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Original Research Article

A Study of Effect of Rosuvastatin on Vitamin D Levels in Patients with Hypertension, Diabetes Mellitus and Coronary Artery Disease

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ABSTRACT

Background: vitamin D deficiency has emerged as a modifiable risk factor for adverse cardiovascular events. Statins improves cardiovascular outcomes through many different mechanisms among which their effect on vitamin D metabolism has been a matter of debate recently.
Aim: To study the effect of Rosuvastatin on serum 25 OH vitamin D levels and to compare the effect of different doses (10 and 20 mg) of rosuvastatin on 25 OH vitamin D levels.
Materials and methods: The study included 80 male patients of diabetes mellitus, hypertension and coronary artery disease between 30 - 50 yrs of age, who were divided into two groups (A & B) randomly with 40 patients in each group. Group A and B were given 10 mg/day and 20 mg/day Rosuvastatin respectively for 8 weeks. Serum 25 OH vitamin D levels were measured at the baseline and after 8 weeks of therapy.
Result: Hypovitaminosis D was highly prevalent in the study group with 97.5 % subjects having subnormal 25 OH vitamin D levels (<30 ng/ml). The mean 25 OH vitamin D levels at the baseline and after 8 weeks in group A were 12.65±7.87 and 17.38±11.65 ng/ml respectively. The mean 25 OH vitamin D levels at the baseline and after 8 weeks in group B were 11.88±7.22 and 17.00±9.85 ng/ml respectively. Thus the 25 OH vitamin D levels increased by 37.39% (4.73±7.64 ng/ml) after 8 weeks of 10 mg/day rosuvastatin ($p<0.001$) and by 43.09% (5.12±5.53 ng/ml) after 8 weeks of 20 mg/day rosuvastatin ($p<0.001$).

Keywords: 25 OH vitamin D, Rosuvastatin, Diabetes mellitus, Hypertension, Coronary artery disease.

INTRODUCTION

Non-communicable diseases including diabetes mellitus (DM), hypertension (HTN) and coronary artery disease (CAD) are the major cause of morbidity and mortality worldwide. [1] Among the various risk factors for them, the low levels of vitamin D have emerged as a new modifiable risk factor and it has been shown that the severity of vitamin D deficiency correlates directly with the risk of cardiovascular diseases. [2,3]

Statins presently form the mainstay of the pharmacotherapy in the prevention and treatment of cardiovascular diseases. Earlier it was thought that beneficial effects of statins are only due to its cholesterol lowering property but now the evidence is building up that there are many other different mechanisms called as pleiotropic effects through which statins exert their benefits. One of the mechanisms is now thought to be the effect on 25 OH vitamin D metabolism.

In some studies statins have been found to increase serum vitamin D levels. Castrillon et al (2006) demonstrated that atorvastatin raises the vitamin D levels. [4] The effect of rosuvastatin on vitamin D levels had been a matter of discussion in the recent past. Yavuz et al (2009) have demonstrated that rosuvastatin increases both 25 OH vitamin D and 1, 25 OH vitamin D levels. [5] Another study by Ertugrul et al (2011) also demonstrated that rosuvastatin not fluvastatin increases 25 OH vitamin D levels. [6] But Demir et al (2011) compared the effect of atorvastatin and rosuvastatin on vitamin D levels and found no significant effects of either drug on vitamin D levels. [7] So the effect of rosuvastatin on vitamin D levels is controversial.

MATERIALS AND METHODS

The study was conducted in the department of medicine, University college of medical sciences & GTB hospital, Delhi from October 2012 to February 2014 (only during winter months - October to February). The study included 80 statin naïve male patients of DM, HTN & CAD between 30 to 50 years of age, who had any indication for starting stat in therapy. Obese patients (BMI > 30 kg/m^2), patients on drugs known to effect serum vitamin D levels, patients with any other chronic illnesses were excluded from the study. Patients were divided into two groups A & B randomly with 40 patients in each group and were then subjected to anthropometric examination and routine investigations. Group A and B were given 10 mg and 20 mg/day rosuvastatin respectively for 8 weeks. Serum 25 OH vitamin D levels were measured at the baseline and after 8 weeks of therapy using commercially available Diasorin 25 (OH) vitamin D RIA kit.

Statistical analysis: Between the group and within the group variability for group A & B were studied using repeated measure ANOVA followed by Tukey's test at 5 % level of significance. Software SPSS 17.0 was used to analyze the data.

RESULTS

Both groups included in our study were comparable with regard to demographic, anthropometric and baseline laboratory parameters.

Out of 80 subjects in both the groups, 70 (87.5%) were found to be vitamin D deficient (25 OH vit D < 20 ng/ml), 8 (10%) were vitamin D insufficient (25 OH vit D - 20-30 ng/ml) and only 2 (2.5 %) subjects had vitamin D levels in the normal range (25 OH vit D > 30 ng/ml) (fig 1).

