Research Article

Cuestiones de Fisioterapia

Medicine

THE DEFICIENCY OF VITAMIN D IS COMMON IN TERTIARY CARE HOSPITAL SUFFICIENTS WITH NONALCOHOLIC FAT LIVER DISEASE, WHICH IS IMPACTED BY HOSPITAL ISSUES

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Abstract

Background: Among the causes of liver disease, non-alcoholic fatty liver disease (NAFLD) is a growing problem. Metabolic syndrome is characterized by fat accumulation in the liver. As an insulin-sensitizing, anti-inflammatory, and antifibrotic compound, vitamin D contributes to NAFLD progression. It is unclear which events caused which events and which events were associated with each other. Methods: In this study, 250 adults with NAFLD who were diagnosed by ultrasound with a Hamaguchi score of 1 were included as subjects. The purpose of this study was to determine serum levels of 25-hydroxyvitamin D [25(OH) D]. Levels of deficiency range from 20 ng/mL to 29 ng/mL, while levels of inadequacy range from 20 to 29 ng/mL. There was an assessment of both the NAFLD Fibrosis Score and the FibroScan. Results: Among the patients, 52.0% were deficient in vitamin D, 28.0% insufficient, and 20.0% sufficient. A higher percentage of those with advanced NAFLD exhibited deficiencies (71.4% compared with 38.2% in Grade 1). Inverse correlation was found between serum 25(OH) D levels and CAP score (r=−0.36) and ALT (r=−0.31). A BMI of 27.5 (an OR of 2.4), metabolic syndrome (an OR of 2.1), and sedentary lifestyle (an OR of 1.8) independently predicted deficiency. Conclusions: Studies have shown that vitamin D deficiency contributes to worsening of hepatic steatosis in patients with NAFLD. Causation should be evaluated in the future, but routine 25(OH) D level screening and lifestyle-optimized vitamin D supplementation may be incorporated into NAFLD management protocols.

Keywords: Non-alcoholic fatty liver disease; NAFLD; vitamin D; 25-hydroxyvitamin D; metabolic syndrome; steatosis; FIB-4.

Introduction

There can be non-alcoholic steatohepatitis, fibrosis, cirrhosis, and hepatocellular carcinomas without alcohol consumption. Globally, NAFLD is the most common chronic liver disease in adults with type 2 diabetes and metabolic syndrome [1,2]. An Indian study sponsored by ICMR estimated the prevalence of NFLD as 38.6% among the urban Indians, and 9.6% among the rural Indians [3].

Among Vitamin D's many effects, synthesis in the skin as a result of ultraviolet B radiation is the major mechanism at work. It has anti-inflammatory, anti-fibrotic, insulin-sensitising and immunomodulatory properties [4].

Although vitamin D deficiency is a paradox because there is much sunlight in India, the prevalence of vitamin D deficiency is high and estimated to be 70-90% among urban people of South Asian decent [5] due to the effect of melanin on the absorption of ultraviolet-B, and the avoidance of sunlight, the lack of vitamin D in food, and the work done indoors. Given the convergence of NAFLD and vitamin D deficiency as two very common diseases with similar metabolic risk factors, it raises the question whether vitamin D deficiency is a co-driving factor of NAFLD progression, or simply a consequence?

Studies have shown that vitamin D contributes to the pathogenesis of NAFLD. As it has been demonstrated, 1,25(OH)2D3 (calcitriol) inhibits fibrosis in the liver by interacting with vitamin D receptors in the stellate cells of the liver [6]. VDR activation decreases the activation and release of inflammatory cytokines in adipose tissue, reducing the accumulation of hepatic lipid associated with free fatty acid overflow in adipose tissue [7]. It has a direct effect on liver lipogenesis and on VLDL catabolism in the liver in the presence of calcitriol [8]. Research based on observational studies has inversely correlated vitamin D supplementation with NAFLD grading or presence [9,10], while RCTs have found the opposite effect. The effects of hypovitaminosis D on adult patients with NAFLD attending a tertiary care hospital were studied during this study, along with the correlation between 25(OH)D levels and markers of hepatic steatosis/fibrosis. Several independent predictors of hypovitaminosis D were identified to help guide clinical care.

