e-ISSN: 0976-822X, p-ISSN:2961-6042

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

International Journal of Current Pharmaceutical Review and Research 2023; 15(12); 447-452

Original Research Article

A Study to Analyze the Possibility of the Diabetogenic Potential of Atorvastatin among Hypercholesterolemic Patients: An Observational Study

Vikas Kumar

Assistant Professor, Department of Pharmacology, Narayan Medical College and Hospital, Sasaram, Bihar, India

Received: 10-09-2023 Revised: 23-10-2023 / Accepted: 26-11-2023
Corresponding author: Dr. Vikas Kumar
Conflict of interest: Nil

Abstract

Aim: The aim of the present study was to analyze the possibility of the diabetogenic potential of atorvastatin among hypercholesterolemic patients.

Methods: The present study is a retrospective cohort study conducted in the Narayan Medical College and Hospital, Sasaram, Bihar, India for 6 months. . Informed written consent was obtained from all the study participants in local vernacular language before their inclusion in the study. The study was conducted according to the Declaration of Helsinki. As per the inclusion criteria, a total of 50 study participants were enrolled in the study.

Results: Among the 50 study participants, 35 (70%) and 15 (30%) study participants were males and females respectively. The majority of patients were between the age groups of 51–65 years. A total of 36 (72%) of patients received Angiotensin converting enzyme inhibitors/Angiotensin receptor blockers (ACEI/ARBs) followed by low-dose aspirin by 32 (64%) patients. The prevalence of NODM among the study participants on atorvastatin therapy based on glycosylated hemoglobin was 30%. 2% and 4% of the study participants on statin therapy for more than 12 years had shown to be prediabetic and diabetic respectively. Different strengths of atorvastatin were prescribed out of which 40 mg (48%) was commonly prescribed followed by 20 mg (36%).

Conclusion: Statins are the most commonly prescribed drug in hypercholesterolemic patients to prevent cardiovascular disorder. Patients on statin therapy should be periodically monitored for glycemic status especially in patients on larger dosage of atorvastatin and also in patients with greater threat for diabetes.

Keywords: diabetes mellitus, glycemic status, atorvastatin, hypercholesterolemic patients

This is an Open Access article that uses a funding model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0) and the Budapest Open Access Initiative (http://www.budapestopenaccessinitiative.org/read), which permit unrestricted use, distribution, and reproduction in any medium, provided original work is properly credited.

Introduction

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-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. [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]

Control of cardiovascular risk factors such as hypertension and hypercholesterolemia in patients with diabetes can prevent complications. It has been reported that appropriate use of statins can prevent symptomatic coronary heart disease as well as acute coronary events in patients with type 2 diabetes in all populations including South Asians. [5,6] Patients with type 2 diabetes have a long term risk of cardiovascular mortality similar to patients without diabetes and overt cardiovascular disease. [6-10]

There are many hypotheses concerned with statins and evolution of NODM, one of them is impaired insulin secretion and diminished insulin sensitivity and another one is, it might encourage beta-cell apoptosis to amplify the production of nitric oxide. [11,12] Koh et al. in their study had shown that study participants treated with atorvastatin had a significant increase in HbA1C level accompanied by increased fasting glucose level. [13]

The aim of the present study was to analyze the possibility of the diabetogenic potential of atorvastatin among hypercholesterolemic patients.

Materials and Methods

The present study is a retrospective cohort study conducted in the department of Pharmacology, Narayan Medical College and Hospital, Sasaram, Bihar, India for 6 months. Informed written consent was obtained from all the study participants in local vernacular language before their inclusion in the study. The study was conducted according to the Declaration of Helsinki. As per the inclusion criteria, a total of 50 study participants were enrolled in the study.

Selection Criteria

Patients attending cardiology out-patient department irrespective of gender, with age more than 18 years diagnosed with hypercholesterolemia on atorvastatin therapy for more than 6 months with baseline fasting blood glucose (FBG) <100 mg/dl or random blood sugar <140 mg/dl during the commencement of therapy were considered for the study and hence included. The study participants with a known case of diabetes, family history of diabetes, history of gestational diabetes, patients on concomitant medication like corticosteroids, thiazide diuretics, atypical anti-psychotics, or any other medication that may raise blood glucose levels were excluded from the study. The baseline investigations like serum lipid profile, FBG level, and glycosylated hemoglobin level done in laboratories other than the study center were excluded from the study.