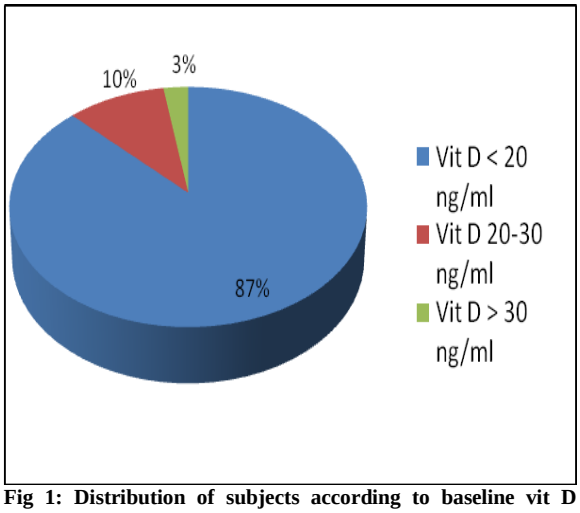

Fig 1: Distribution of subjects according to baseline vit D levels (n = 80)

The mean baseline serum 25 OH vitamin D levels in group A and group B were 12.65±7.87 (2.58-44.27) ng/ml and 11.88±7.22 (2.86-31.49) ng/ml respectively. The values in both the groups were comparable with the difference being statistically insignificant (p=0.650).

Table 1: Vitamin D levels in group A at baseline and after 8 weeks:

Parameters (ng/ml) (mean±SD) (range)	At baseline (o week)	After 8 weeks	Increase (8 wk – o wk) (%)	p-value*
25 OH VIT D	12.65±7.87 (2.58-44.27)	17.38±11.65 (5.85-62.87)	4.73 ± 7.64 (37.39%)	<0.001

*p-value significant <0.05, Data has been described as mean±SD (range)

Table 2: Vitamin D levels in group B at baseline and after 8 weeks

Parameters(ng/ml) (mean±SD) (range)	At baseline (o week)	After 8 weeks	Increase (8 wk - o wk) (%)	p-value*
25 OH Vit D (baseline)	11.88±7.22 (2.86-31.49)	17.00±9.85 (4.57-45.4)	5.12±5.53 (43.09%)	<0.001

*p-value significant <0.05, Data has been described as mean±SD (range)

The mean value of vitamin D in group A increased from 12.65±7.87 ng/ml to 17.38±11.65 ng/ml i.e. increased by 37.39 % after 10 mg/day rosuvastatin therapy. The increase in vitamin D level was statistically highly significant. (P < 0.001) (Table 1).

The mean value of vitamin D in group B increased from 11.88±7.22 ng/ml to 17.00±9.85 ng/ml i.e. increased by 43.09 % after 20 mg/day rosuvastatin therapy. The increase in vitamin D level was statistically highly significant. (p<0.001) (Table 2).

Although the rise in vitamin D levels was more with 20 mg/day Rosuvastatin (43.09%) as compared to 10 mg/day (37.39%), the difference between them was not statistically significant (p=0.768) (table 3, Fig 2).

Table 3: Comparison of increase in vitamin D levels in study groups after 8 weeks of rosuvastatin therapy

	Group A	Group B	p-value*
Increase in 25 OH vit D (8 wk - o wk) (%)	4.73 ± 7.64 (37.39%)	5.12 ± 5.53 (43.09)	0.768

**p-value significant <0.05, Data has been described as mean±SD*

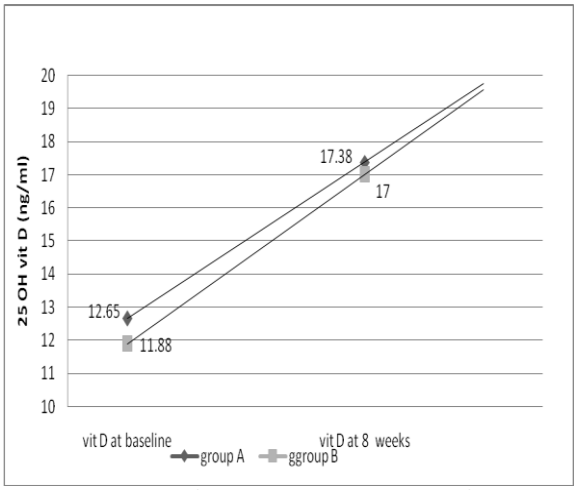

Fig 2: Comparison of vitamin D in study groups after 8 weeks of rosuvastatin therapy

DISCUSSION

We found a strikingly high prevalence of vitamin D deficiency among the study population as 97.5 % of our subjects had vitamin D levels either in insufficient or deficient range. As we included patients with high cardiovascular risk in our study, this high prevalence of vitamin D deficiency strengthens the fact that low levels of vitamin D are associated with increased cardiovascular risk as shown in earlier studies. [2,3]

The results of our study showed a statistically significant rise of 37.39% and 43.09% in serum vitamin D levels after 8 weeks of 10 mg and 20 mg/day rosuvastatin respectively. These results are in concordance with other studies reported in western literature.

