To study impact of treatment with Rosuvastatin versus Atorvastatin on 25 hydroxy Vitamin D concentrations among adult Indian men-a randomized control trial

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Abstract:
BACKGROUND: Dyslipidemias are on the rise and are increasingly being treated with statins. As the metabolism of cholecalciferol and cholesterol are interrelated, reduction in cholesterol synthesis by statins is likely to affect Vitamin D status.

OBJECTIVES: (1) The aim is to study the effect of treatment with statins (Atorvastatin/Rosuvastatin) on 25-hydroxy-Vitamin-D (25OHD) among newly detected subjects with dyslipidemia for 6 months (2) To study the impact of 25OHD concentrations on the efficacy of statin treatment.

MATERIALS AND METHODS: This was a prospective, balanced randomized (1:1), open-label, parallel-group study, in apparently healthy Indian adult men (south Asian, 40–60 years). At baseline, serum lipids and 25OHD concentrations were measured. Based on the Adult Treatment Panel III guidelines, subjects were divided as per lipid concentrations into controls (who did not require statin treatment) and intervention (who required statin treatment) groups. Random allocation of subjects was done in two groups for receiving intervention for 6 months: Atorvastatin group (n = 52, received Atorvastatin) or Rosuvastatin group (n = 52, received Rosuvastatin). Lipids and 25OHD concentrations were measured at the end line.

RESULTS: Atorvastatin group presented significant reduction (P < 0.05) in 25OHD, total cholesterol (TC) and low-density-lipoprotein-cholesterol (LDL-C) concentrations at the end line. In the Rosuvastatin group, significant drop in TC, LDL-C and high-density lipoprotein cholesterol (concentrations (P < 0.05) was observed, while 25OHD concentrations showed no significant change. Mean 25OHD concentrations were significantly correlated with a reduction in LDL-C concentrations in Atorvastatin group.

CONCLUSIONS: Treatment with Atorvastatin resulted in a reduction in 25OHD concentrations; further, its efficacy in reducing LDL-C concentrations was related to the 25OHD concentrations.

Keywords: Atorvastatin, cholesterol, rosuvastatin, statins, Vitamin D

Introduction

As per the World Health Organization (WHO), cardiovascular ailments are leading causes of mortality in developing countries and account for 26% of deaths in India.[1] Among the adult male population >20 years of age, high prevalence of coronary artery disease (CAD) is reported in rural and urban areas (4% and 10%...
respectively), representing double in rural and a 6-times rise in urban areas from 1960 to 2000.[10] The prescription of different molecules of statins is rapidly increasing in India for the treatment of CAD.[11]

β-Hydroxy β-methylglutaryl-CoA (HMG-CoA) reductase is critical for cholesterol synthesis and is the enzyme which is inhibited by statins. Various available statins have different pharmacokinetic and metabolic properties. Lipophilic statins (e.g., Fluvastatin, Pitavastatin, Simvastatin, Lovastatin and Atorvastatin) are metabolized by gut and liver in the first pass, and thus their oral bioavailability is low. Hydrophilic statins such as Rosuvastatin and Pravastatin have better oral bioavailability. CYP3A4 metabolizes Atorvastatin, Simvastatin, and Lovastatin, while, CYP enzymes do not significantly metabolize Rosuvastatin and Pravastatin. Atorvastatin undergoes aromatic hydroxylation by CYP3A4 and its metabolites carry out desired HMGCoA enzyme inhibition.[4]

Statins apart from their desired hypolipidemic pharmacological actions, are known to affect other important metabolites in the body such as Ubiquinone leading to statin-induced myopathy.[5] Vitamin D concentrations may also be affected with the use of statins as cholesterol and cholecalciferol are produced through a common pathway, and thus, interventions inhibiting cholesterol synthesis are likely to also affect Vitamin D synthesis. Various studies have also shown that Vitamin D status is related to cardiometabolic outcomes[6] as well as cardiovascular events.[7] Vitamin D insufficiency has been reported to be associated with statin-induced myopathy.[8]

Considering the large number of Indian patients who are likely to be on statins and further, given that 25-hydroxy-Vitamin-D (25(OH)D) deficiency is being commonly described in India,[9] it is important to assess the impact of statins on 25(OH)D status.

Thus, our specific objectives were (1) To study the effect of 6 months treatment with Atorvastatin versus Rosuvastatin on 25OHD concentrations in newly detected dyslipidemic subjects, (2) To study the impact of mean 25OHD concentrations on the efficacy of statin treatment.