Study Procedure

The study participants were enrolled in the study as per the inclusion criteria. The demographic details, personal history, family history, drug history, and clinical characteristics like body mass index (BMI), waist circumference were recorded from the old medical records of the study participants. The duration and dosage of atorvastatin therapy given for each participant were recorded from the old medical documents of the study participants. The baseline laboratory investigations such as serum lipid profile, FBG level, and glycosylated hemoglobin level that were done in the laboratory in the study center were recorded from the old medical documents of the study participants. Similarly, the laboratory investigations were estimated once during the 6 months' study period in the same laboratory of the study center for all the enrolled patients and recorded. Adverse drug effects to atorvastatin were also recorded and the WHO-UMC causality assessment was performed. The data collected were entered into an excel sheet and statistically analyzed. The end result of this research was the occurrence of prediabetes or NODM among patients with hypercholesterolemia on atorvastatin therapy.

Analysis of Statistical Data

The analysis of statistical data was performed using Excel Microsoft Windows operating system. Descriptive statistics were performed for baseline and demographic characteristics. Continuous variables were expressed as mean ± standard deviation. Categorical variables were expressed as the number of patients (n) and percentage (%). Correlation between dose and duration of atorvastatin therapy and change in glycosylated hemoglobin were expressed as numbers and percentages. Adverse drug reactions were expressed by descriptive statistics.

Results

Table 1: Baseline demographic parameters of the patients included in the study

Parameters	N=50
Male/female, n (%)	35 (70)/15 (30)
Age (years), mean±SD	56.74±12.06
BMI (kg/m2), mean±SD	
Normal (n=16; 32%)	23.63±0.64
Over weight (n=20; 40%)	25.95±1.22
Obese (n=14; 28%)	31.32±1.38
Waist circumference (cm), mean±SD	
Male	94.96±6.34
Female	86.44±4.68
Concomitant disease, n (%)	
Hypertension	18 (36)
Ischemic heart disease	16 (32)
Coronary artery disease	11 (22)

Concomitant medication, n (%)	
ACEI/ARBs	36 (72)
Aspirin low dose	32 (64)
Clopidogrel	24 (48)
Diuretics	26 (52)
Antianginal drugs	10 (20)
Others, n (%)	
Smokers	26 (52)
Alcoholics	16 (32)
Mixed diet	46 (92)
Physical activity	
Sedentary	32 (64)
Mild to moderate	18 (36)

Among the 50 study participants, 35 (70%) and 15 (30%) study participants were males and females respectively, and mean age of study participants was 56.74±12.06 years. The majority of patients were between the age groups of 51–65 years. The BMI of 16 (32%) study participants were in the normal category, 20 (40%) were in the overweight category and 14 (28%) were in the obese category. The mean waist circumference of the male was 94.96±6.34 and the female was 86.44±4.68. 26 (52%) study participants had a clinical history of smoking and 16 (32%) had a history of alcohol intake, 46 (92%) were on a mixed diet and finally 32 (64%) study patients were leading a sedentary life. Nearly 18 (36%), 16 (32%), and 11 (22%) of study participants had hypertension, ischemic heart disease, and coronary artery disease, respectively. A total of 36 (72%) of patients received Angiotensin converting enzyme inhibitors/ Angiotensin receptor blockers (ACEI/ARBs) followed by low-dose aspirin by 32 (64%) patients.