Yavuz et al evaluated the effect of rosuvastatin on vitamin D levels in 91 hyperlipidemic patients and found a significant increase in 25 OH vitamin D i.e. from mean 14.0 (range 3.7 - 67) to mean 36.3 (range 3.8 - 117) ng/ml ($p < 0.001$). [5] The same group of investigators (Ertugrul et al (2010)) in STATIN D study also reported a significant increase in 25 OH vitamin D levels from a mean of 11.8 ng/ml to 35.2 ng/ml after 8 weeks therapy with rosuvastatin treatment ($P < 0.001$), whereas no significant change in 25 OH vitamin D was observed with fluvastatin therapy. [6]

The validity of conclusions drawn from study by yavuz et al & Ertugrul et al were seriously doubted by glossman and Blumthaler who argued that claiming or believing in a novel pleiotropic effect of rosuvastatin may be misleading and premature. [8] They argued that UV-B data are missing and rise of 25 OH vitamin D is identical in two studies, although two trials were performed a year apart. Subsequently Demir et al (2012) also reported that neither rosuvastatin nor atorvastatin made significant changes in 25 OH vit D levels at the end of 12 weeks therapy. [7]

Recently Evangelos N. Liberopoulos et al (2013) reported in a study that therapy with combination of simvastatin 10 mg with ezetimibe 10 mg for 3 months showed a 36.7% rise in serum vitamin D levels while simvastatin 40 mg showed a 79.1% increase in vitamin D levels. [9]

our results are also in accordance to study by Makriou et al (2012) who reported that rosuvastatin monotherapy was associated with 53% increase in 25 (OH) vitamin D (from 14.6 to 17.8ng/ml) and rosuvastatin plus micronized fenofibrate & rosuvastatin plus omega 3 fatty acids were associated with increase of 64% (from 14.1 to 18.4 ng/ml) and 61% (from 10.4 to 14.0 ng/ml) respectively. [10]

Thus from the observations of our study we conclude that rosuvastatin therapy significantly increases serum 25 OH vitamin D levels. Several potential mechanisms have been proposed to explain the observed increase in vitamin D concentration after statin therapy. Yavuz et al have hypothesized that some statins may enhance the expressions of cholesterol transporters in the gut leading to increased absorption of vitamin D. [11] Another hypothesis is that rosuvastatin by interfering with the metabolism of vitamin D leads to increase in vitamin D levels vitamin D levels. [11]

Several other potential mechanisms have been proposed as used by Makriou et al to explain the observed increase in 25 (OH) Vitamin D concentrations after statin therapy. Since the catabolism of both 25 (OH) Vitamin D and statins in liver and intestine is caused by CYP3A4 (along with CYP3A5), it might lead to a competition in this common metabolic pathway that could be the cause for the increased 25 (OH) Vitamin D levels observed in patients taking statins. [10] The other proposed mechanism is that the inhibition of 3-hydroxy-3methylglutaryl coenzyme A reductase by statins leads to increase in the levels of 7-hydrocholesterol which is the common precursor of cholesterol and 25 (OH) vitamin D thus providing an abundance of substrate for the synthesis of 25 (OH) Vitamin D by ultraviolet radiation of the skin. [12]

Comparison of effect of different doses of rosuvastatin on 25 OH vitamin D levels:

In our study although the mean rise in serum vitamin D levels was higher with 20 mg/day rosuvastatin therapy as compared to 10 mg/day, the difference was statistically not significant (p=0.768).

This observation suggests that the incremental response of 25 OH vitamin D levels to rosuvastatin does not increase much with increase in the dose of rosuvastatin. Its clinical implication cannot be precisely commented upon, but this observation suggests that rosuvastatin in dose of 10 mg/day is comparable to dose of 20 mg/day in terms of increasing vitamin D levels. The mean levels of vitamin D after 8 weeks of both forms of rosuvastatin therapy (10 mg & 20 mg/day) increased, but still remained in deficient range i.e. 17.38 ±11.65 & 17.00 ±9.85 ng/ml respectively. It indicates that rosuvastatin therapy alone may not be sufficient to increase vitamin D to satisfactory levels. Other adjuvant therapy like vitamin D itself may be considered for this purpose. Although addition of fenofibrate or omega 3 fatty acids to rosuvastatin also has been reported to cause further increase in vitamin D levels than rosuvastatin alone, [10] but concerns about toxicity or higher cost also should be taken into account. From our study it cannot be commented that how much rise in vitamin D levels will occur with lower dose of rosuvastatin (<10 mg/day). However further studies are required before deriving any definite conclusion.

CONCLUSION

Rosuvastatin mono therapy significantly increases vitamin D levels. Lower dose (10 mg/day) may be equally efficacious to higher dose (20 mg/day) in increasing vitamin D levels. Although rosuvastatin can increase vitamin D levels, it alone may not be sufficient enough to increase vitamin D levels to normal range in vitamin D deficient population.

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