



## 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.© 2016 Published by Elsevier B.V. on behalf of Cardiological Society of India. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## 1. Introduction

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

American College of Cardiology/American Heart Association (ACC/AHA) Guidelines 2013 recommended high dose of statin therapy for patients ( $\geq 21$  years of age) having any form of CVD or serum low density lipoprotein-cholesterol (LDL-C)  $\geq 190$  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  $\geq 7.5\%$ , without any evidence of CVD.<sup>5</sup> The ASCVD events reduce significantly with both moderate and high intensity statin therapy,<sup>5</sup> 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.<sup>6</sup> 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.<sup>7–10</sup> 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.<sup>10–12</sup> 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.<sup>5</sup> 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.<sup>6</sup> 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.<sup>6</sup> Study protocol was approved by the Institutional Human Ethical Committee, Lady Harding 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.<sup>5</sup> Patients with a score of pill count  $\geq 80\%$  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  $\mu\text{g/mL}$  and 0.0078  $\mu\text{g/mL}$  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  $\pm$  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  $55.15 \pm 10.23$  years (range, 23–82 years). The mean duration of prescription for statin at the time of enrollment was  $8.6 \pm 13.08$  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%).

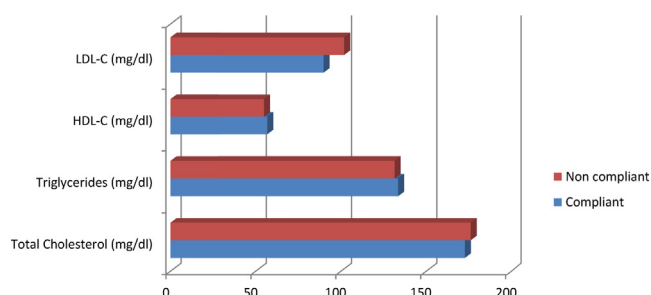
The mean dose of moderate intensity of atorvastatin and rosuvastatin was  $16.66 \pm 9.78$  mg and  $9.41 \pm 8.09$  mg per day respectively whereas the mean dose for high intensity treatment with atorvastatin and rosuvastatin was 40 mg and 20 mg respectively.

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  $\geq 80\%$  to the statins.

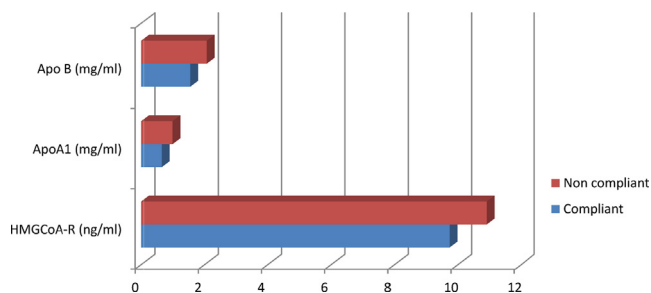
Overall, the serum levels of TC, TG, LDL-C and HMGCoA-R in compliant group were  $172.65 \pm 28.42$  mg/dL,  $133.52 \pm 28.66$  mg/dL,  $89.81 \pm 22.55$  mg/dL and  $9.74 \pm 2.47$  ng/mL respectively whereas

**Table 1**  
Patients' demographic characteristics and clinical profile.

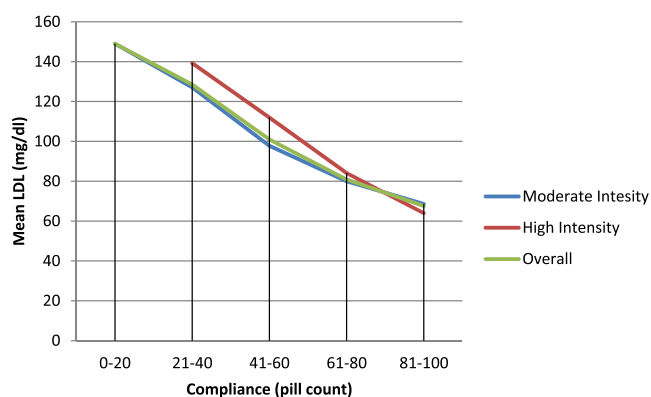
Parameters studied	Compliant patients (N=83)			Non-compliant patients (N=117)		
	Moderate intensity (N=69)	High intensity (N=14)	Overall	Moderate intensity (N=91)	High intensity (N=26)	Overall
Age (years) (Mean $\pm$ SD)	52.83 $\pm$ 10.93	54.93 $\pm$ 7.94	53.18 $\pm$ 10.48	53.8 $\pm$ 9.49	66.18 $\pm$ 6.6	56.54 $\pm$ 10.21
Gender	36 (52.17)	6 (42.8)	42 (50.6)	51 (56.04)	8 (30.7)	59 (50.4)
Females, N (%)						
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)



**Fig. 1.** Comparison of lipid profile levels after 3 months of statin therapy in compliant and noncompliant patients.



**Fig. 2.** Comparison of ApoA1, ApoB and HMGCoA-R levels after 3 months of statin therapy in compliant and non-compliant patients.



