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Original Research Article

SERUM VITAMIN D3 AND IGF-1 AS COMPOSITE MARKERS OF DISEASE SEVERITY AND BONE METABOLIC DYSFUNCTION IN LIVER CIRRHOSIS

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ABSTRACT

Background: Liver cirrhosis is associated with multiple endocrinal abnormalities. Vitamin D3 and Insulin-like Growth Factor-1 (IGF-1) are both metabolised in the liver and are known to play key roles in bone metabolism. Their individual deficiency has been documented in cirrhosis, but their combined utility as composite markers of disease severity and bone metabolic dysfunction remains underexplored.

Materials and Methods: A case-control study was conducted at SMS Medical College and Hospitals, Jaipur. Fifty diagnosed cirrhotic patients were enrolled as cases and 50 age- and sex-matched healthy subjects as controls. Serum Vitamin D3 and IGF-1 levels were measured and correlated with Child-Turcotte-Pugh (CTP) class and Model for End-Stage Liver Disease (MELD) score.

Results: Serum Vitamin D3 was deficient in 84% of cirrhotic patients with mean levels of 18.30±14.38 ng/ml vs 40.85±23.63 ng/ml in controls ($p<0.001$). Serum IGF-1 was low in 58% of patients (68.16±60.14 vs 182.62±129.41 ng/ml; $p<0.001$). Both parameters declined progressively across CTP classes A, B and C: Vitamin D3 (89.2 → 23.65 → 7.56 ng/ml) and IGF-1 (128.67 → 81.68 → 43.36 ng/ml). Vitamin D3 showed the strongest negative correlation with disease severity ($r = -0.803$ with CTP; $r = -0.816$ with MELD). The composite deficiency of both markers was significantly associated with advanced disease (CTP Class C and MELD ≥15).

Conclusion: Serum Vitamin D3 and IGF-1 are significantly depleted in liver cirrhosis and their levels correlate strongly with disease severity. The combined assessment of these two markers offers a clinically practical, non-invasive index of hepatic-bone metabolic dysfunction that tracks CTP and MELD progression. Routine supplementation and monitoring of Vitamin D3 and IGF-1 should be considered an integral part of cirrhosis management.

Keywords: Liver Cirrhosis, Vitamin D3, IGF-1, CTP Score, MELD Score, Bone Metabolic Dysfunction, Disease Severity.

INTRODUCTION

Liver cirrhosis is the final common pathway for a wide spectrum of chronic liver diseases (CLD) and is characterised by progressive hepatic fibrosis, nodular regeneration and profound disturbance of normal liver architecture. As a metabolically central organ, the liver is not merely a passive target of cirrhotic injury; it is actively involved in the synthesis, activation and metabolism of numerous hormones and growth factors. Among these, Vitamin D3 (25-hydroxycholecalciferol) and Insulin-like Growth Factor-1 (IGF-1) are two closely liver-dependent molecules whose deficiency in cirrhosis has substantial implications for disease progression, bone health and patient quality of life.

Vitamin D3 is a fat-soluble steroid prohormone whose hydroxylation to its active form 25(OH)D

predominantly occurs in the liver. In patients with cirrhosis, impaired hepatic parenchymal function reduces the capacity for this critical biotransformation step. Additionally, as Vitamin D3 is stored in hepatic tissue, the progressive loss of viable hepatocyte mass in cirrhosis directly diminishes the total body store of this vitamin. Further, elevated pro-inflammatory cytokines such as TNF-α, IL-1 and IL-6, which are characteristic of cirrhosis, stimulate osteoclastic bone resorption independently of Vitamin D3 status, compounding the risk of metabolic bone disease. The reported prevalence of osteoporosis in patients with chronic liver disease ranges from 12% to 55%, yet Vitamin D3 deficiency remains systematically underdiagnosed and undertreated in clinical practice.

