Original Article

Association of Vitamin D Deficiency with Metabolic Dysfunction-Associated Steatohepatitis (MASH): A Cross-Sectional Analytical Study

Tariq Mohd Khan[1], Deepak Goyal[1], Veeresh Kumar Dhanni[2]

[1]Associate Professor, Department of Medicine, NCRIMS Meerut, Uttar Pradesh, India. [2]Assistant Professor, Department of Medicine, NCRIMS Meerut, Uttar Pradesh, India

Abstract

Background: "Metabolic dysfunction-associated steatohepatitis (MASH)" is a progressive inflammatory disease associated with obesity, insulin resistance, type 2 diabetes mellitus and dyslipidemia. The link between vitamin D and severity of MASH is not fully examined although vitamin D has been recognized to drive hepatic inflammation and progression of fibrosis. This study aimed to assess the prevalence of vitamin D deficiency in patients with MASH and to correlate with the metabolic parameters and the severity of the disease. **Material and Methods:** This was a cross-sectional analytical study conducted at the hospital from January 2024 to December 2025 with the study group consisting of 180 adults age range 18-65 years with diagnosis of MASH. Diagnosis was made based on clinical assessment, biochemical parameters, ultrasonography and the FibroScan results according to the current criteria of MASLD. 25-hydroxyvitamin D [25(OH)D] levels were defined as deficient (< 20 ng/mL), insufficient (20–30 ng/mL), and sufficient (>30 ng/mL). Anthropometric parameters, glycemic profile, lipid profile, liver enzymes, HOMA-IR and liver stiffness index were assessed. Predictors of severe MASH were identified using a multivariate logistic regression analysis. **Results:** 68.9% of the patients showed the presence of vitamin D deficiency, 21.1% insufficiency, and 10.0% sufficiency. Deficient patients had significantly higher BMI (p=0.003), HOMA-IR (p<0.001), ALT (p=0.002), AST (p=0.005), triglycerides (p=0.01), and liver stiffness measurements (p=0.001). Vitamin D deficiency was more prevalent among advanced fibrosis patients as compared to more normal patients (42.7 % vs 16.7 % respectively, p<0.001). Severe MASH (aOR: 95% CI: 1.61–4.98, p<0.001) was independently predicted by vitamin D deficiency. **Conclusion:** Vitamin D deficiency is greatly common in MASH and is an independent predictor for metabolic dysfunction and hepatic inflammation and severity of fibrosis. Treatment and correction of vitamin D deficiency as a routine part of overall care for MASH can be beneficial.

Keywords: Vitamin D deficiency; MASH; Hepatic fibrosis; Insulin resistance.

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Introduction

"Non-alcoholic fatty liver disease" (NAFLD), which is now commonly known as "Metabolic dysfunction-associated steatotic liver disease" (MASLD)) has become the leading cause of chronic liver disease globally, involving almost 25–30% of the adult population, and representing a significant global health challenge.[1,2] MASLD is a spectrum of hepatic disorders, from simple steatosis to metabolic dysfunction-associated steatohepatitis (MASH), progressive fibrosis, cirrhosis, and hepatocellular carcinoma.[3] MASLD is more inflammatory and is experienced as MASH with hepatocyte damage, inflammation, and at varying levels, fibrosis and also MASH is well correlated with obesity, insulin resistance, type 2 diabetes mellitus, dyslipidemia, and metabolic syndrome.[4,5] MASLD or MASH can be seen in countries all over the world, including Asia, which is now becoming very common, along with the worldwide obesity and diabetes epidemic which has been growing at an alarming rate in recent years in India.[6]

MASH is a multifactorial process with intricate relationships between insulin resistance, lipotoxicity, oxidative stress, inflammatory cytokines, mitochondrial dysfunction and genetic susceptibility.[7] Chronic liver inflammation and enhanced HSC activity are involved in the progression of liver fibrosis and deleterious liver outcomes.[8] Of these, vitamin D deficiency has garnered much attention recently as a component of metabolic and nutritional factors that are linked to disease progression, but with several important properties: immunomodulatory, anti-inflammatory and antifibrotic.[9]

Vitamin D is a fat soluble secosteroid hormone, which acts via the vitamin D receptor (VDR), which is highly expressed in hepatocytes, hepatic stellate cells, adipose tissue and immune cells.[10] Experimental studies have shown that the effects of vitamin D on hepatic lipid metabolism, insulin sensitivity, suppression of inflammatory pathways and the inhibition of hepatic fibrogenesis.[11] It was demonstrated that vitamin D

Address for correspondence: Dr. Veeresh Kumar Dhanni, Assistant Professor, Department of Medicine, NCRIMS Meerut, Uttar Pradesh, India. E-mail: drvkdhanni91@gmail.com