2. ASSESSMENT AND METHOD

2.1 The design of the study and the population

Study conducted retrospectively in a tertiary care hospital for 12 months. The adults ≥18 years who were diagnosed with NAFLD by ultrasonography (Hamaguchi grading criteria: Those with Grade 0 steatosis, Grade 1 mild steatosis, Grade 2 moderate steatosis, and Grade 3 severe steatosis were recruited. Exclusion: significant alcohol use (>20/g/day in males and >10/g/day in females), HBsAg or anti-HCV reactive, autoimmune hepatitis, haemochromatosis, steatogenic medications (tamoxifen, amiodarone, methotrexate, corticosteroids), current vitamin D supplementation, or secondary causes of vitamin D deficiency (malabsorption syndromes, renal failure eGFR <30, parathyroid disorders). Sample size: n=250, minimum sample size=196 (based on data published in India on prevalence of vitamin D deficiency=50%, absolute precision=5%, 95% CI).

2.2 Investigations

If you have less than 20ng/mL of 25(OH)D, insufficient between 20-29.9ng/mL, and sufficient greater than 30ng/mL, you should get a serum 25(OH)D test (Roche) ECLIA (deficient if less than 20ng/mL, insufficient between 20-29.9ng/mL, and sufficient if more than 30ng/mL; see Endocrine Society guidelines). Tests include fasting lipid profile, HbA1c, fasting glucose, insulin (HOMA-IR = fasting glucose (mmol/L) / 22.5), liver enzymes (ALT, AST, GGT, ALP), albumin, bilirubin, CBC, serum calcium, phosphorus and PTH (prostate hormone). The criteria of NCEP/ATP III have been adapted for use with Asian Indians: Males must have a waist circumference > 90 cm, and females must have one > 80 cm; Triglycerides must be > 150 mg/dL, and HDL must be > 40 mg/dL (males), or HDL must be > 50 mg/dL (females); Blood pressure must be > 130/85 mmHg; Fasting glucose must be > 100 mg/dL; Three of the five criteria must be met. The NAFLD Fibrosis Score is calculated based on age, AST, platelets and ALT and gives an idea of the severity of fibrosis. We used a subset of 80 fibrosis patients to determine controlled attenuation parameters and liver stiffness.

2.3 Statistical Analysis

SPSS v26. Descriptive statistics. One-way ANOVA / Kruskal-Wallis for continuous variables between

vitamin D categories. Correlation of 25(OH)D with CAP, ALT, HOMA-IR and BMI using Pearson/Spearman correlation. Multivariable binary logistic regression (outcome: vitamin D deficient <20 ng/mL). Adjusted OR (95% CI); p<0.05 significant.

3. RESULTS

3.1 Vitamin D Status and NAFLD Grade

According to the study, serum 25(OH) D levels averaged 18.4 ng/mL (range 4.1–48.6 ng/mL). In 52.0% of the samples (n=130), there was insufficient (n=70) and sufficient (n=50). NAFLD patients with advanced stages of vitamin D deficiency were significantly more likely to be deficient: Grade 1 (n=72): 38.2%; Grade 2 (n=118): 52.5%; Grade 3 (n=60): 71.7% (p0.001). According to Table 1, baseline data were stratified according to vitamin D status.

Table 1. Vitamin D Status and Baseline Characteristics of NAFLD Patients (n=250)

