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Vitamin D's Role in Improving Hypothyroidism-Induced Liver Dysfunction: Insights from Histological and Biochemical Evidence

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ABSTRACT

Background: Hypothyroidism is a common endocrine disorder that significantly impacts liver function, often leading to elevated liver enzymes, oxidative stress, and structural damage. Emerging evidence suggests that vitamin D is crucial in modulating immune responses and metabolic pathways, offering potential therapeutic benefits in managing hypothyroidism-associated liver dysfunction. This study evaluated the efficacy of vitamin D supplementation in alleviating liver dysfunction in hypothyroid patients through biochemical, oxidative, and histological assessments.

Methods: A prospective observational study was conducted at Pak International Medical College, Peshawar, from January 2023 to January 2024. A total of 101 participants were enrolled, including hypothyroid patients with liver dysfunction and healthy controls. Participants were divided into four groups: control, untreated hypothyroid, vitamin D-treated, and combination therapy (vitamin D and levothyroxine). Biochemical parameters, including thyroid and liver function tests, oxidative stress markers, and inflammatory indicators, were measured pre- and post-treatment. Histological liver assessments were performed to evaluate structural changes. Data analysis was conducted using paired t-tests, ANOVA, and Pearson's correlation.

Results: Vitamin D supplementation significantly improved liver function markers (ALT, AST, ALP, and total bilirubin) and reduced oxidative stress and inflammatory markers (MDA, SOD, GPx, CRP, IL-6, and TNF-α) in the treated groups ($p < 0.001$). Histological analysis revealed notable improvements in hepatocyte morphology, reduced Kupffer cell activation, and lower fibrosis scores. The combination therapy group demonstrated the most substantial improvements, highlighting the synergistic effect of vitamin D and levothyroxine. A positive correlation between serum vitamin D levels and liver function restoration was observed.

Conclusion: This study provides compelling evidence for the therapeutic potential of vitamin D in managing hypothyroidism-associated liver dysfunction. By improving liver function, reducing oxidative stress and inflammation, and restoring hepatic structure, vitamin D offers a promising adjunctive therapy. Incorporating vitamin D supplementation into hypothyroidism management protocols could enhance treatment outcomes and minimize liver-related complications.

Keywords: Hypothyroidism, Vitamin D, Liver Dysfunction, Oxidative Stress, Inflammatory Markers, Histological Analysis, Thyroid Hormones, Adjunctive Therapy.

INTRODUCTION

Hypothyroidism, a condition characterized by reduced thyroid hormone production, affects multiple physiological systems and has a profound impact on metabolic and immune functions(1). The thyroid gland plays a critical role in regulating various biochemical processes, including those related to liver function. Liver dysfunction in hypothyroidism is a well-documented consequence of altered metabolic homeostasis, often presenting with elevated liver enzymes, oxidative stress, and structural damage(2). These manifestations highlight the interconnectedness of thyroid and liver physiology, emphasizing the need for comprehensive management strategies for hypothyroid patients(3).

The liver, as a key metabolic organ, is highly susceptible to systemic changes caused by thyroid dysfunction(4). Thyroid hormones regulate crucial hepatic processes, including lipid metabolism, bile acid synthesis, and detoxification pathways. Hypothyroidism disrupts these processes, leading to hepatic steatosis, fibrosis, and inflammation. Additionally, oxidative stress and chronic inflammation,

common in hypothyroidism, exacerbate liver damage. These challenges underline the importance of exploring adjunctive therapies to mitigate liver dysfunction in hypothyroid patients(5-7).

Vitamin D, a fat-soluble secosteroid, has emerged as a vital regulator of immune and metabolic health(8). Beyond its classical role in bone metabolism, vitamin D influences various non-skeletal functions, including immune modulation, anti-inflammatory activity, and antioxidant defense. Growing evidence suggests a link between vitamin D deficiency and thyroid disorders, with vitamin D playing a potential role in improving thyroid function and reducing systemic inflammation. Moreover, vitamin D's hepatoprotective properties make it a promising candidate for managing liver dysfunction in hypothyroid patients(9).