Materials and Methods

The study design was randomized (1:1), open-label, prospective, study which was conducted at, Hirabai Cowasji Jehangir Medical Research Institute, Pune, India (South Asia). Various local institutes, non-governmental organizations, offices, tertiary care centers, residential living areas were selected, and healthy males were approached to volunteer in the study. Males, satisfying inclusion criteria such as apparently healthy, between ages of 40 and 60 years, willingly participating and providing consent for the study were included. Subjects with known ailments interfering with sterol parameters and 25(OH)D metabolisms, for example, hepatic disorders, diabetes,[10] kidney disorders and deranged thyroid functions or pre-existing cardiac issues were excluded from the study [Figure 1]. Institutional Ethics Committee permissions were obtained for the study, and participants gave written informed consent.

Study groups

Estimation of lipid concentrations, i.e., total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), and 25OHD concentrations were performed on all subjects. Among eligible candidates, risk assessment for dyslipidaemia was performed using the Adult Treatment Panel (ATP III) guidelines.[11] Based on the results, participants were enrolled in groups as follows:

Controls

Two hundred and seven subjects who, as per the ATPIII guidelines, did not have dyslipidaemia and thus did not require statin therapy were identified from the entire study population. Out of these 50 subjects were randomly chosen for randomized controlled trial (RCT) based on computer generated random number table. Controls were studied to record the effect of seasonal change, if any, on 25OHD concentrations.

Intervention with statins

Subjects (n = 104) who, as per the ATPIII guidelines had dyslipidaemia and required statins were further divided randomly by using computer generated allocation sequence into two groups to receive either Atorvastatin or Rosuvastatin. Allocation sequence generation and assigning participants to interventions were done by statistician (SAC). These (Atorvastatin and Rosuvastatin) were selected for use in the study as they are commonly used statins in India[12] and also as they have different pharmacokinetic properties.[13]

a. First group received Tablet Atorvastatin 10 mg/day for 6 months[14]

b. Second group received Tablet Rosuvastatin 5 mg/day for 6 months.[14]

The qualified physician examined all the participants for assessing current health status with recording past and present medical history.

Biochemical parameters

After an overnight fast of 12 h, venous blood sample (8 ml) was collected from participants using vacutainers (BD Franklin lakes NJ USA). Vacutainers were centrifuged
at 2500 rpm) for 15 min, separated serum was stored at −80°C until further analysis. Fresh samples were used for estimating blood sugar - fasting (fasting blood sugar [FBS]), serum glutamic pyruvic transaminase (SGPT) and serum creatinine (CR) using standard protocols (Hexokinase method for FBS, Jaffe method for serum creatinine and an enzymatic method for SGPT).

The enzymatic method was used to estimate lipid parameters (i.e., TC, HDL-C, and TG. Using the Friedewald equation, LDL-C and very LDL-C concentrations were calculated.\textsuperscript{15} 25OHD was estimated by ELISA method (DLD diagnostics, Germany, intra-assay and inter-assay CV <8%).

**Anthropometry**
Height was measured to the nearest 0.1 cm using Leicester height meter, Child growth foundation, UK, (range 60–207 cm); weight measurements were performed on an electronic digital scale to the nearest 0.1 kg. Body mass index (BMI) was computed as weight in kg/height in meter square.

**Body composition**
Using Lunar DPX-PRO total body pencil beam Densitometer (GE Healthcare, WI) on a medium mode scan (software encore 2005 version 9.30.044) (with CV-1.9% for total fat percentage), total body fat percentage was measured (as body fat percentage affects 25(OH)D concentrations).\textsuperscript{16,17}

**Compliance**
Compliance for treatment was measured at quarterly and 6 monthly follow-up visits and telephonically for both intervention groups.

**Follow-up visits**
Patients were assessed clinically, and SGPT was measured at the end of 3 months to assess effectiveness of the drug as well as drug toxicity.\textsuperscript{18} At the end line of the study, lipids and 25OHD were measured. In the event of detection of any adverse reaction in the subject, he was omitted from the study.

**Statistical procedures**
SPSS software for Windows (version 16.0, 2001, SPSS Inc., Chicago, IL) was used for data analysis. One sample Kolmogorov-Smirnov test was applied for testing the normality of the variables before performing statistical analysis. Data are presented as mean ± SD for normally distributed variables and median (inter-quartile range) for non-normally distributed variables. For examining changes in variables of interest at the beginning and end of the study, appropriate tests like paired t-tests and

![Figure 1: Consort diagram](image-url)
one-way ANOVA were used. Effects of statin on 25OHD and vice versa were assessed and compared within and in between intervention groups.