Characteristic	Deficient <20 ng/mL (n=130)	Insufficient 20–29 ng/mL (n=70)	Sufficient ≥30 ng/mL (n=50)	p-value
Years of age (mean + SD)	46.2±11.4	44.8±10.9	43.6±12.1	0.41
N (%) of males	72 (55.4%)	40 (57.1%)	28 (56.0%)	0.97
BMI, kg/m² (mean ±SD)	29.8±4.2	27.6±3.8	25.9±3.4	<0.001
Waist circumference, cm	96.4±9.8	92.1±8.6	88.4±7.9	<0.001
Metabolic syndrome, n (%)	92 (70.8%)	42 (60.0%)	22 (44.0%)	0.003
Type 2 diabetes, n (%)	68 (52.3%)	32 (45.7%)	18 (36.0%)	0.10
HOMA-IR, median (IQR)	4.8 (3.2–7.4)	3.9 (2.6–5.8)	2.8 (2.0–4.2)	<0.001
Serum ALT (U/L), mean	62.4±28.6	48.2±22.4	38.6±19.8	<0.001
NAFLD Grade 3, n (%)	43 (33.1%)	14 (20.0%)	3 (6.0%)	<0.001
FIB-4 >1.30, n (%)	42 (32.3%)	18 (25.7%)	10 (20.0%)	0.16
Sedentary lifestyle, n (%)	98 (75.4%)	46 (65.7%)	26 (52.0%)	0.005
ng/mL of serum 25(OH)D	13.2±3.8	24.2±2.6	36.4±5.2	<0.001

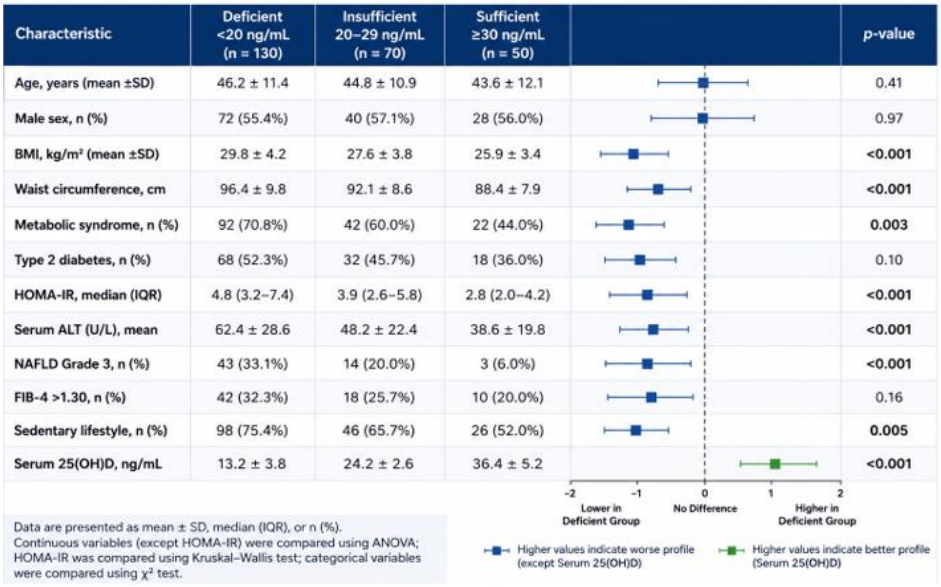


Figure 1: Clinical and Metabolic Characteristics According to Vitamin D Status

3.2 Correlation Analysis and Predictors

In the FibroScan subset (n=80), serum 25(OH)D showed significant inverse correlation with CAP score ($r=-0.36$, $p=0.001$) and LSM ($r=-0.28$, $p=0.012$). In the full cohort, 25(OH)D inversely correlated with ALT ($r=-0.31$, $p<0.001$), HOMA-IR ($r=-0.34$, $p<0.001$), BMI ($r=-0.38$, $p<0.001$), and waist circumference ($r=-0.36$, $p<0.001$). Multivariable predictors of vitamin D deficiency are shown in table 2.

Table 2: Using a multivariable logistic regression model, we examined vitamin D deficiencies in patients with NAFLD (n=250).

