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Original Article

Correlation of compliance to statin therapy with lipid profile and serum HMGCoA reductase levels in dyslipidemic patients

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ABSTRACT

Background: The efficacy of statin therapy may be lost or vary with reduction in compliance and intensity of statin therapy.
Objective: To study and correlate the quantitative effect of compliance on lipid profile and 3-hydroxyl-3-methylglutaryl coenzyme A reductase (HMGCoA-R) levels in dyslipidemic patients.
Methods: Compliance to different intensity of statin therapy assessed by pill count was correlated with serum levels of total cholesterol (TC), low density lipoprotein-cholesterol (LDL-C), high density lipoprotein-cholesterol (HDL-C), triglycerides (TG), apolipoprotein A1 (ApoA1), apolipoprotein B (ApoB) and HMGCoA-R.
Results: Out of 200 patients, 160 received moderate intensity statin therapy whereas 40 were on high intensity statin therapy. The overall mean compliance of patients was 56.7%. The compliance of patients on moderate intensity statin therapy was higher (56.8%) than those on high intensity (56.4%) ($p = 0.92$). There was significant inverse correlation ($p < 0.05$) between compliance and TC, TG, LDL-C and HMGCoA-R levels and positive correlation ($p < 0.05$) with HDL-C levels. The mean serum HMGCoA-R levels did not fall below 9–10 ng/mL when compliance to either moderate or high intensity statin therapy was increased above 60%.
Conclusions: It is appropriate to improve the compliance to existing statin therapy than switching over to higher intensity statin therapy. Estimation of HMGCoA-R levels may be explored as a surrogate marker to monitor and assess the compliance of patients to statin therapy.

1. Introduction

Dyslipidemia is a major risk factor for cardiovascular diseases (CVD) contributing to more than 25% of all deaths worldwide.[1,2] Indians are more prone to CVD due to higher prevalence of dyslipidemia (45.6%) as compared to the Western world (29.3%).[3,4]

American College of Cardiology/American Heart Association (ACC/AHA) Guidelines 2013 recommended high dose of statin therapy for patients (≥21 years of age) having any form of CVD or serum low density lipoprotein-cholesterol (LDL-C) ≥ 190 mg/dL. Moderate or high doses of statin therapy is suggested for patients with diabetes (age 40–75 years, and serum LDL-C levels of 70–189 mg/dL), having a predicted 10-year atherosclerotic cardiovascular disease risk of ≥7.5%, without any evidence of CVD.[5] The ASCVD events reduce significantly with both moderate and high intensity statin therapy,[5] but low compliance may be a factor which can negate this outcome.

Compliance is defined as the extent to which a person's behavior coincides with medical or health advice.[6] A meta-analysis of more than 90,000 patients demonstrated that statins are the most effective lipid-modifying agents with a 17–26% reduction in risk of coronary events.[7–10] The benefit of statin therapy on the desired clinical outcomes may be lost when patients are poorly compliant to therapy as only 30–40% of patients who are being treated with statins continue medication after one year.[10–12] This aspect needs to be explored whether patients despite having less compliance continue to get the benefits of statins in terms of reduction in serum levels of total cholesterol (TC), low density lipoprotein-cholesterol (LDL-C), triglycerides (TG), non-HDL-C and increase in high density lipoprotein-cholesterol (HDL-C) level or not.

Hence, the present study was planned to correlate the extended serum lipid profile levels and 3-hydroxyl-3-methylglutaryl

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coenzyme A-reductase (HMGCoA-R) levels with compliance to low, moderate and high intensity statin therapy.

2. Methodology

2.1. Subjects

Dyslipidemic Indian patients with age above 18 years, elevated LDL-C levels (>190 mg/dL in non-diabetics and 70–189 mg/dL in diabetics) and/or TG levels (>200 mg/dL), and/or low HDL-C levels (<40 mg/dL) as per ACC–AHA guidelines receiving statin therapy for any duration were included in the study.[5] The patients were taking either statin or statin fibrate fixed dose combination for dyslipidemia and antidiabetics if they had diabetes or antihypertensives for hypertension. Patients who had acute coronary syndrome within the last 3 months, history of hypothyroidism, pregnancy/lactation and hypersensitivity or intolerance to statins were excluded from the study.

2.2. Study design

In a prospective observational study information of patients' personal, demographic and socioeconomic status was recorded. All the patients received medicines (statins) from the hospital pharmacy every month for a period of 3 months. They were assessed for compliance to statins using pill count method at the end of 3 month.[6] Pill count is an indirect method to measure adherence and is calculated by comparing the number of doses taken by the patient with the actual number of doses the patient should have taken.[6] Study protocol was approved by the Institutional Human Ethical Committee, Lady Hardingre Medical College, New Delhi (*vide number* ECR/435/Inst/DL/2013). A written informed consent for participation in the study was taken from all the enrolled patients.