The prevalence of vitamin D deficiency is alarmingly high worldwide, particularly in individuals with chronic conditions such as hypothyroidism. Deficient vitamin D levels further compound the challenges of managing hypothyroidism-associated liver dysfunction. Studies have shown that vitamin D supplementation can improve liver enzyme levels, reduce oxidative stress, and restore hepatic architecture in various liver conditions. However, research specifically focusing on its role in hypothyroidism-related liver dysfunction remains limited, necessitating further exploration.

This study aimed to evaluate the efficacy of vitamin D supplementation in alleviating liver dysfunction associated with hypothyroidism. By assessing biochemical markers, oxidative stress indicators, inflammatory parameters, and histological changes, this research sought to provide comprehensive evidence of vitamin D's therapeutic potential. The study also investigated the synergistic effects of combining vitamin D with conventional thyroid hormone replacement therapy, providing valuable insights into optimizing treatment strategies for hypothyroid patients.

The findings of this study contribute to the growing body of evidence supporting vitamin D's multifaceted role in managing chronic conditions. By addressing the gap in understanding the relationship between vitamin D and hypothyroidism-associated liver dysfunction, this research provides a foundation for developing more effective and targeted treatment protocols. The results underscore the importance of integrating vitamin D supplementation into the clinical management of hypothyroidism, potentially improving patient outcomes and reducing liver-related complications.

METHODOLOGY

This prospective, observational study was conducted at Pak International Medical College, Peshawar, from January 2023 to January 2024. The primary objective was to evaluate the impact of vitamin D supplementation on hypothyroidism-associated liver dysfunction using biochemical and histological evidence. A total of 101 participants were included in the study, recruited from outpatient and inpatient departments through convenience sampling. Strict inclusion and exclusion criteria were applied to maintain a uniform sample population. Participants eligible for inclusion were adults aged 18 to 60 years diagnosed with hypothyroidism, exhibiting elevated thyroid-stimulating hormone (TSH) levels (>4.0 mIU/L), and showing signs of liver dysfunction, such as abnormal liver enzyme levels. Those with baseline serum 25-hydroxyvitamin D [25(OH)D] levels below 50 nmol/L were also eligible. Individuals with chronic liver conditions unrelated to hypothyroidism, long-term steroid use, pregnancy, lactation, severe vitamin D toxicity, malignancies, or autoimmune diseases were excluded.

The participants were divided into four groups. The control group consisted of healthy individuals with no hypothyroidism or liver dysfunction. The second group included untreated hypothyroidism patients who did not receive any intervention. The third group comprised patients who received vitamin D supplementation (4000 IU/day) for 12 months. The fourth group included individuals treated with both vitamin D and levothyroxine to assess the combined effects. Before the intervention, comprehensive baseline data were collected, including demographic details, medical history, lifestyle factors (e.g., smoking and physical activity), and dietary habits. Blood samples were obtained to measure thyroid function markers (TSH, Free T4, and Free T3), liver function tests (ALT, AST, ALP, and total

bilirubin), oxidative stress markers (MDA, SOD, and GPx), inflammatory markers (CRP, IL-6, and TNF-α), and serum vitamin D levels. Liver biopsies were performed in selected cases to analyze hepatocyte morphology, Kupffer cell activation, steatosis, inflammation, and fibrosis.

Participants in the treatment groups received oral vitamin D3 (4000 IU/day), and those in the combination therapy group continued their prescribed levothyroxine dosage alongside vitamin D. Follow-up visits were conducted every three months to monitor adherence and record any side effects. Post-treatment assessments were carried out at the end of 12 months, focusing on biochemical parameters and histological findings. The outcomes were compared to baseline values to determine the efficacy of the interventions.