Table 2: Mean distribution of lipid profile and blood glucose and glycosylated hemoglobin of study population

Parameters	Mean±SD
Lipid profile (mg/dl)	
Triglycerides	178.22±18.62
Total cholesterol	214.76±24.30
Low-density lipoprotein	154.36±12.16
High-density lipoprotein	36.24±6.10
FBG (mg/dl)	
Before statin therapy	88.02±7.83
After starting statin	115.2±28.62
Normal, n (%)=18	84.36±6.68
Prediabetes, n (%)=16	111.91±7.73
NODM, n (%)=16	152.64±20.08
HbA1c level (%)	
Before statin therapy	4.76±0.42
After starting statin	6.04±0.82
Normal, n (%)=20	5.26±0.54
Prediabetes, n (%)=15	5.95±0.25
NODM, n (%)=15	7.22±0.51

Mean total cholesterol was 214.76 ± 24.30, triglyceride was 178.22 ± 18.62, low-density lipoprotein was 154.36 ± 12.16, and high-density lipoprotein was 36.24 ± 6.10. The mean FBG and glycosylated hemoglobin before initiating statin therapy were 88.02 ± 7.83 and 4.76 ± 0.42, respectively. After initiating atorvastatin therapy the mean glycosylated hemoglobin was 6.04 ± 0.82 and 15 (30%) of study participants were prediabetic with a value of 5.95 ± 0.25 and 15 (30%) of participants had NODM with a value of 7.22 ± 0.51. The prevalence of NODM among the study participants on atorvastatin therapy based on glycosylated hemoglobin was 30%.

Table 3: Glycemic status of study participants based on the duration of atorvastatin therapy

Duration of atorvastatin	Frequency, n (%)	Total, n (%)
6 months-3 years		
Normal	18 (36)	20 (40)
Prediabetic	2 (4)	
NODM	Nil	
>3 years–6 years		
Normal	1 (2)	10 (20)
Prediabetic	4 (8)	
NODM	5 (10)	
>6 years–9 years		
Normal	1 (2)	10 (20)
Prediabetic	6 (12)	
NODM	3 (6)	
>9 years–12 years		
Normal	Nil	4 (8)
Prediabetic	1 (2)	
NODM	3 (6)	
Normal	Nil	3 (6)
Prediabetic	1 (2)	
NODM	2 (4)	

2% and 4% of the study participants on statin therapy for more than 12 years had shown to be prediabetic and diabetic respectively.

Table 4: Glycemic status of study participants based on dose of atorvastatin therapy

Dose of atorvaststin therapy	Frequency, n (%)	Total, n (%)
20 mg atorvastatin		
Normal	8 (16)	18 (36)
Prediabetic	4 (8)	
NODM	6 (12)	
40 mg atorvastatin		
Normal	11 (22)	24 (48)
Prediabetic	8 (18)	
NODM	5 (10)	
80 mg atorvastatin		
Normal	4 (8)	8 (16)
Prediabetic	3 (6)	
NODM	1 (2)	

Different strengths of atorvastatin were prescribed out of which 40 mg (48%) was commonly prescribed followed by 20 mg (36%).

Discussion

Cardiovascular disease (CVD) now has become the foremost reason for death globally which includes coronary artery disease, peripheral artery disease, and cerebrovascular disease, is mostly caused by atherosclerosis and its considerable risk factor is an elevation of low-density lipoprotein cholesterol (LDL-C) level. [14-16] According to the WHO Global Action Plan 2013, non-communicable disease will account for 80% of the global disease burden by 2020. [17] Premature mortality before the age of 70 years has increased drastically in India due to CVDs and metabolic disorders. [16] The Framingham heart study revealed the correlation between hypercholesterolemia and CVD. Endothelial dysfunction and insulin resistance are characteristic of coronary heart disease and statins have beneficial effects on atherosclerosis by decreasing LDL-C and improving endothelial function. Statin therapy will be recommended and intensively used to treat the South Asian population suffering from hypercholesterolemia.

Among the 50 study participants, 35 (70%) and 15 (30%) study participants were males and females respectively, and mean age of study participants was 56.74±12.06 years. The majority of patients were between the age groups of 51–65 years. Aiman et al [11] in their study had shown that there was an increased incidence of diabetes seen in the mean age of 66 years and the results described in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid-Lowering Arm (ASCOT-LLA) trial 63 years

was the mean age for the evolution of diabetes. The BMI of 16 (32%) study participants were in the normal category, 20 (40%) were in the overweight category and 14 (28%) were in the obese category. Similar to the present study, in West of Scotland Coronary Prevention Study, Long-term Intervention with Pravastatin in Ischemic Disease and ASCOTT trials, overweight group was maximum in number. [17]