**Fig. 3.** Correlation of HMGCoA-R in moderate and high intensity statin therapy groups with compliance using pill count.

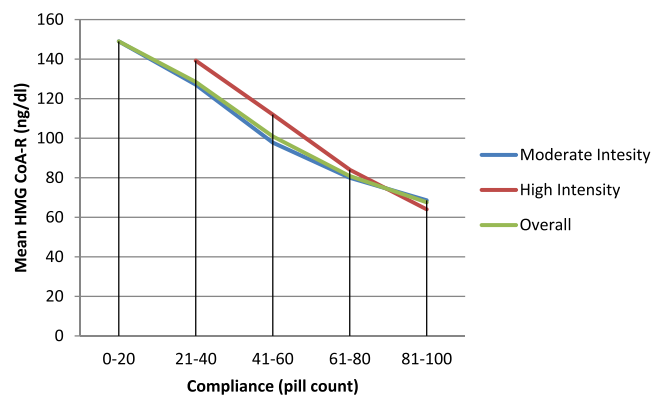
in non-compliant group TC and TG values were non-significantly higher while LDL-C and HMGCoA-R values were significantly higher (Figs. 1 and 2).

The overall levels of total cholesterol ( $r = -0.709$ ;  $p = 0.000$ ), TG ( $r = -0.475$ ;  $p = 0.000$ ), LDL-C ( $r = -0.751$ ;  $p = 0.000$ ) and ApoA1 ( $r = -0.327$ ;  $p = 0.000$ ) were inversely correlated with compliance.

**Table 2**

Correlation of compliance (pill count) in moderate and high intensity statin therapy groups with lipid profile parameters including HMGCoA-R levels after 3 months.

Intensity of statin	TC	TG	LDL-C	HDL-C	HMGCoA-R	ApoA1	ApoB
Moderate intensity							
Pearson correlation	-0.727	-0.565	0.785	-0.795	-0.119	-0.278	0.028
p value	<b>0.000</b>	<b>0.000</b>	<b>0.000</b>	<b>0.000</b>	<b>0.000</b>	<b>0.000</b>	0.722
High intensity							
Pearson correlation	-0.820	-0.086	-0.906	0.768	-0.211	-0.402	-0.382
p value	<b>0.000</b>	0.599	<b>0.000</b>	<b>0.000</b>	<b>0.000</b>	<b>0.010</b>	<b>0.015</b>
Overall							
Pearson correlation	-0.709	-0.475	-0.751	0.731	-0.111	-0.327	-0.050
p value	<b>0.000</b>	<b>0.000</b>	<b>0.000</b>	<b>0.000</b>	<b>0.000</b>	<b>0.000</b>	0.495



**Fig. 4.** Correlation of HMGCoA-R in moderate and high intensity statin therapy groups with compliance using pill count.

Whereas compliance in the moderate intensity statins therapy showed similar impact on total cholesterol ( $r = -0.727$ ;  $p = 0.000$ ), TG ( $r = -0.565$ ;  $p = 0.000$ ), LDL-C ( $r = -0.785$ ;  $p = 0.000$ ) and ApoA1 ( $r = -0.278$ ;  $p = 0.000$ ) levels (Table 2). The inhibition of HMGCoA-R was also inversely correlated with compliance. The inhibition of HMGCoA-R, TC, LDL-C, ApoA1 was more inversely correlated with compliance in higher intensity statin therapy than that in moderate intensity (Table 2).

Levels of LDL-C were between 60 and 80 mg/dL when compliance to moderate and high intensity statin therapy was greater than 60% (Fig. 3). To attain these LDL-C levels, statin therapy reduced the HMGCoA-R enzyme levels to 9–10 ng/mL thereafter maintaining a plateau despite increase in compliance (Fig. 4).