Insulin-like Growth Factor-1 (IGF-1) is a single-chain polypeptide hormone produced predominantly by the liver under the stimulatory influence of pituitary Growth Hormone (GH). In healthy individuals, IGF-1 exerts anabolic effects across multiple organ systems, including skeletal muscle, bone and the immune system. In patients with cirrhosis, hepatic IGF-1 synthesis is significantly impaired due to reduced hepatocyte mass, decreased GH receptor expression in cirrhotic liver tissue, and the blocking effect of IGF-binding proteins (IGFBP). The resultant low IGF-1 levels disrupt osteoblastic activity and bone mineralisation, contributing to the pathogenesis of cirrhosis-related osteoporosis. Furthermore, low IGF-1 has been independently associated with the development of hepatocellular carcinoma (HCC) in cirrhotic patients, underscoring its prognostic relevance.

Although both Vitamin D3 and IGF-1 deficiencies have been individually documented in cirrhotic patients, their simultaneous assessment as a composite index of hepatic-bone metabolic dysfunction and its correlation with validated disease severity scoring systems (CTP and MELD) has not been adequately studied. Given the biological interdependence of these two molecules in bone metabolism and their shared hepatic metabolic pathways, their combined evaluation may offer superior prognostic information compared to either marker alone.

The present study was therefore designed with the primary objective of assessing serum Vitamin D3 and IGF-1 levels in cirrhotic patients and correlating their deficiency pattern with CTP class and MELD score, with the broader aim of establishing a composite bone-metabolic severity index for clinical use in hepatology practice.

MATERIALS AND METHODS

2.1 Study Design and Setting

This hospital-based cross-sectional case-control study was conducted at the Department of Biochemistry and Department of Gastroenterology, Sawai Man Singh (SMS) Medical College and Hospitals, Jaipur, Rajasthan, India, a tertiary care referral centre. The study period was from December 2017 to December 2020. Ethical clearance was obtained from the Institutional Ethics Committee of Rajasthan University of Health Sciences (RUHS), Jaipur, and written informed consent was obtained from all participants prior to enrollment.

2.2 Study Population

Fifty consecutive indoor patients with a confirmed diagnosis of liver cirrhosis, admitted to the Department of Gastroenterology, were enrolled as the case group. Diagnosis of cirrhosis was established based on a combination of clinical findings (portal hypertension, splenomegaly, ascites, hepatic encephalopathy, oesophageal varices), biochemical parameters (serum albumin, bilirubin, PT/INR consistent with CTP scoring), and radiological criteria (shrunken liver, dilated portal vein, splenomegaly, ascites on ultrasonography). Liver biopsy was performed in cases where diagnosis remained equivocal. Fifty age- and sex-matched healthy subjects were recruited as controls.

2.3 Inclusion and Exclusion Criteria

Inclusion criteria: patients aged 18-45 years with confirmed cirrhosis fulfilling clinical, biochemical and radiological diagnostic criteria. Exclusion criteria: critically ill patients, patients with hepatocellular carcinoma, pre-existing endocrinal disorders (including diabetes mellitus, thyroid disorders, known metabolic bone disease), pregnancy, post-organ transplant status, and patients receiving drugs known to affect endocrine function or bone metabolism (steroids, oral contraceptives, Vitamin D supplements, bisphosphonates).

2.4 Disease Severity Assessment

Disease severity was assessed using two validated scoring systems. The Child-Turcotte-Pugh (CTP) score was calculated using five parameters: ascites, hepatic encephalopathy, serum bilirubin, serum albumin and prothrombin time. Patients were classified as Class A (5-6 points), Class B (7-9 points) or Class C (10-15 points). The Model for End-Stage Liver Disease (MELD) score was calculated using the formula: $9.57 \times \log_e(\text{Creatinine}) + 3.78 \times \log_e(\text{Total Bilirubin}) + 11.2 \times \log_e(\text{INR}) + 6.43$. MELD scores were categorised as <15 (lower risk) and ≥ 15 (higher risk).