The mean waist circumference of the male was 94.96±6.34 and the female was 86.44±4.68. 26 (52%) study participants had a clinical history of smoking and 16 (32%) had a history of alcohol intake, 46 (92%) were on a mixed diet and finally 32 (64%) study patients were leading a sedentary life. Nearly 18 (36%), 16 (32%), and 11 (22%) of study participants had hypertension, ischemic heart disease, and coronary artery disease, respectively. A total of 36 (72%) of patients received Angiotensin converting enzyme inhibitors/ Angiotensin receptor blockers (ACEI/ARBs) followed by low-dose aspirin by 32 (64%) patients. Meta-analysis conducted by Rajpathak et al., six studies were considered and 57,593 patients were randomized, during their follow-up, a total of 2,082 new cases of diabetes were reported. The study results showed substantial possibility of surge in diabetes among patients on therapy with statin. [18] In a meta-analysis conducted by Sattar et al [19] in which thirteen trials were included and they inferred that statin was related with increased chance of occurrence of diabetes in ratio of 1:255 patients on statin therapy for 4 years.

Mean total cholesterol was 214.76 ± 24.30, triglyceride was 178.22 ± 18.62, low-density lipoprotein was 154.36 ± 12.16, and high-density lipoprotein was 36.24 ± 6.10. The mean FBG and glycosylated hemoglobin before initiating statin therapy were 88.02 ± 7.83 and 4.76 ± 0.42, respectively. After initiating atorvastatin therapy the mean glycosylated hemoglobin was 6.04 ± 0.82 and 15 (30%) of study participants were prediabetic with a value of 5.95 ± 0.25 and 15 (30%) of participants had NODM with a value of 7.22 ± 0.51. The meta-analysis conducted by Presiss et al [20] confirmed that there is a correlation between the dose and diabetogenic potential of statin and has shown that when compared to low-dose statins, a higher dose of statins developed a 12% risk of NODM with 4.9 years of median follow-up. Navarese et al [21] in their meta-analysis concluded, the occurrence of NODM with a dosage 80 mg atorvastatin was 15%. [22]

The prevalence of NODM among the study participants on atorvastatin therapy based on glycosylated hemoglobin was 30%. 2% and 4% of the study participants on statin therapy for more than 12 years had shown to be prediabetic and diabetic respectively. Different strengths of atorvastatin were prescribed out of which 40 mg (48%) was commonly prescribed followed by 20 mg (36%). The finding of this study was found to be consistent with studies conducted by Thomson et al. and Rao et al. [16,17] The strength of the study was the association of statin therapy with prediabetes and NODM with parameters of FBG and HbA1c.

Conclusion

Statins are the most commonly prescribed drug in hypercholesterolemic patients to prevent cardiovascular disorder. Patients on statin therapy should be periodically monitored for glycemic status especially in patients on larger dosage of atorvastatin and also in patients with greater threat for diabetes. 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.

References

1. Nethan S, Sinha D, Mehrotra R. Non communicable disease risk factors and their trends in India. APJCP. 2017;18(7):2005.
2. WHO | Global Action Plan for the Prevention and Control of NCDs 2013-2020.
3. Stancu C, Sima A. Statins: mechanism of action and effects. J Cellular Molecular Med. 2001;5(4):378-87.
4. Choudhry NK, Dugani S, Shrank WH, Polinski JM, Stark CE, Gupta R, Prabhakaran D, Brill G, Jha P. Despite increased use and sales of statins in India, per capita prescription rates remain far below high-income countries. Health Affairs. 2014 Feb 1;33(2):273-82.
5. Sattar N, Gill JM. Type 2 diabetes in migrant south Asians: mechanisms, mitigation, and management. The lancet Diabetes & endocrine-ology. 2015 Dec 1;3(12):1004-16.
6. Yadav, S. , Gupta, D. K., Patil, P. H., Tiwari, A., & soni, P. . (2023). To Study the Pharmacotherapy of Diabetes Mellitus Type 2 Patient in Echo Health Care & Research Centre, Indore". Jour Med Resh and Health Sci, 6(2), 2389–2397. https://doi.org/10.52845/JMRHS/2023-6-2-1
7. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of

Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 201 4 Jun 24;129(25_suppl_2):S1-45.
8. Stamler J, Vaccaro O, Neaton JD, Wentworth D, Multiple Risk Factor Intervention Trial Research Group. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. Diabetes care. 1993 Feb 1; 16(2):434-44.
9. Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. New England journal of medicine. 1998 Jul 23;339(4):229-34.
10. Barr EL, Zimmet PZ, Welborn TA, Jolley D, Magliano DJ, Dunstan DW, Cameron AJ, Dwyer T, Taylor HR, Tonkin AM, Wong TY. Risk of cardiovascular and all-cause mortality in individuals with diabetes mellitus, impaired fasting glucose, and impaired glucose tolerance: the Australian Diabetes, Obesity, and Lifestyle Study (AusDiab). Circulation. 20 07 Jul 10;116(2):151-7.
11. Rana JS. Is diabetes really a CHD risk equivalent.
12. Aiman U, Najmi A, Khan RA. Statin induced diabetes and its clinical implications. J Pharmacol Pharmacother. 2014 Jul;5(3):181-5.
13. Padmavathi S, Laisana R, Manimekalai K. Dose and time dependent effects of statins on glycemic status and their association with new onset diabetes mellitus. Asian J Pharm Clin Res. 2015;8:125–8.
14. Koh KK, Quon MJ, Han SH, Lee Y, Kim SJ, Shin EK. Atorvastatin causes insulin resistance and increases ambient glycemia in hypercholesterolemic patients. J Am Coll Cardiol. 2010 Mar 23;55(12):1209-1216.
15. Umeda T, Hayashi A, Harada A, Okuyama K, Baxter CA, Tokita S, Teramoto T. Low-Density Lipoprotein Cholesterol Goal Attainment Rates by Initial Statin Monotherapy Among Patients With Dyslipidemia and High Cardiovascular Risk in Japan - A Retrospective Database Analysis. Circ J. 2018 May 25;82(6):1605-1613.
16. Prabhakaran D, Jeemon P, Roy A. Cardiovascular Diseases in India: Current Epidemiology and Future Directions. Circulat-ion. 2016 Apr 19;133(16):1605-20.
17. Rao KN, Vankayala A, Sayana SB, Raju DS. Effect of statins treatment on glycemic status and development of new onset diabetes mellitus in a tertiary care teaching hospital: A cross sectional study.
18. Thomson SR, Chogtu B, Shetty R, Devasia T. Analysis of glycemic status in diabetes-naïve patients on statins: A hospital-based cross-sectional study. Indian J Pharmacol. 2018 Nov -Dec;50(6):320-325.
19. 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 Oct; 32 (10):1924-9.
20. Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, de Craen AJ, Seshasai SR, McMurray JJ, Freeman DJ, Jukema JW, Macfarlane PW, Packard CJ, Stott DJ, Westendorp RG, Shepherd J, Davis BR, Pressel SL, Marchioli R, Marfisi RM, Maggioni AP, Tavazzi L, Tognoni G, Kjekshus J, Pedersen TR, Cook TJ, Gotto AM, Clearfield MB, Downs JR, Nakamura H, Ohashi Y, Mizuno K, Ray KK, Ford I. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet. 2010 Feb 27;375(9716):735-42.
21. Preiss D, Seshasai SR, Welsh P, Murphy SA, Ho JE, Waters DD, DeMicco DA, Barter P, Cannon CP, Sabatine MS, Braunwald E, Kastelein JJ, de Lemos JA, Blazing MA, Pedersen TR, Tikkanen MJ, Sattar N, Ray KK. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. JAMA. 2011 Jun 22;305(24) :2556-64.
22. Navarese EP, Buffon A, Andreotti F, Kozinski M, Welton N, Fabiszak T, Caputo S, Grzesk G, Kubica A, Swiatkiewicz I, Sukiennik A, Kelm M, De Servi S, Kubica J. Meta-analysis of impact of different types and doses of statins on new-onset diabetes mellitus. Am J Cardiol. 2013 Apr 15;111(8):1123-30.