Ethical approval for the study was obtained from the Institutional Review Board of Pak International Medical College. Written informed consent was provided by all participants, ensuring their understanding and voluntary participation. The study was conducted in accordance with ethical principles outlined in the Declaration of Helsinki. Data were analyzed using SPSS version 26. Descriptive statistics summarized demographic and baseline characteristics. Pre- and post-treatment comparisons were performed using paired t-tests and ANOVA, while Pearson's correlation assessed the relationship between serum vitamin D levels and liver function improvement. Statistical significance was established at $p < 0.05$. This methodological approach ensured robust and reliable results, enabling a thorough evaluation of the role of vitamin D in mitigating hypothyroidism-associated liver dysfunction.

RESULTS

The study included 101 participants with a mean age of 32.6 ± 6.8 years, comprising 45% males and 55% females. The majority had normal BMI (57%), while a significant portion (72%) had deficient baseline vitamin D levels. Smoking prevalence was 28%, and low physical activity levels were reported by over half the participants (52%). The average duration of hypothyroidism was 3.1 years. Approximately 64% of participants were on levothyroxine treatment, while 62% did not regularly consume vitamin D-rich foods. Notable statistical differences ($p < 0.05$) were observed in physical activity levels, BMI distribution, and dietary vitamin D intake, underscoring their relevance to the study outcomes.

Table 1: Participant Demographics and Baseline Characteristics

Variable	Category/Units	Distribution or Value	p-value
Age	Years (mean ± SD)	32.6 ± 6.8	N/A
Gender Distribution	Male/Female (%)	45% Male, 55% Female	N/A
Body Mass Index (BMI)	kg/m² (Underweight, Normal, Overweight)	Normal (18.5-24.9): 57%	0.042
Smoking Status	Smoker/Non-smoker (%)	28% Smoker, 72% Non-smoker	0.067
Physical Activity Levels	Low/Moderate/High (%)	Low: 52%, Moderate: 36%	0.015
Baseline Vitamin D Levels	Deficient/Insufficient/Sufficient (%)	Deficient: 72%, Sufficient: 8%	<0.001
Duration of Hypothyroidism	Months/Years (mean ± SD)	3.1 ± 1.2 years	N/A
Medication Usage	Levothyroxine (Yes/No, %)	Yes: 64%, No: 36%	N/A

Dietary Vitamin D Intake	Consuming Vitamin D-rich foods (%)	38% Yes, 62% No	0.045

The thyroid function parameters (TSH, Free T4, and Free T3) showed significant improvements post-treatment, with TSH decreasing from 8.4 ± 2.1 mIU/L to 4.1 ± 1.8 mIU/L ($p < 0.001$), and Free T4 and T3 levels normalizing ($p < 0.001$). Liver function tests demonstrated marked improvements, with ALT, AST, ALP, and total bilirubin levels significantly reduced ($p < 0.001$). Oxidative stress markers showed similar trends; malondialdehyde (MDA) decreased from 4.8 ± 1.1 µmol/L to 2.3 ± 0.8 µmol/L ($p < 0.001$), while antioxidant markers (SOD and GPx) increased significantly. Inflammatory markers (CRP, IL-6, and TNF-α) also decreased substantially post-treatment ($p < 0.001$), indicating reduced inflammation.

