insulin resistance was interpreted by using homeostatic model assessment and quantitative insulin sensitivity check index (HOMA) value of greater than 2.27 was considered as insulin resistance. All patients who developed NODM had >2.27 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 who developed NODM had severe insulin resistance in the present study. 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. [21] 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. [22] 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.

A total of 55 (55%) study participants developed mild to moderate drug related adverse effects (ADRs). Statin-induced myalgia (54.54%) was the most common ADR, followed by headache (36.36%), GI complaints (25.45%). ADRs associated with statin treatment were classified according to the WHO-UMC causality assessment scale. 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. [23-25]

Conclusion

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.

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