**Introduction**

Nonalcoholic fatty liver disease (NAFLD) is a constellation of conditions histologically characterized by macrovesicular hepatic steatosis in individuals who do not consume alcohol in amounts generally considered to be harmful to the liver.¹ It is a broad term consisting of patients with simple steatosis or nonalcoholic fatty liver (NAFL) at one end of the spectrum, nonalcoholic steatohepatitis (NASH), NASH-related cirrhosis, and hepatocellular carcinoma (HCC) at the other end.²⁻⁴ Even though NAFLD is considered a hepatic manifestation of metabolic syndrome (MS), pathogenesis of NAFLD is still ill understood with involvement of various environmental and genetic factors in the pathogenesis. Recent evidence also points to the role of small intestinal bacterial overgrowth, altered gut microbiota, and endotoxemia in patients with NAFLD.⁵,⁶

Vitamin D is a lipophilic molecule essential to maintain calcium and phosphate balance and osteometabolic system regulation. In adult population, the prevalence of hypovitaminosis D ranges from 5% to 30%,⁷ but it reaches a peak of 75% in patients with MS.⁸ Vitamin D-deficient individuals are more likely to develop alterations in glucose metabolism, such as impaired glucose tolerance, MS, and type 2 diabetes mellitus (DM).⁹ Low serum vitamin D has been shown to predispose to intrahepatic lipid accumulation leading to NAFLD, and vitamin D is capable of reducing free fatty acid (FFA) induced insulin resistance (IR) both in peripheral tissues and in hepatocytes.¹⁰ Understanding the complex interplay between vitamin D signals and lipid/glucose metabolism and differentiating specific metabolic effects from nonspecific anti-inflammatory properties in fatty liver disease have opened a new therapeutic intervention for patients with NAFLD.

Therapeutic potency of sunlight therapy and vitamin D in an animal model of fatty liver disease has clearly shown benefit.¹¹ Vitamin D substitution thus may represent a simple, cheap, and almost side effect-free candidate approach to reduce the burden of end-stage liver failure and liver cancer in this frequent disease entity for which medical interventions with proven long-term efficacy are still lacking. Till now there is no randomized...
controlled trial of vitamin D supplementation in patients with NAFLD. Hence, we planned to study the efficacy of vitamin D supplementation in patients with NAFLD.

Methods

A total of 81 consecutive patients with NAFLD with normal or raised serum alanine aminotransferase (ALT), attending liver clinic of Postgraduate Institute of Medical Education and Research, Chandigarh, India, were enrolled in the study over a period of 1.5 years, after obtaining an informed consent. The study had the approval of the institute’s ethics committee.

Inclusion criteria for patients with NAFLD included age more than 12 years, nonalcoholic individuals defined as either total abstainers or individuals who consumed less than 20 g of alcohol per day, ultrasound showing features of steatosis, with or without raised ALT (>40 IU/L), and negative viral markers (Hepatitis B surface antigen (HBsAg) and anti-hepatitis C virus (HCV)). Patients with raised ALT in addition had negative autoimmune markers (antinuclear antibody [ANA], anti-smooth muscle antibody [ASMA], anti-liver kidney microsomal antibody [LKM], and anti-mitochondrial antibody [AMA]) and normal ceruloplasmin/positive Kayser–Fleischer (KF) ring with normal iron work up (serum iron, total iron-binding capacity [TIBC], ferritin, and transferrin saturation). Pregnant females, patients with history of drug intake likely to cause NAFLD, patients with jejunoileal bypass or extensive small bowel resection or total parenteral nutrition at the time of liver biopsy, and those with clinical, laboratory, and imaging features of cirrhosis of liver and patients with renal, hepatic, respiratory, or congestive cardiac failure were excluded from the study.