Variable	Unadj. OR (95% CI)	p	Adj. OR (95% CI)	p
BMI ≥27.5 kg/m²	3.0 (1.6–5.4)	<0.001	2.4 (1.3–4.6)	0.007
Metabolic syndrome (NCEP-ATP III)	2.6 (1.4–4.8)	0.002	2.1 (1.1–4.0)	0.024
Sedentary lifestyle	2.2 (1.2–4.0)	0.008	1.8 (1.0–3.5)	0.048
HOMA-IR >2.5	2.4 (1.3–4.4)	0.005	1.7 (0.9–3.3)	0.10
NAFLD Grade 3 (vs 1)	2.8 (1.3–6.2)	0.010	1.9 (0.8–4.3)	0.14
Type 2 diabetes	1.9 (1.0–3.4)	0.042	1.4 (0.7–2.7)	0.32

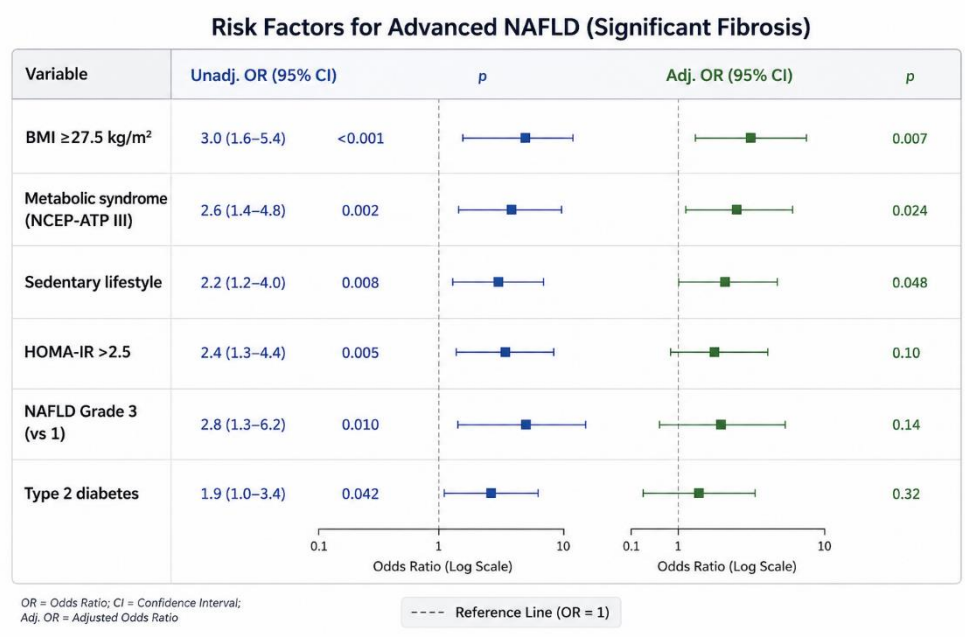
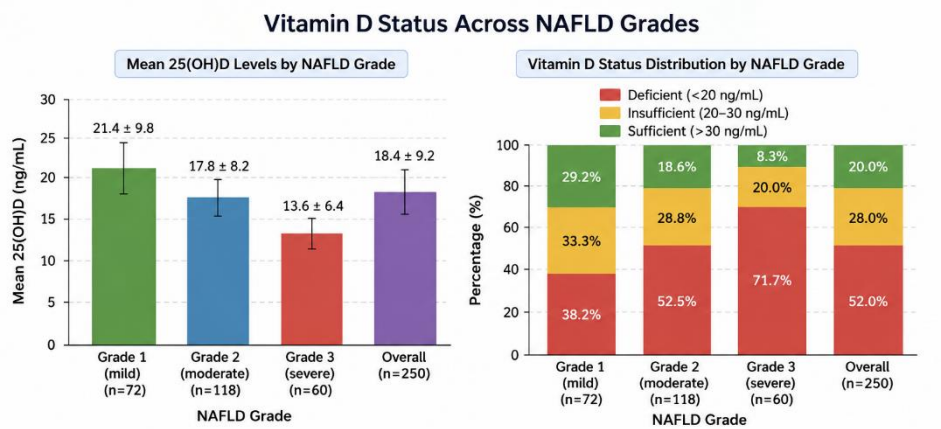


Figure 2: Predictors of Advanced NAFLD: Multivariable Logistic Regression Analysis

Table 3: Levels of serum 25(OH)D and Vitamin D Status by NAFLD Grade (n=250)