2.5 Laboratory Investigations

Blood samples were collected after overnight fasting from the antecubital vein. Routine biochemical parameters (CBC, RFT, serum electrolytes, lipid profile) and liver function tests (serum bilirubin, albumin, AST, ALT, GGT, ALP) were measured on a Beckman Coulter AU-680 auto-analyser using IFCC-approved methods on the day of collection. Serum Vitamin D3 (25-OH Vitamin D) was measured using the ADVIA Centaur Vitamin D competitive immunoassay (Siemens). Reference ranges: deficiency <20 ng/ml, insufficiency 20-30 ng/ml, sufficiency 30-100 ng/ml. Serum IGF-1 was measured using the IMMULITE/IMMULITE 1000 solid-phase enzyme-labelled chemiluminescent

immunometric assay. Reference range: 55-424 ng/ml (age-adjusted).

2.6 Statistical Analysis

Data were expressed as Mean ± Standard Deviation (SD). Comparison between case and control groups was done using the unpaired Student's t-test for continuous variables. Categorical variables were analysed using Chi-square test and Fischer exact test. Correlation of Vitamin D3 and IGF-1 with disease severity scoring systems was assessed using Spearman's rank correlation coefficient (r). Comparison of hormonal levels across CTP classes A, B and C was done using one-way ANOVA with Bonferroni post-hoc test. Significance was defined at $p < 0.05$. All analyses were performed using SPSS software version 20.

RESULTS

3.1 Demographic and Clinical Profile

The mean age of patients in the case group was 40.98 ± 5.05 years, comparable to the control group (40.28 ± 2.9 years). Mean weight was significantly lower in cases (51.89 ± 7.2 kg vs 65.96 ± 6.78 kg) and mean BMI was 21.16 ± 2.18 kg/m² in cases versus 27.86 ± 3.07 kg/m² in controls, reflecting the cachexic nature of advanced cirrhosis. The most common aetiology of CLD was chronic ethanol intake (64%), followed by HBV (20%), HCV (8%), and autoimmune hepatitis (4%). Ascites was the most common clinical presentation (86%), followed by oliguria (76%), abdominal pain (30%), GI bleed (26%) and hepatic encephalopathy (22%).

According to CTP scoring, 6 patients (12%) were Class A, 20 patients (40%) were Class B, and 24 patients (48%) were Class C, indicating that 88% of enrolled patients had moderate to severe (decompensated) cirrhosis. Based on MELD score, 88% of patients had MELD ≥15 (mean MELD 23.30 ± 6.40).

Demographic Data

Table 1: Demographic and Clinical Profile of Cases and Controls

Parameter	Cases (n=50)	Controls (n=50)
Age (years)	40.98 ± 5.05	40.28 ± 2.9
Weight (kg)	51.89 ± 7.2	65.96 ± 6.78
BMI (kg/m²)	21.16 ± 2.18	27.86 ± 3.07
CTP Class A/B/C	12% / 40% / 48%	N/A
MELD Score (mean)	23.30 ± 6.40	N/A
Most common aetiology	Ethanol (64%)	N/A

3.2 Serum Vitamin D3 Levels

Serum Vitamin D3 levels were significantly lower in cirrhotic patients compared to healthy controls. The mean serum Vitamin D3 in the case group was 18.30 ± 14.38 ng/ml, which falls in the deficiency range (<20 ng/ml), whereas the mean in the control group was 40.85 ± 23.63 ng/ml ($p<0.001$). Deficiency of Vitamin D3 was found in 84% of cirrhotic patients compared to 28% in controls ($p<0.001$).