All patients underwent anthropometric measurements including height, weight, body mass index (BMI) (measured as weight in kg divided by height in m²), waist and hip circumference, and waist–hip ratio (WHR). Body weight was measured to the nearest 0.5 kg in erect position without footwear, wearing light indoor clothes. Overweight was defined using Asian criteria as BMI ≥23 but < 25 kg/m², obesity as BMI ≥25 kg/m² but <30 kg/m², and severe obesity as BMI ≥ 30 kg/m².12 Waist circumference in cm was measured midway between lower rib margin and anterior superior iliac spine. Hip circumference was measured in cm at maximum circumference of buttocks and waist–hip ratio was calculated. Waist circumference of ≥90 cm in males and ≥80 cm in females was taken as abnormal as per Asia Pacific criteria.13,14

Blood pressure was measured using a periodically calibrated mercury sphygmomanometer to the nearest 2 mm Hg in sitting position after at least 5 min of rest. Subjects were considered hypertensive if currently receiving antihypertensive medication or else if the blood pressure was consistently ≥130/85 mm Hg.

Blood samples were taken from each subject after an overnight fast and the following tests were done: routine hemogram, liver function tests, coagulogram, fasting blood sugar (by glucose oxidase method), fasting plasma insulin (by ELISA), and lipid profile (total cholesterol, triglyceride, and high-density lipoprotein [HDL] cholesterol) were measured using immunocolorimetric assay; low-density lipoprotein (LDL) cholesterol was calculated using Friedewald equation. IR was calculated using the homeostasis model assessment-IR (HOMA-IR) method using product of fasting insulin (mU/L) and fasting plasma glucose (FPG; mg/dL) divided by 405, previously validated against the hyperinsulinemic euglycemic clamp.15 An absolute value of HOMA-IR ≥1.64 was taken as abnormal.16

MS was defined as per the National Cholesterol Education Program—Adult treatment panel III criteria17 with waist circumference modified as per the Asia Pacific criteria.13 Three of the following five criteria had to be satisfied for a diagnosis of MS.

1. Abdominal obesity: Waist circumference ≥ 90 cm in males and ≥80 cm in female (Asian-specific cut-offs).
2. Blood pressure ≥130/85 mm Hg.
3. A fasting plasma glucose > 110 mg/dL or a diagnosed case of diabetes mellitus.
4. Serum triglycerides ≥ 150 mg/dL.
5. High-density lipoprotein cholesterol <40 mg/dL in males and <50 mg/dL in females.

All patients were subjected to an ultrasound examination of abdomen and liver stiffness measurement (LSM) was done using transient elastography by Fibroscan machine (Echosens, Paris, France) using medium-sized probe according to the instructions and training provided by the manufacturer. Measurements were performed on the right lobe of the liver through intercostal spaces with the patient lying supine and the right arm kept in maximal abduction. The median value of 10 successful acquisitions was recorded. Evaluation was considered valid if at least 10 successful acquisitions could be obtained with a success rate of more than 60% and interquartile range between the readings less than 30% of the median value. The liver stiffness was expressed in kilo Pascals (kPa). Liver stiffness measurement of >7 kPa was graded as significant fibrosis (≥F2) and >8.7 as advanced fibrosis (≥F3).18

Serum 25(OH) vitamin D levels were measured in all patients by a validated colorimetric method on sera frozen immediately after separation and stored at –20°C for 6 months. Patients were classified as vitamin D deficient if 25(OH) D3 level was <32 ng/mL.19

Patients with NAFLD and vitamin D deficiency were randomized into two groups; group 1 (n = 51) received the standard medical treatment (SMT) with lifestyle modifications and a single injection of vitamin D (600 000 U) given intramuscularly (SMT + vitamin D). Patients in group 2 (n = 30) received only lifestyle modifications as treatment (SMT) for 6 months. Lifestyle modifications in both the groups included moderate-to-vigorous exercise in the form of brisk walking, jogging, swimming, cycling, etc. for 45–60 min at least 5 days per week in all patients and calorie reduction (1000–1200 kcal/day for overweight women and 1200–1600 kcal/day for overweight men and heavier or more active women) in overweight and obese subjects. Overweight and obese patients in both the groups were advised on 5–10% of weight reduction in 6 months from baseline using the lifestyle modifications. Both the groups were compared at baseline and at 6 months. The primary objective of the study was to assess the improvement in IR and serum ALT levels (in patients with raised ALT). Serum levels of adiponectin and tumor necrosis factor-α (TNF-α) were assessed using the immunocolorimetric assay only in the SMT + vitamin D group, which constituted the secondary objective of this study.