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deficiency is associated with greater hepatic fat accumulation, higher transaminases, insulin resistance, and severity of fibrosis in people who have MASLD.[12,13] Moreover, hypocalcaemic 25-hydroxyvitamin D [25(OH)D] serum levels could be linked with worse metabolic profiles and the development of advanced liver disease.[14]

Although strong evidence is building that vitamin D deficiency is associated with MASLD, this association is not well established with regard to severity of MASH disease in the literature.[15] Hepatic steatosis or fibrosis has been negatively correlated with serum vitamin D in several observational studies and meta-analyses but the inverse correlation is no longer significant when adjusted for obesity and metabolic confounders. Several studies and meta-analyses have shown an inverse relationship between serum vitamin D concentrations and hepatic steatosis or fibrosis while others did not find an independent relationship after adjustment for metabolic and obesity-related factors. Furthermore, studies on the Indian population are still scarce as both vitamin D deficient and metabolic liver disease were prevalent in such an area.[2]

The present study was designed to assess the prevalence of vitamin D deficiency in patients with MASH and the correlation with various biochemical parameters, liver enzyme abnormalities, insulin resistance and degree of fibrosis among MASH patients in a tertiary care hospital.

Materials and Methods

Study Design: A cross sectional study and analytical in nature, conducted in General medicine Department of A Tertiary care teaching hospital from January 2024 to December 2025. All 180 adults (18–65 years of age) with metabolic dysfunction-associated steatohepatitis (MASH) were included. Clinical diagnosis, laboratory investigations, abdominal sonography and FibroScan values based on current "MASLD" criteria were used as the basis for the diagnosis.

Patients who had a significant alcohol consumption history, viral hepatitis, autoimmune liver disease, malignancy, pregnancy, chronic kidney disease and previous vitamin D supplementation were excluded from the study.

Data Collection: Detailed demographic and clinical data were documented. Laboratory Assessment: Laboratory assessment was detailed. Body mass index (BMI) and waist circumference were obtained. Fasting blood glucose, HbA1c, fasting insulin, serum 25-hydroxyvitamin D [25(OH)D] levels, lipid profile and liver function tests were made in the blood. Vitamin D levels was determined by chemiluminescence immunoassay, and categorized as deficient (<20 ng/mL), insufficient (20–30 ng/mL) or sufficient (>30 ng/mL). The Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) was used to assess insulin resistance.

Liver Disease Severity Assessment: All patients had abdominal ultrasonography and transient elastography (FibroScan) to assess hepatic steatosis and fibrosis. Fibrosis stage was determined by liver stiffness measurements. Fibscores were calculated based on conventional hepatic fibrosis cutoffs.

Statistical analysis: Data was analysed in SPSS software (v29.0). The means and standard deviations of continuous variables and frequencies and percentages of categorical variables are displayed. Student t-test and chi-square test were used as appropriate in comparing scores of the groups. Independent risk factors for severe MASH were determined using multivariate logistic regression analysis. A p-value <0.05 was considered statistically significant.

Results

Demographic, metabolic, and hepatic data in the study subjects are summarized in table 1. Most of the patients were obese, and had other metabolic comorbidities such as diabetes, dyslipidaemia and elevated liver stiffness measurements. The distribution of serum vitamin D level in MASH patients is shown in Table 2. Vitamin D deficiency was very common – for almost one-third of the study subjects. Metabolic and biochemical parameters are shown to differ significantly between those with a low level of vitamin D and those who do not as seen in Table 3. Vitamin D deficiency was associated with significantly higher BMI, insulin resistance, liver enzyme levels, triglycerides and liver stiffness values in individuals with vitamin D deficiency.

Multivariate logistic regression analysis was performed for predictors of severe MASH as shown in table 4. Multivariate regression analysis showed that vitamin D deficiency was found as an independent factor risking for the development of severe disease, even after the researchers included potential confounding variables such as obesity, diabetes, and insulin resistance. As seen in Graph 1, the liver stiffness factors (LSF) have a negative correlation with serum vitamin D levels. Increasing fibrosis severity was related to progressive decrease of vitamin D levels. Graph 2 shows the HOMA-IR levels for each vitamin D group. The insulin resistance level was the highest in vitamin D deficient patients than in the patients with vitamin D deficiency (less than 12 ng/dl).