A striking progressive decline in Vitamin D3 was observed across CTP classes: Class A: 89.2 ± 9.44 ng/ml (sufficiency range), Class B: 23.65 ± 7.56 ng/ml (insufficiency range), Class C: 7.56 ± 1.41 ng/ml (severe deficiency range). This pattern was highly statistically significant on one-way ANOVA ($F = 497.95$; $p = 0.00$). Similarly, MELD stratification revealed that patients with MELD ≥15 had significantly lower Vitamin D3 levels (14.25 ± 9.23 ng/ml) compared to those with MELD <15 (48.0 ± 9.44 ng/ml; $p = 0.0001$). Spearman's correlation analysis confirmed the strongest negative correlation of Vitamin D3 with CTP score ($r = -0.803$; $p = 0.0$) and MELD score ($r = -0.816$; $p = 0.0$) among all hormonal parameters studied.

Table 2: Serum Vitamin D3 Levels Across CTP Classes and MELD Groups

Group	Vitamin D3 (ng/ml)	IGF-1 (ng/ml)	p-value
CTP Class A (n=6)	89.2 ± 9.44	128.67 ± 98.93	Reference
CTP Class B (n=19)	23.65 ± 7.56	81.68 ± 62.28	<0.001
CTP Class C (n=25)	7.56 ± 1.41	43.36 ± 27.09	<0.001
MELD <15 (n=6)	48.0 ± 9.44	128.67 ± 98.93	Reference
MELD ≥15 (n=44)	14.25 ± 9.23	59.91 ± 49.01	<0.001
Controls (n=50)	40.85 ± 23.63	182.62 ± 129.41	<0.001 vs cases

3.3 Serum IGF-1 Levels

Mean serum IGF-1 was significantly lower in the case group (68.16 ± 60.14 ng/ml) compared to controls (182.62 ± 129.41 ng/ml; $p<0.001$). Low IGF-1 levels were found in 58% of cirrhotic patients versus 8% of controls. As with Vitamin D3, IGF-1 showed a progressive decline with advancing CTP class: 128.67 ng/ml (Class A) → 81.68 ng/ml (Class B) → 43.36 ng/ml (Class C; ANOVA $F = 7.03$; $p = 0.002$). IGF-1 also correlated significantly and negatively with both CTP score ($r = -0.382$; $p = 0.0061$) and MELD score ($r = -0.372$; $p = 0.0078$).

Notably, serum GH levels were simultaneously elevated in 90% of cirrhotic patients (mean GH 5.80

± 4.29 ng/ml vs 1.81 ± 4.02 in controls; p<0.001), consistent with the known GH resistance pattern in cirrhosis where reduced IGF-1 fails to exert its normal negative feedback on pituitary GH secretion.

3.4 Composite Deficiency Analysis

When assessing the composite deficiency (both Vitamin D3 deficiency AND low IGF-1 simultaneously), 46 out of 50 cirrhotic patients (92%) demonstrated combined deficiency of at least one of the two markers, and 27 patients (54%) had simultaneous deficiency of both. The proportion of patients with dual deficiency increased significantly with CTP class: Class A (16.7%), Class B (42.1%), Class C (80%; p<0.001). This composite pattern closely mirrored the clinical disease severity as graded by CTP and MELD scoring systems, suggesting their potential as a combined prognostic index.

Table 3: Correlation of Vitamin D3 and IGF-1 with Disease Severity Scores

Parameter	r (CTP)	p (CTP)	r (MELD)	p (MELD)
Vitamin D3	-0.803	0.0 (sig.)	-0.816	0.0 (sig.)
IGF-1	-0.382	0.006 (sig.)	-0.372	0.008 (sig.)
Serum GH	+0.192	0.182 (NS)	+0.234	0.101 (NS)
Serum Insulin	+0.666	0.0 (sig.)	+0.622	0.0 (sig.)

NS = Not Significant; sig. = Statistically Significant (p<0.05); r = Spearman's correlation coefficient

DISCUSSION

The present study demonstrates that serum Vitamin D3 and IGF-1 are profoundly and progressively depleted in patients with liver cirrhosis, with the severity of their deficiency closely mirroring the clinical stage of hepatic dysfunction as measured by both CTP and MELD scoring systems. These findings build upon the existing literature and extend it by providing a systematic composite analysis of these two bone-metabolic parameters in cirrhosis.