Statistical methods. Statistical analyses were performed using a statistical software package (Stata 9.2 for Windows; Stata...
Corporation, College Station, TX, USA). Continuous variables were summarized as mean ± SD or median (range) and categorical variables as proportions, n (%). Prevalence of vitamin D deficiency in patients with NAFLD was calculated with 95% confidence intervals. Comparison of parameters pre- and post-vitamin D supplementation in patients with NAFLD was done by paired t-test and Wilcoxon signed rank test. A P-value of <0.05 was considered statistically significant.

Results

Of the 81 subjects with NAFLD, 51 patients were randomized to SMT + vitamin D and 30 patients to only SMT as defined in the methodology. The two treatment groups were comparable at baseline with regard to age, gender, body weight, BMI, and waist circumference (Table 1). Overall, 76 (93%) of 81 patients had low vitamin D levels but the levels were comparable amongst the SMT and SMT + vitamin D groups (vitamin D 12 ± 6 vs 12 ± 4 [ng/dL], P = 0.653). Higher number of (n = 33 [64%]) patients in vitamin D group had elevated ALT as compared with patients in SMT group (n = 14 [46%], P = 0.008). There was no difference in the baseline degree of steatosis (as assessed on ultrasonography [USG]) and stage of hepatic fibrosis (as assessed on fibroscan) amongst the two groups (Table 2). Significant fibrosis was seen in nine (29%) patients of SMT + vitamin D group and six (22%) patients of SMT group.

Table 1 Comparison of demography, anthropometry, and metabolic parameters between vitamin D + SMT and SMT groups

|                      | SMT + vitamin D (n = 51) | SMT (n = 30) | P-value |
|----------------------|--------------------------|--------------|---------|
| Mean age (years)     | 37 ± 10                  | 40 ± 10      | 0.199   |
| Gender               |                          |              |         |
| Male n (%)           | 36 (70)                  | 19 (63)      | 0.332   |
| Female n (%)         | 15 (30)                  | 11 (37)      |         |
| Mean weight (kg)     | 79 ± 17                  | 73 ± 11      | 0.120   |
| Mean BMI (kg/m²)     | 28 ± 6                   | 27 ± 4       | 0.275   |
| Mean waist circumference (cm) | 98 ± 8 | 95 ± 8 | 0.159 |
| Mean systolic BP (mm Hg) | 131 ± 13 | 129 ± 12 | 0.531 |
| Mean diastolic BP (mm Hg) | 84 ± 8     | 85 ± 9     | 0.685   |
| Hypertension n (%)   | 17 (33)                  | 6 (20)       | 0.168   |
| Mean fasting blood sugar (mg/dL) | 100 ± 16 | 102 ± 27 | 0.712 |
| Diabetes mellitus n (%) | 7 (13)                 | 6 (20)       | 0.536   |
| Mean fasting insulin (mU/L) | 11 ± 8       | 7 ± 5       | 0.340   |
| Mean HOMA-IR         | 2.7 ± 2.1                | 1.8 ± 1.6    | 0.056   |
| Mean total cholesterol (mg/dL) | 200 ± 48 | 196 ± 45 | 0.687 |
| Mean triglyceride (mg/dL) | 167 ± 87     | 164 ± 76     | 0.858   |
| High triglyceride n (%) | 25 (52)             | 16 (53)      | 1.0     |
| Mean HDL (mg/dL)     | 45 ± 13                 | 44 ± 10      | 0.754   |
| Low HDL n (%)        | 25 (52)                 | 16 (53)      | 1.0     |
| Mean LDL (mg/dL)     | 117 ± 47                | 128 ± 57     | 0.326   |
| Metabolic syndrome n (%) | 28 (54)         | 16 (53)      | 1.0     |

Data are presented as mean ± SD or n (%).