For sample size calculation, paired sample two-sided equality t-test was used. For 80% power of the study and with the alpha of 0.05, the desired sample size was 40 subjects in each group based on previous intervention studies.\[19\]

**Results**

Out of 450 men between the age of 40 and 60 years who volunteered for participation in the study, 328 participants were randomly pre-screened for the study. After receiving reports of preliminary investigations, 17 patients were excluded from the study (FBG >125 mg/dl – 11, SGPT >40 IU/dl – 3, abnormal ECG-3). Of the 311 subjects who were eligible to be randomized, 104 (33%) fulfilled ATP III guidelines for starting statin therapy and were included in the intervention group and were randomly allocated to Atorvastatin or Rosuvastatin group (52 each). Of the remaining 207 subjects who did not require statin therapy as per ATP III guidelines, 50 subjects were randomly selected as controls. Among 3 arms, 39 from the control group, 48 from Atorvastatin group and 42 from Rosuvastatin groups completed 6 months of intervention. Remaining subjects discontinued intervention prematurely for being not interested in continuing or relocated. None of the subjects had adverse drug reactions or intolerance to medication. Consort diagram illustrates details of randomization as per strobe RCT guidelines [http://www.consort-statement.org/-as Figure 1].

In all three groups age, BMI, body fat percent, HDL-C and TG were similar at baseline (P > 0.1). Serum 25OHD concentrations, TC, LDL-cholesterol were also similar in Rosuvastatin and Atorvastatin groups. However, control group comprising of healthy subjects showed significantly lower values of TC and LDL-Cholesterol (P < 0.01) and higher values of 25OHD than the intervention groups (P < 0.01) as shown in Table 1.

In the control group, none of the measured parameters (25OHD and lipids) changed significantly over 6 months, indicating the minimal influence of seasonal change on their lifestyle patterns. In both groups receiving statins, TC, LDL-C and LDL to HDL ratio reduced significantly when compared with the control group. However, reduction in LDL-C was significantly lower with Rosuvastatin than Atorvastatin (P < 0.05). TG was unaltered in both groups while HDL-C reduced significantly in the Rosuvastatin group. In the group on Atorvastatin, comparison of parameters at baseline and end of intervention showed that there was a significant reduction (P < 0.05) in 25OHD. In the Rosuvastatin group, 25OHD concentrations did not change significantly at the end line [Table 2]. The change in 25OHD concentrations from baseline to end line was significantly different between Atorvastatin and Rosuvastatin group (P < 0.05).

Pearson’s correlation to assess the impact of mean 25OHD concentrations (mean of baseline and end line 25OHD) on LDL-C concentration reduction in each group showed that mean 25OHD concentrations were significantly positively correlated with an absolute reduction in LDL-C concentrations in the Atorvastatin group (r = 0.413). Rosuvastatin group did not show any significant correlation [Table 3 and Figure 2].

**Table 1: Baseline parameters of control and intervention groups**

| Parameters         | Controls (n=50) | Atorvastatin (n=52) | Rosuvastatin (n=52) |
|--------------------|----------------|---------------------|---------------------|
| Age (years)        | 46.4±12.6      | 45.5±13.2           | 49.1±6.7            |
| BMI (kg/m\(^2\))  | 26.2±4.3       | 25.1±3.4            | 25.2±2.7            |
| Body fat percent   | 29.3±12.7      | 28.7±10.3           | 29.2±10.8           |
| 25OHD (ng/ml)      | 26.5±5.5\(\text{a,b}\) | 20.4±7.1            | 17.6±9.5            |
| TC (mg/dl)         | 173.9±30.2\(\text{a,b}\) | 224.8±22.9          | 229.8±24.2          |
| HDL-C (mg/dl)      | 38.6±8.4       | 39.4±8.6            | 38.9±7              |
| LDL-C (mg/dl)      | 111.2±24.2\(\text{a,b}\) | 155.2±17.2          | 161.1±20            |
| TG (mg/dl)         | 120.8±57.1     | 150.9±67.8          | 148.8±51.6          |
| LDL-C to HDL-C ratio | 3.0±0.91\(\text{a,b}\) | 4.1±0.89            | 4.2±0.81            |