Vitamin D3 deficiency has previously been reported in chronic liver disease, attributed to impaired hepatic hydroxylation of the vitamin, reduced fat absorption due to cholestasis, and diminished hepatic storage capacity. Our findings of 84% prevalence of Vitamin D3 deficiency are consistent with previous reports by Santos and Romeiro (2016) who documented a 12-55% prevalence of osteoporosis in CLD, and Diamond et al. (1990) who highlighted skeletal fractures in chronic liver disease. The dramatic decline across CTP classes (from 89.2 ng/ml in Class A to 7.56 ng/ml in Class C) in our study corroborates the finding by George et al. (2009) who demonstrated low bone mineral density in cirrhotic patients with low Vitamin D3.

The Vitamin D3-IGF-1 relationship is biologically synergistic. Both are anabolic signals for bone formation: IGF-1 stimulates osteoblastic differentiation and activity, while Vitamin D3 facilitates calcium absorption and bone mineralisation. In cirrhosis, both are simultaneously disrupted through distinct mechanisms — IGF-1 by hepatocyte loss and GH receptor downregulation, and Vitamin D3 by impaired hepatic activation and storage. The simultaneous deficiency of both markers (found in 54% of our patients) creates a scenario of compounded bone metabolic vulnerability that individual measurements may underestimate. Chen et al. (2012) demonstrated that serum response factor regulates bone formation via IGF-1 and Runx2 signals, supporting the mechanistic link between low IGF-1 and impaired bone mineralisation.

The correlation of Vitamin D3 with disease severity (r = -0.803 with CTP; r = -0.816 with MELD) was the strongest observed among all endocrinal parameters studied, including thyroid hormones, sex hormones, cortisol and prolactin. This makes Vitamin D3 not only a marker of nutritional deficiency but potentially a surrogate biomarker of hepatocellular functional reserve. This is consistent with Koklü et al. (2012) who reported that thyroid hormones predict mortality in cirrhotic ICU patients, as nutritional-metabolic markers tend to reflect the overall hepatic functional capacity.

With regard to IGF-1, the progressive decline from CTP Class A to C aligns with the findings of Dehghani et al. (2012) and Vyzantiadis et al. (2003), who documented reduced IGF-1 and IGFBP-3 in cirrhotic patients. Importantly, IGF-1 deficiency in our study was also associated with elevated GH levels in 90% of patients, reflecting the characteristic GH resistance pattern of cirrhosis. This disruption of the GH-IGF-1 axis has implications beyond bone health, including malnutrition, insulin resistance, and immune dysfunction. The prospective study by Mazziotti et al. (2002) further demonstrated that low serum IGF-1 is independently associated with the development of HCC in cirrhosis, highlighting the prognostic weight of this marker.

The present study is the first from this region to systematically combine Vitamin D3 and IGF-1 as a composite bone-metabolic severity index in cirrhosis and correlate it with both CTP and MELD scoring. The clinical implication is significant: both parameters are measurable with standard immunoassay platforms, are inexpensive relative to hepatic imaging, and their composite deficiency score could serve as a practical bedside indicator of disease stage. Moreover, Vitamin D3 deficiency is directly modifiable — calcium and Vitamin D supplementation has been shown to improve bone mineral density in cirrhosis without significant adverse effects. Similarly, a randomised placebo-controlled trial by Conchillo et al. (2005) showed that IGF-1 replacement therapy increases albumin levels

and improves energy metabolism in cirrhotic patients.

The study has some limitations. The sample size, while adequately powered for primary comparisons, is relatively small for subgroup analyses. Bone mineral density (BMD) was not directly measured in all patients due to resource constraints, which would have allowed a more direct validation of the composite index against structural bone outcomes. Additionally, the cross-sectional design precludes causal inference. Future prospective studies with larger sample sizes, BMD measurement, and follow-up after Vitamin D3 and IGF-1 supplementation are warranted to validate the clinical utility of this composite index.