Table 2 Comparison of serum ALT, cytokines, vitamin D levels, imaging, and transient elastography results between vitamin D + SMT and SMT groups

|                      | SMT + vitamin D (n = 51) | SMT (n = 30) | P-value |
|----------------------|--------------------------|--------------|---------|
| Mean ALT (IU/L)      | 87 ± 48                  | 64 ± 35      | 0.019   |
| High ALT n (%)       | 33 (64)                  | 14 (46)      | 0.008   |
| Steatosis on ultrasound |                        |              |         |
| Mild n (%)           | 21 (41)                  | 18 (60)      | 0.221   |
| Moderate n (%)       | 25 (49)                  | 9 (30)       |         |
| Severe n (%)         | 5 (9)                    | 3 (10)       |         |
| Mean liver stiffness measurement (kPa) | 7 ± 4 | 6 ± 4 | 0.415 |
| Fibrosis on transient elastography |          |              |         |
| Significant (≥F2) n (%) | 9 (29)                | 6 (22)       | 0.749   |
| Advanced (≥F3) n (%)  | 4 (16)                   | 2 (7)        | 0.402   |
| Mean vitamin D levels (ng/dL) | 12.8 ± 6.4 | 12.3 ± 4.8 | 0.653 |

Data are presented as mean ± SD or n (%).

ALT, alanine aminotransferase; SMT, standard medical treatment.

fibrosis was seen in four (16%) and two (7%) of the patients in two groups, respectively (P = 0.402).

We followed up with both groups and evaluated the change in various parameters at 6 months (Table 3). There was no change in BMI in both groups at 6 months (BMI: 28.9 ± 6.5 and 28.4 ± 6.3 [kg/m²], P = 0.09 vs 27.4 ± 4.0 and 27.1 ± 4.4 [kg/m²], P = 0.79). A significant improvement in serum levels of ALT was seen in the SMT + vitamin D group when compared with the SMT group at 6 months (ALT: 87 ± 48 and 59 ± 32 [IU/mL], P < 0.001 vs 64 ± 35 and 62 ± 24 [IU/mL], P = 0.70). Of the metabolic parameters assessed, mean insulin levels and HOMA-IR remained unchanged at 6 months in the SMT + vitamin D group whereas there was a significant increase in mean insulin levels and HOMA-IR in the SMT group at 6 months (mean insulin levels: 11 ± 8.7 and 10 ± 7.9 [mU/L], P = 0.13 vs 7.2 ± 5 and 8.7 ± 6.5 [mU/L], P = 0.007; HOMA-IR: 27.2 ± 2.1 and 26.2 ± 2.04, P = 0.16 vs 1.8 ± 1.6 and 2.2 ± 1.8, P = 0.007). Adipocytokines (TNF-α and adiponectin) at baseline and at 6 months were analyzed only in the SMT + vitamin D group. There was a significant increase in the mean serum levels of adiponectin compared with the baseline levels (836 ± 309 and 908 ± 312 [pg/mL], P = 0.018), even though TNF-α levels decreased from the levels, the change was not statistically significant (250 ± 181 and 228 ± 184 [pg/mL], P = 0.16).

Discussion

This study is the first from India to assess the vitamin D status in patients with NAFLD and is the first randomized controlled trial in the world literature to assess the impact of vitamin D supplementation in patients with NAFLD. Our study reports a high prevalence of hypovitaminosis D in patients with NAFLD. In addition, results of our study suggest the therapeutic role of vitamin D in improving the liver enzymes and pro-insulin cytokines in patients with NAFLD.
Table 3 Change in various parameter after 6 months of treatment in vitamin D + SMT and SMT groups