\(\text{a,b}\) Significant (P<0.05) difference between control and Atorvastatin group,
\(\text{a}\)Significant (P<0.05) difference between the control and Rosuvastatin group.
LDL-C=Low-density lipoprotein cholesterol, HDL-C=High-density lipoprotein cholesterol, TG=Triglyceride, TC=Total cholesterol, 25OHD=25-hydroxy-Vitamin-D, BMI=Body mass index

Discussion

We found that the group of subjects who were on Atorvastatin showed a small but significant reduction in 25OHD concentrations while the group on Rosuvastatin showed a small insignificant rise at the end line. Atorvastatin is lipophilic, has the larger volume of distribution (381 L) than the hydrophilic Rosuvastatin (134 L)\[20,21\] and thus possibly has a better concentration in skin and subcutaneous tissues where Vitamin D synthesis occurs. Thus, inhibition of cholesterol synthesis and substrate depletion in the skin is possibly higher with Atorvastatin than Rosuvastatin leading to reduced synthesis of Vitamin D. Another reason could be that Atorvastatin is a more potent inducer of the CYP3A4 than Rosuvastatin which is responsible for the catabolism of 25OHD by 24 and 25 hydroxylation producing inactive metabolites.\[22\]

Although statins are known to deplete the substrate for Vitamin D synthesis and increase catabolism of Vitamin D, most studies have reported either no change or increased concentrations of 25OHD after treatment with statins.\[23\] In studies by Anagnostis et al., Demir et al. and Thabit et al., no change was observed in
25OHD concentrations with Atorvastatin, Rosuvastatin or Simvastatin.\[19,24,25\] However, earlier studies also report that Rosuvastatin treatment improved the serum concentrations of 25OHD.\[26,27\] Further, Sathyapalan et al. and Pérez-Castrillón et al. have shown that, with Atorvastatin treatment, there was a significant rise in 25OHD concentrations.\[28,29\] One of the possible explanations for the above results, which are contradictory to our study results, could be the higher dietary Vitamin D intake and increased absorption in their study subjects who received statins. Studies have shown an increase in the absorption of cholesterol by statins.\[30,31\]

There is an increase in the absorption of cholesterol with statin-related inhibition of cholesterol synthesis by up-regulation of membrane transporters.\[30,31\] Membrane transporters such as the Scavenger Receptor B-I (SR-B1), are responsible for the intestinal cholesterol absorption.\[32\] Recent research has shown that intestinal absorption of vitamin D occurs by the same membrane transporters. Transfection of mouse intestinal explants through SR-B1, CD36 and NPC1L1 enhanced 25(OH)D uptake significantly and reduced by the addition of SRB1, CD36 else NPC1L1 inhibitors, respectively.\[33\] When drugs reducing the absorption of cholesterol were added to statin therapy, rise in 25OHD was not observed.\[34\]

Thus, in populations where there is increased dietary intake of Vitamin D, statin treatment possibly increases 25OHD concentrations by improved intestinal absorption. In our study population, dietary Vitamin D was almost negligible\[35\] and we have used minimum doses of statins, thus showing results which were different from other existing studies. In an Indian cross-sectional study, it has been shown that statin therapy is associated with lower 25OHD concentrations.\[23\]

Our study also showed that 25OHD concentrations significantly influenced the reduction in TC and LDL-cholesterol concentrations in Atorvastatin group but not so in the Rosuvastatin group. Similar observations have been recorded in another study where plasma 25OHD concentrations above 30nmol/L were required.
for effective action of Atorvastatin,[29] 1,25 (OH)₂D is a known to induce CYP3A4 enzyme, thus increasing the metabolism of Atorvastatin into its active metabolite. As Rosuvastatin is not metabolized by CYP3A4 enzyme, it is less likely to be influenced by 25OHD concentrations.[4]

One of the strengths of our study is measuring the effect of statins on Vitamin D status of newly diagnosed dyslipidemic subjects, there are very few studies in this area in the Indian context. Our limitations are that we have used a minimum dose of statins, assessed only male subjects and had an open-label design. We also had around 15% dropouts in the study. A study with larger sample size and higher statin doses may throw more light on this important issue. Similarly, results need to be assessed in women as well.

**Conclusions**

There are possible metabolic relationships between statins and 25(OH)D, and thus, statin treatment may deplete 25OHD concentrations in populations where dietary Vitamin D intake is already poor. Therefore, it is essential to maintain optimum concentrations of 25(OH)D in patients who receive Atorvastatin to obtain a satisfactory reduction in lipid concentrations.

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**Conflicts of interest**

There are no conflicts of interest.

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