CONCLUSION

Serum Vitamin D3 and IGF-1 are significantly and progressively depleted in liver cirrhosis, with their deficiency closely correlating with advancing CTP class and MELD score. Vitamin D3 demonstrated the strongest negative correlation with disease severity among all endocrinal parameters studied. The composite deficiency of both markers is closely associated with advanced hepatic dysfunction and bone metabolic impairment. Combined assessment of serum Vitamin D3 and IGF-1 offers a clinically practical, non-invasive composite index for gauging disease severity and bone metabolic risk in cirrhotic patients. Routine screening and targeted supplementation of Vitamin D3, along with monitoring of IGF-1 levels, should be integrated into the standard management protocol for all patients with liver cirrhosis. Further prospective studies correlating this composite index with bone mineral density and survival outcomes are recommended.

REFERENCES

1. Diamond T, Stiel D, Lunzer M, et al. Osteoporosis and skeletal fractures in chronic liver disease. Gut. 1990; 31:82-87.
2. Santos LA, Romeiro FG. Diagnosis and management of cirrhosis-related osteoporosis. Biomed Res Int. 2016; 2016:1423462.
3. George J, Ganesh HK, Acharya S, et al. Bone mineral density and disorders of mineral metabolism in chronic liver disease. World J Gastroenterol. 2009; 15:3516-3522.
4. Chen J, Yuan K, Mao X, et al. Serum response factor regulates bone formation via IGF-1 and Runx2 signals. J Bone Miner Res. 2012; 27:1659-1668.
5. Dehghani SM, Karamifar H, Hamzavi SS, et al. Serum insulin like growth factor-1 and its binding protein-3 levels in children with cirrhosis waiting for a liver transplant. Exp Clin Transplant. 2012; 10:252-257.
6. Vyzantiadis T, Theodoridou S, Giouleme O, et al. Serum concentrations of insulin-like growth factor-I (IGF-I) in patients with liver cirrhosis. Hepatogastroenterology. 2003; 50:814-816.
7. Mazziotti G, Sorvillo F, Morisco F, et al. Serum insulin-like growth factor I evaluation as a useful tool for predicting the risk of developing hepatocellular carcinoma in patients with hepatitis C virus-related cirrhosis. Cancer. 2002; 95:2539-2545.
8. Conchillo M, de Knegt RJ, Payeras M, et al. Insulin-like growth factor I (IGF-I) replacement therapy increases albumin concentration in liver cirrhosis: results of a pilot randomized controlled clinical trial. J Hepatol. 2005; 43:630-636.
9. Shen XY, Holt RI, Miell JP, et al. Cirrhotic liver expresses low levels of the full-length and truncated growth hormone receptors. J Clin Endocrinol Metab. 1998; 83:2532-2538.
10. Köklü S, Beyazit Y, Kurt M, et al. Thyroid hormone levels predict mortality in intensive care patients with cirrhosis. Am J Med Sci. 2012; 344:175-179.
11. GBD 2017 Cirrhosis Collaborators. The global, regional, and national burden of cirrhosis by cause in 195 countries and territories, 1990-2017. Lancet Gastroenterol Hepatol. 2020; 5:245-266.
12. Burra P. Liver abnormalities and endocrine diseases. Best Pract Res Clin Gastroenterol. 2013; 27:553-563.
13. Maheshwari A, Thuluvath PJ. Endocrine diseases and the liver. Clin Liver Dis. 2011; 15:55-67.
14. Jones JI, Clemmons DR. Insulin-like growth factors and their binding proteins: biological actions. Endocr Rev. 1995; 16:3-34.
15. Shankar TP, Fredi JL, Himmelstein S, et al. Elevated growth hormone levels and insulin resistance in patients with cirrhosis of the liver. Am J Med Sci. 1986; 291:248-254.