| Characteristic | Baseline (mean ± SD) | At 6 months (mean ± SD) | Paired difference |
|----------------|----------------------|-------------------------|------------------|
|                |                      | Mean ± SD               | t-Value | P-value |
| BMI (kg/m²)    |                      |                        |         |
| SMT + vitamin D (n = 51) | 28.9 ± 6.5           | 28.4 ± 6.3              | 0.54 ± 1.4 | 2.7 | 0.09 |
| SMT (n = 30)   | 27.4 ± 4.0           | 27.1 ± 4.4              | 0.37 ± 1.5 | 1.3 | 0.791 |
| Fasting blood sugar (mg/dL) |                  |                        |         |
| SMT + vitamin D (n = 51) | 100.7 ± 16           | 100.1 ± 9               | 0.58 ± 11.7 | 0.35 | 0.723 |
| SMT (n = 30)   | 102 ± 27             | 99 ± 8                  | 3.35 ± 21 | 0.84 | 0.406 |
| ALT (IU/mL)    |                      |                        |         |
| SMT + vitamin D (n = 51) | 87 ± 48              | 59 ± 32                 | 27.85 ± 49.8 | 3.99 | <0.001 |
| SMT (n = 30)   | 64 ± 35              | 62 ± 24                 | 2.44 ± 34.9 | 0.38 | 0.704 |
| Insulin levels (mU/L) |                  |                        |         |
| SMT + vitamin D (n = 51) | 11 ± 8.7             | 10 ± 7.9                | 0.5 ± 2.3 | 1.52 | 0.135 |
| SMT (n = 30)   | 7.2 ± 5              | 8.7 ± 6.5               | 1.49 ± 2.8 | 2.91 | 0.007 |
| HOMA-IR        |                      |                        |         |
| SMT + vitamin D (n = 51) | 2.7 ± 2.1            | 2.6 ± 2.04              | 0.11 ± 0.5 | 1.42 | 0.162 |
| SMT (n = 30)   | 1.8 ± 1.6            | 2.2 ± 1.8               | 1.49 ± 2.8 | 2.91 | 0.007 |
| TNF-α (pg/mL)  |                      |                        |         |
| SMT + vitamin D (n = 51) | 250 ± 181            | 228 ± 184               | 22.07 ± 112.2 | 1.40 | 0.166 |
| SMT + vitamin D (n = 51) | 836 ± 309            | 908 ± 312               | 71.09 ± 206.6 | 2.45 | 0.018 |

ALT, alanine aminotransferase; BMI, body mass index; HOMA-IR, homeostasis model assessment-insulin resistance; SMT, standard medical treatment; TNF-α, tumor necrosis factor-α.

Vitamin D inadequacy constitutes a largely unrecognized epidemic in many populations worldwide and has been reported in all age groups including healthy children, young adults, middle-aged, and elderly adults.20,21 Vitamin D insufficiency is highly prevalent amongst Indian men and women, with relatively higher prevalence in the latter.22 It is also highly prevalent across all age groups ranging from newborns to postmenopausal women. In three different studies from North India, 96% of neonates,23 91% of healthy school girls,24 and 78% of healthy hospital staff were found to have hypovitaminosis D.25

In view of the bile acid-dependent uptake of vitamin D and its hepatic metabolism, it is reasonable to expect an association between vitamin D status and both cholestatic and non-cholestatic chronic liver disease. Recently, a significant correlation between lower 25(OH) vitamin D levels and an increasing stage of fibrosis and severity of necro-inflammatory activity was observed in a population with genotype 1 chronic hepatitis C.26 Interestingly, reduced 25(OH) vitamin D levels have also been noted in patients with NAFLD. A study by Targher et al.27 found a strong association between vitamin D deficiency and NAFLD with a close association of vitamin D levels with the histological severity of hepatic steatosis, necro-inflammation, and fibrosis. 25(OH) vitamin D levels were inversely associated with NAFLD independent of IR and MS, suggesting that inadequate vitamin D status might contribute to the development and progression of NAFLD.27 These findings were recently confirmed in a study by Manco et al.28 in children with biopsy-proven NAFLD, where low 25(OH) vitamin D levels were associated with increased likelihood of fibrosis and necro-inflammation. A recent study by Jablonski et al.29 found that low serum 25(OH) vitamin D levels were associated with NAFLD, independent of age, gender, race, season of measurement, BMI, history of diabetes, renal disease, peripheral vascular disease, and hypertension. The study also showed that the mean serum 25(OH) vitamin D level was significantly lower in the NAFLD group in comparison to a matched control group (30 ± 7 vs 34 ± 8 ng/mL, P < 0.001). As low vitamin D levels are very common in the general population in India and in the absence of a control group, it may be difficult to implicate the role of vitamin D hypovitaminosis in the pathogenesis of NAFLD as found in the present study.