Table 1: Baseline Clinical and Metabolic Characteristics of the Study Population (n = 180)

Variable	Value
Age (years), mean ± SD	46.8 ± 10.7
Male sex, n (%)	105 (58.3)
Female sex, n (%)	75 (41.7)
BMI (kg/m²), mean ± SD	30.1 ± 4.6
Waist circumference (cm), mean ± SD	101.4 ± 11.2
Type 2 diabetes mellitus, n (%)	92 (51.1)
Hypertension, n (%)	74 (41.1)
Dyslipidemia, n (%)	101 (56.1)
Fasting glucose (mg/dL), mean ± SD	128.2 ± 26.7
HOMA-IR, mean ± SD	5.2 ± 2.3

ALT (U/L), mean ± SD	70.8 ± 24.1
AST (U/L), mean ± SD	63.2 ± 21.4
Triglycerides (mg/dL), mean ± SD	205.3 ± 44.8
Liver stiffness measurement (kPa), mean ± SD	10.9 ± 4.1

Table 2: Distribution of Vitamin D Status in Patients with MASH

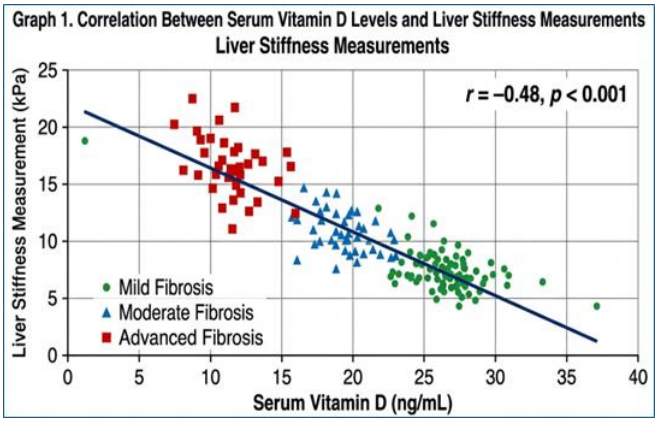
Vitamin D Category	Serum 25(OH)D Level	Frequency (%)
Deficient	<20 ng/mL	124 (68.9)
Insufficient	20–30 ng/mL	38 (21.1)
Sufficient	>30 ng/mL	18 (10.0)

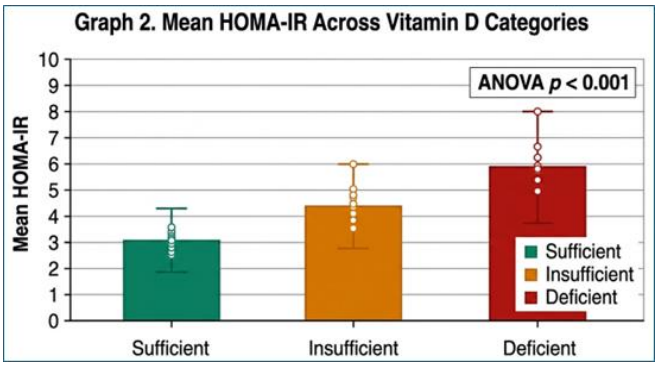
Table 3: Comparison of Biochemical and Hepatic Parameters According to Vitamin D Status

Parameter	Deficient (n=124)	Non-deficient (n=56)	Mean Difference	p-value
BMI (kg/m²)	31.2 ± 4.8	28.1 ± 3.9	3.1	0.003
Fasting glucose (mg/dL)	132.6 ± 28.4	118.5 ± 21.7	14.1	0.011
Fasting insulin (µIU/mL)	24.8 ± 8.6	17.2 ± 6.4	7.6	<0.001
HOMA-IR	5.9 ± 2.1	3.8 ± 1.7	2.1	<0.001
ALT (U/L)	76.4 ± 25.2	58.3 ± 20.4	18.1	0.002
AST (U/L)	68.1 ± 22.5	52.6 ± 17.8	15.5	0.005
Triglycerides (mg/dL)	214.7 ± 46.3	182.4 ± 39.6	32.3	0.010
Liver stiffness (kPa)	12.3 ± 4.5	8.2 ± 2.9	4.1	0.001

Table 4: Multivariate Logistic Regression Analysis for Severe MASH

Variable	Adjusted OR	95% CI	Wald χ^2	p-value
Vitamin D deficiency	2.84	1.61–4.98	14.72	<0.001
BMI >30 kg/m²	1.92	1.08–3.41	4.91	0.026
Type 2 diabetes mellitus	2.17	1.19–3.96	6.42	0.011
HOMA-IR >4	2.63	1.44–4.79	9.66	0.002
Hypertriglyceridemia	1.58	0.89–2.82	2.61	0.104





Discussion

Metabolic dysfunction-associated steatohepatitis (MASH) is considered to be the advanced inflammatory stage of metabolic dysfunction-associated steatotic liver disease (MASLD) and is strongly associated with obesity, insulin resistance, dyslipidemia and type 2 diabetes mellitus.[1,2] Advancements in understanding show that vitamin D deficiency could play a role in hepatic inflammation, metabolic dysfunction, and fibrosis in MASLD/MASH [3,4]. Vitamin D deficiency was often present in the present study, present in 68.9% of patients with MASH, and was independently correlated with higher insulin resistance, liver enzymes, and liver fibrosis stage.