#### 4. Discussion

The patients compliant to statin therapy in our study were 41.5%, i.e. with a pill count >80% at the end of 3 months. Ho et al. reported higher proportion (70–80%) of the patients compliant to the statins<sup>13</sup> and in another study only 60–70% of patients were compliant.<sup>14,15</sup>

On the other hand mean pill count of all the subjects in this study was 56.71% despite 41.5% of the patients being compliant as most patients had compliance between 20% and 90% with only 1 patient below 20%. Whereas, Perrault et al. reported a higher mean compliance of 74% during the first year and 53% after 1 year of follow-up.<sup>16</sup> Higher cost of statin therapy and higher incidence of adverse events is known to adversely affect compliance but those may not be the deterrents for good compliance in our study as medication was provided free of cost to the patients and also, no serious or severe adverse events were reported.<sup>17</sup> In light of this, lower education levels leading to inadequate awareness about the

alarming consequences of the disease and benefits of therapy could be the factors for lower compliance.<sup>18</sup>

Virani et al. reported association of high-intensity statin use with a modest reduction in compliance (proportion of days covered) when compared with low and moderate-intensity statin use.<sup>19</sup> Similarly, in the present study, slightly lower pill count was seen in patients on high intensity statin therapy (56.4%) as compared to those on moderate intensity (56.8%).

In our study, there existed a significant inverse correlation between compliance to statin therapy and serum TC, TG, LDL-C, ApoA1 and HMGCoA-R levels but it was more inversely correlated with high intensity statin therapy suggesting an association between stain intensity and inhibition of enzyme along with favorable change in lipid parameters. Vodonos et al. reported a greater reduction in serum LDL-C levels with high intensity statin as compared to moderate intensity with increase in adherence.<sup>20</sup> Since this was the first study to correlate serum HMGCoA-R levels with compliance, so it was not possible to compare these findings.

In the present study, rise in HDL-C showed a positive correlation ( $r = 0.731$ ,  $p = 0.000$ ) with statin compliance in both moderate and high intensity statin therapy. On the contrary, Vodonos et al. in a cross-sectional study, could not demonstrate a rise in HDL-C levels with an increase in compliance probably due to inclusion of simvastatin and lovastatin apart from atorvastatin and rosuvastatin as the latter are associated with greater fall in LDL-C and TG leading to a higher rise in HDL-C levels.<sup>20,21</sup>

In our study, a plateau in the levels of HMGCoA-R was achieved when compliance to moderate and high intensity statin therapy was beyond 60%. Beyond this, the fall in LDL-C levels was not as much as when compliance was below 60% (Figs. 3 and 4). In this context, Vodonos et al. also observed a plateau in LDL-C levels when compliance was more than 80% but they did not estimate HMGCoA-R levels.<sup>20</sup> On this basis, if the patients miss to take few doses of atorvastatin or rosuvastatin in between, perhaps it may not compromise their cardiovascular benefits. The optimum clinical benefit despite poor compliance of statins viz. atorvastatin and rosuvastatin could be due to their pharmacokinetic (longer half-life) and pharmacodynamics (active metabolite) properties which may suffice to inhibit HMGCoA-R enzyme adequately.<sup>21</sup> This finding also supports the use of every other day dosing of statins to treat dyslipidemia.<sup>22–30</sup>

The levels of LDL-C and HMGCoA-R fell with increase in adherence in both moderate and high intensity statin therapy (Figs. 3 and 4) suggesting improvement in compliance up to 60% should be considered. Compliance can be improved by patient education, patient–physician communication enhancement, extended care through ancillary health care providers, simplification of drug regimens, and increased patient monitoring and follow-up.<sup>31</sup> Switching to a higher intensity statin therapy may be another option which needs to be explored further in larger prospective longitudinal studies.

This study unveils the association and correlation of TC, TG HDL-C, LDL-C, ApoA1, ApoB and HMGCoA-R levels with compliance of patient to statins. These findings suggested that estimation of HMGCoA-R levels in dyslipidemic patients on statins needs to be explored further as a tool to optimize the statin therapy and guide the physicians in decision making for dose modification and patients' counseling for compliance improvement.

## 5. Conclusion

It is concluded that improvement in compliance to statins up to 60% should be considered along with the option of switching over to a higher intensity statin. HMGCoA-R may be explored as a tool to aid physicians in optimizing and individualizing statin therapy.

## Authors' contribution

Abhinav Grover – Hypothesis generation, protocol writing, estimation of various parameters.

Madhur Yadav – Screening of the patients.

Lalit Kumar Gupta – Data handling, critical evaluation of manuscript.

Harmeet Singh Rehan – Hypothesis generation, manuscript writing.

## Conflicts of interest

The authors have none to declare.

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