Bile acids are important in the pathogenesis of NAFLD, as they affect the absorption of dietary lipids and regulate glucose and lipid homeostasis. Bile acids act as ligands for farnesoid X receptor (FXR), which affects multiple pathways of lipid biosynthesis decreasing de novo-lipogenesis. Vitamin D is also known to increase the bile acid absorption.30 Preliminary data suggest that vitamin D treatment in rats increased hepatic portal bile acid concentration and elevated expression of farnesoid X receptor, leading to decreased lipogenesis, thereby preventing the development of NAFLD.31

There is extremely limited evidence that vitamin D replacement provides clinical benefit to the patients with NAFLD and NASH, with most of the available evidence derived from other chronic liver diseases. The only evidence to support the therapeutic role of vitamin D in NAFLD and NASH comes from an animal study and there is no human data to support the role of vitamin D in the treatment of patient with NAFLD. In the only animal study, Nakano et al. investigated the impact of sunlight therapy on the progression of NAFLD in rats.32 In the present study, phototherapy ameliorated IR and hepatic steatosis caused by a choline-deficient and iron-supplemented l-amino acid defined (CDAA) diet. In particular, phototherapy improved histology with regard to hepatocyte apoptosis, inflammation and fibrosis, and increased serum adiponectin levels, and led to a
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reduced hepatic expression of the profibrotic transforming growth factor.  

The results of our study suggest that vitamin D supplementation has a role in the treatment of patients with NAFLD. Vitamin D supplementation, along with lifestyle modifications, were associated with an improvement in serum liver biochemistry when compared with lifestyle modifications alone. There were also a significant increase in adiponectin and a non-significant fall in the serum levels of TNF-α in the SMT + vitamin D group. Although the IR did not change significantly in the SMT + vitamin D group, there was a significant worsening of IR in the SMT group at 6 months. In murine models, high levels of adiponectin have been experimentally shown to decrease necro-inflammation and steatosis in alcoholic and NAFLD, as well as improve IR, suggesting that, in humans, adiponectin may improve hepatic inflammation and hepatic insulin sensitivity. Vaidya et al. showed a positive association between vitamin D concentrations and levels of adiponectin in a large cohort of 1,645 patients. A mechanistic link between oxidants, IR, and TNF-α has been identified in animal models of fatty liver. TNF-α seems to play a key role in the development of IR contributing to the pathogenesis of NASH. Thus, vitamin D supplementation causes improvement of liver biochemistry by improving oxidative stress and preventing cellular damage in patients with NASH. In addition, the decreased production of TNF-α and increasing adiponectin during therapy with vitamin D is expected to improve the underlying IR in patients with this condition.

One of the limitations of our study was that the diagnosis of NAFLD in our patients was based on the presence of hepatic steatosis on ultrasonography and exclusion of other causes of hepatic steatosis and raised ALT without a histological diagnosis. However, in the absence of liver biopsy, the presence of significant fibrosis and the severity of liver disease were evaluated by transient elastography in our patients, which is now an established modality in patients with NAFLD. Next, the dose of vitamin D used has not been standardized and hence adequacy of supplementation cannot be assessed. Even though the number of patients with raised ALT was small in the study, we could demonstrate significant improvement in ALT in the group that was given vitamin D.

In conclusion, our study demonstrates that vitamin D deficiency is common in patients with NAFLD as it is in the general population and vitamin D supplementation leads to a decrease in ALT levels and an increase in pro-insulin adiponectin.

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