NAFLD Grade	n	Mean 25(OH)D (ng/mL, ±SD)	Vitamin D Deficient n (%)	Insufficient n (%)	Sufficient n (%)
Grade 1 (mild)	72	21.4 ± 9.8	27 (38.2%)	24 (33.3%)	21 (29.2%)
Grade 2 (moderate)	118	17.8 ± 8.2	62 (52.5%)	34 (28.8%)	22 (18.6%)
Grade 3 (severe)	60	13.6 ± 6.4	43 (71.7%)	12 (20.0%)	5 (8.3%)

Overall	250	18.4 ± 9.2	130 (52.0%)	70 (28.0%)	50 (20.0%)



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Overall	250	18.4 ± 9.2	130 (52.0%)	70 (28.0%)	50 (20.0%)

25(OH)D: 25-hydroxyvitamin D; SD: Standard Deviation

Figure 3. Distribution of Vitamin D Levels Across NAFLD Grades

Discussion

In the adult population of tertiary care hospital, vitamin D levels were deficient in 52.0% and increased with the progression of NAFLD (38.2% in Grade 1 to 71.7% in Grade 3). These findings have been corroborated by several meta-analyses: The level of 25(OH)D in NAFLD is significantly lower than that in controls [8 - 12] and there is an inverse correlation between severity and 25(OH)D. This worry is compounded in the Indian scenario as the sun-loving South Asians are severely vitamin D deficient owing to the melanin-mediated UVB absorption, sun-avoidance, vegetarianism and the indoor lifestyle pattern [5]. This study revealed that vitamin D status and severity of steatosis as measured by ultrasound were significantly negatively correlated (r = 0.36). The assessment of hepatic steatosis could be done non-invasively with FibroScan, a procedure measuring CAP [12]. As indicated by the inverse relationship between vitamin D deficiency and hepatic fibrosis (r=0.28), this may be because VDR-calcitriol signaling suppresses hepatic stellate cells [6]. However, because of the cross sectional design, it is not possible to attribute causal direction, it can also be argued that the reduction in circulating 25(OH)D is due to the adipocyte sequestration of fat-soluble vitamin D (adipose 'sequestration hypothesis'), without any causal relationship with hepatic steatosis [13].

The most closely independent risk factor for deficiency was BMI ≥27.5 kg/m2 (aOR 2.4): Adipose sequestration mechanism, the more adipose tissue, the less is available in the systemic circulation as vitamin D3 [13]. Also, in accordance with the reduced exposure to sunlight of sedentary indoor activities and the common metabolic risk profile of obesity, insulin resistance and dyslipidaemia, metabolic syndrome (aOR 2.1) and sedentary lifestyle (aOR 1.8) were also independent risk factors.

As a consequence of the findings of this study, two clinical implications are possible. If an adult has NAFL Grade 2-3 steatoses, metabolic syndrome or obesity and is considering weight loss or metabolic status with NAFLD, a routine blood test for 25(OH)D is recommended. In light of the high incidence of 25(OH)D deficiency, as well as the potential for 25(OH)D correction, it would seem that 25(OH)D correction would be beneficial. Second, lifestyle combined vitamin D optimisation (outdoor activity, dietary counselling,

vitamin D supplementation for levels >30 ng/mL) is in line with the holistic metabolic management approach recommended by the guidelines of the AASLD, EASL and INASL [1,14]. No RCTs which specifically target NAFLD are available, but those that are available do not include sufficient baseline measurements of 25(OH)D levels to consider supplementation as a disease modifying intervention.
Limitations: operator variability in the hepatic steatosis grading by ultrasound, no histological NAFLD grading (NASH CRN score) performed due to the cross-sectional design, no control for seasonal variation in 25(OH)D (all seasons included), no inter-group comparison possible due to missing non-NAFLD control group.

5. CONCLUSION

Vitamin D deficiency is also found in a large proportion of adults with NAFLD (52.0%) and is closely related to the advanced steatosis grade, elevated CAP score, insulin resistance and metabolic syndrome (52.0%). These are independent of each other: BMI ≥27.5, metabolic syndrome, and sedentary lifestyle. Regularly assessing 25(OH) D levels and making changes if needed should be incorporated into NAFLD treatment guidelines, until there is confirmation from RCTs of 25(OH) D supplementation as a disease-modifying treatment

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