In our study, most patients with MASLD were vitamin D deficient and this is similar to prior research showing that patients with MASLD are significantly more likely to be deficient in vitamin D. As vitamin D plays a central role in lipid pathways, in inflammatory pathways and insulin sensitivity, vitamin D deficiency is often seen to be associated with liver steatosis and metabolic dysfunction, according to Aggeletopoulou et al,[3] Likewise, Fuentes-Barría et al. have pointed to decreased vitamin D activity as a way that can activate the hepatic stellate cell, lead to oxidative stress and help the progression toward fibrosis.[4]

The current study revealed that the patients with vitamin D deficiency showed significant higher body mass index, fasting glucose, fasting insulin, triglycerides and HOMA-IR levels. The results of these findings strengthen the notion of a strong correlation between VDR and impaired metabolism and insulin resistance in MASLD/MASH. Dua et al. have reported that IR is a key mechanism that links hepatic steatosis and inflammatory progression in MASLD.[5] Other researchers, Dungubat et al., also highlighted the modulatory effects of nutritional and metabolic drivers of hepatic inflammation and lipid deposition.[6] Furthermore, our results are consistent with those of Chan et al. who found that obesity and MASLD

components were high risk factors for disease severity during MASLD.[7]

Thus, the current study demonstrated a significantly high ALT and AST with vitamin D Deficiency patients, representing higher hepatocellular injury and inflammatory activity. Lorek et al. proposed that factors such as the environment, metabolism, and nutrients could impact the inflammatory process in MASLD.[8] Basil et al. referred to MASLD as present in the liver and represents the expression of systemic metabolic syndrome involving chronic inflammation and an abnormal regulation of metabolism caused by adiposity.[9] An upregulation of liver enzymes has been observed in vitamin D deficient people, which could then mirror added inflammatory damage to the liver.

An important finding of our study was the significant association between vitamin D deficiency and fibrosis severity. Vitamin D deficiency was associated with significantly higher LSM and higher proportion of advanced fibrosis among patients with low levels. The findings are corroborated with the mechanistic findings indicating that Vitamin D has anti-fibrotic effects by modulating activation of hepatic stellate cells and inflammatory cytokine pathways.[10,11] Another study by Zhao et al. also showed that vitamin D deficiency is related to the dys-regulated immune and metabolic pathways in chronic inflammatory disorders and fibrogenesis.[12]

After controlling for obesity, diabetes mellitus and insulin resistance in the present study, multivariate logistic regression analysis revealed vitamin D deficiency as an independent predictor of severe MASH. Basil et al. presented an innovative meta-analysis recently, showing that there is an association between low levels of vitamin D and the severity of MASLD in patients with T2DM.[13] Barchetta et al., also noted that the reduction in vitamin D levels could prove to be not just a result of obesity but may play a more active role in the pathogenesis of hepatic steatosis and fibrosis.[14]

There is current therapeutic research investigating the use of vitamin D supplementation and 'nutraceuticals' as treatment for MASLD/MASH. In this regard, Vrentzos et al. emphasized on the prominent role of nutraceutical interventions aimed at addressing metabolic disturbances and inflammatory response in MASLD.[15] Moreover, Martinekova et al. showed that vitamin D can positively affect inflammatory factors and metabolic parameters in chronic liver disease, while the studies on reversing the fibrosis are still pending.[11] Thus, regular screening and correction of Vitamin D deficiency could be a valuable additional therapeutic approach in the management of all cases of MASH.

Limitation: There are some constraints of the present study. Confirming causality between vitamin D deficiency and MASH severity was not possible due to the nature of the study being a single centre cross-sectional study. Liver biopsy, which is the gold standard fibrosis assessment technique was not performed in all patients as this would result in unethical and practical issues and FibroScan was used as a non-invasive technique for this fibrosis assessment. Furthermore, seasonal variation in vitamin D level, dietary intake and sun exposure were not evaluated, and this could have provoked some variation in serum vitamin D levels.

Conclusion

Patients with metabolic dysfunction-associated steatohepatitis (MASH) have a high prevalence of Vitamin D deficiency and Vitamin D deficiency was significantly associated with obesity, insulin resistance, hepatic inflammation and severity of fibrosis. The relationship between low vitamin D and severe MASH disease and advanced hepatic fibrosis was confirmed in the present study, suggesting that vitamin D may play a role in disease course. Periodic vitamin D levels monitoring of patients with MASLD/MASH could be useful to identify high-risk individuals and may be a crucial complementary tool to be included in the management of these patients' metabolic and hepatic disease treatment.

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Conflicts of interest

There are no conflicts of interest.

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