Statin therapy was categorized into low (simvastatin 10 mg), moderate (atorvastatin 10, 20 mg and rosuvastatin 5, 10 mg) and high (atorvastatin 40, 80 mg and rosuvastatin 20 mg) intensity as per ACC/AHA guidelines for dyslipidemia.[5] Patients with a score of pill count ≥80% were considered compliant.

The decision to start the statins or to escalate their doses if required was at the discretion of the attending physician as per ACC/AHA guidelines for dyslipidemia. Patients whose dose was modified from one intensity statin therapy to another with in the follow up period were excluded from the study analysis.

A 5 mL venous blood sample was collected at the end of 3 months period to estimate extended lipid profile (TC, LDL-C, HDL-C, TG, ApoA1 and ApoB) and serum HMGCoA-R enzyme levels. TC, TG, LDL-C and HDL-C were measured by enzymatic assay calorimeter of Randox Reagents. BMAssay HMGCoA-R (kit number – 26215,96T), AssayPro ApoA1 (kit number – 02681524) and AssayPro ApoB ELISA kit (kit number – 06982406) were used to measure HMGCoA-R levels. The minimum detectable levels of HMGCoA-R, ApoA1, ApoB were 0.06 ng/mL, 0.7 μg/mL and 0.0078 μg/mL respectively. ELISA analysis was done by the investigator.

2.3. Statistical considerations

The compliance data are presented as percentages whereas lipid profile parameters are presented as mean ± standard deviation. Analysis of data of extended lipid profile among the compliant and non-compliant patients was done using unpaired Student's *t*-test. The Pearson's correlation analysis was used for correlation of compliance with lipid profile and serum HMGCoA-R levels. A p value of less than 0.05 was considered statistically significant. The data was analyzed using SPSS (Statistic package for Social Sciences) Version 21.0.

3. Results

Out of a total of 200 patients included in the study 101 (50.5%) were females. The overall mean age of all the patients was 55.15 ± 10.23 years (range, 23–82 years). The mean duration of prescription for statin at the time of enrollment was 8.6 ± 13.08 months (range, 1–72 months). The frequently associated co-morbid condition with dyslipidemia among the study patients was diabetes mellitus (68%) followed by hypertension (47.5%) and ischemic heart disease (8%) (Table 1).

A total of 105 (52.5%) patients were prescribed atorvastatin while 95 (47.5%) patients received rosuvastatin daily. Majority (80%) of the patients received moderate intensity statin therapy either atorvastatin (10 or 20 mg) or rosuvastatin (5 or 10 mg) while 40 (20%) patients received high intensity statin therapy. None of the patients received low intensity statin therapy. Twenty-seven patients (13.5%) were prescribed only statin. Patients with hypertriglyceridemia received statins and fibrates (7.5%). along with the medication for comorbid conditions, i.e. antidiabetics (73%) and antihypertensives (47.5%).

The mean dose of moderate intensity of atorvastatin and rosuvastatin was 16.66 ± 9.78 mg and 9.41 ± 8.09 mg per day respectively whereas the mean dose for high intensity treatment with atorvastatin and rosuvastatin was 40 mg and 20 mg respectively.

Mean pill count score at the end of 3 months was 56.71% (range, 12.2–94.4%) collectively in both moderate and high intensity statin therapy. With regard to compliance, only 83 (41.5%) patients were compliant, i.e. with a pill count of ≥80% to the statins.

Overall, the serum levels of TC, TG, LDL-C and HMGCoA-R in compliant group were 172.65 ± 28.42 mg/dL, 133.52 ± 28.66 mg/dL, 89.81 ± 22.55 mg/dL and 9.74 ± 2.47 ng/mL respectively whereas

Table 1
Patients' demographic characteristics and clinical profile.

Parameters studied	Compliant patients (*N* = 83)			Non-compliant patients (*N* = 117)		
	Moderate intensity (*N* = 69)	High intensity (*N* = 14)	Overall	Moderate intensity (*N* = 91)	High intensity (*N* = 26)	Overall
Age (years) (Mean ± SD)	52.83 ± 10.93	54.93 ± 7.94	53.18 ± 10.48	53.8 ± 9.49	66.18 ± 6.6	56.54 ± 10.21
Gender Females, *N* (%)	36 (52.17)	6 (42.8)	42 (50.6)	51 (56.04)	8 (30.7)	59 (50.4)
Mean pill count (%)	83	45				
Comorbid conditions						
Diabetes mellitus, *N* (%)	57 (82.6)	11 (78.5)	68 (81.9)	55 (60.4)	13 (50)	78 (66.6)
Hypertension, *N* (%)	36 (52.17)	4 (28.5)	40 (48.1)	50 (54.9)	5 (19.2)	55 (47.0)
Ischemic heart disease, *N* (%)	4 (5.7)	1 (7.1)	5 (6.02)	11 (12.08)	0 (0)	11 (9.4)

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