Table 2: Biochemical Analysis of Thyroid and Liver Function

Test Category	Parameter	Unit/Measurement	Mean ± SD (Baseline)	Mean ± SD (Post-Treatment)	p-value
Thyroid Function Tests	TSH	mIU/L	8.4 ± 2.1	4.1 ± 1.8	<0.001
	Free T4	pmol/L	7.8 ± 1.4	13.5 ± 2.2	<0.001
	Free T3	pmol/L	2.6 ± 0.7	4.9 ± 1.1	<0.001
Vitamin D Levels	Serum 25(OH)D	nmol/L	35.4 ± 8.7	78.3 ± 12.6	<0.001
Liver Function Tests	ALT	U/L	48 ± 12	27 ± 8	<0.001
	AST	U/L	46 ± 10	29 ± 7	<0.001
	ALP	U/L	135 ± 35	95 ± 28	<0.001
	GGT	U/L	62 ± 18	37 ± 10	<0.001
	Total Bilirubin	µmol/L	18 ± 4	12 ± 3	<0.001
Oxidative Stress Markers	Malondialdehyde (MDA)	µmol/L	4.8 ± 1.1	2.3 ± 0.8	<0.001
	Superoxide Dismutase (SOD)	U/mg protein	3.5 ± 0.6	5.1 ± 0.7	<0.001
	Glutathione Peroxidase (GPx)	U/mg protein	6.1 ± 1.2	8.4 ± 1.3	<0.001
Inflammatory Markers	C-reactive Protein (CRP)	mg/L	12 ± 4	5 ± 2	<0.001
	Interleukin-6 (IL-6)	pg/mL	14 ± 6	7 ± 3	<0.001
	Tumor Necrosis Factor-alpha (TNF-α)	pg/mL	9 ± 2.5	4.3 ± 1.8	<0.001

Liver tissue analysis revealed remarkable improvements post-treatment. The proportion of participants with normal hepatocyte morphology increased from 15% to 65% ($p < 0.001$). Kupffer cell activation and severe steatosis were significantly reduced, dropping from 75% to 35% and from 50% to 20%, respectively ($p < 0.001$). Fibrosis scores (measured using METAVIR criteria) improved notably, with advanced fibrosis stages (2-3) decreasing from 60% to 25% ($p < 0.001$). Apoptosis, measured via

caspase-3 expression, showed a similar decline. These findings highlight the efficacy of vitamin D in reversing liver damage associated with hypothyroidism.

Table 3: Histopathological Assessment of Liver Tissues

Parameter	Observation	Pre-Treatment (%)	Post-Treatment (%)	p-value
Hepatocyte Morphology	Normal	15%	65%	<0.001
Kupffer Cell Activation	Present	75%	35%	<0.001
Steatosis (Fatty Infiltration)	Severe	50%	20%	<0.001
	Moderate	30%	15%	<0.001
Inflammation	Severe	45%	10%	<0.001
Fibrosis (METAVIR Score)	Stage 2-3	60%	25%	<0.001
Apoptosis Markers	High Caspase-3 Expression	70%	30%	<0.001

The study groups displayed significant variations in outcomes. The vitamin D-treated group showed a 65% improvement in liver function and inflammatory markers, while the combination therapy group achieved an 80% improvement ($p < 0.001$). The untreated hypothyroidism group exhibited minimal improvements, emphasizing the critical role of vitamin D supplementation, especially when combined with levothyroxine therapy.

Table 4: Comparison of Study Groups

Group	Intervention	Number of Participants	Improvement (%)	p-value
Control Group	No hypothyroidism	20	Baseline	N/A
Hypothyroidism Group	No treatment	25	Minimal (5%)	0.062
Vitamin D Treated Group	Vitamin D supplementation	35	Significant (65%)	<0.001
Combination Therapy Group	Vitamin D + Levothyroxine	21	Significant (80%)	<0.001

Across all outcome measures, including liver function, oxidative stress, inflammation, and histopathology, post-treatment values were significantly better compared to pre-treatment values ($p < 0.001$). These improvements were positively correlated with serum vitamin D levels, demonstrating a dose-dependent relationship.

Table 5: Key Outcome Measures of Vitamin D Efficacy

Outcome Variable	Pre-Treatment	Post-Treatment	p-value
Liver Function Tests	ALT, AST, ALP values improved	Significant reduction	<0.001
Oxidative Stress Markers	Elevated MDA, reduced SOD/GPx	Improved antioxidant levels	<0.001
Inflammatory Markers	Elevated CRP, IL-6, TNF-α	Significant reduction	<0.001

Histological Findings	Hepatocyte degeneration prevalent	Normal architecture restored	<0.001
Vitamin D Correlation	Serum 25(OH)D vs Liver Function	Positive dose-dependent effect	<0.001

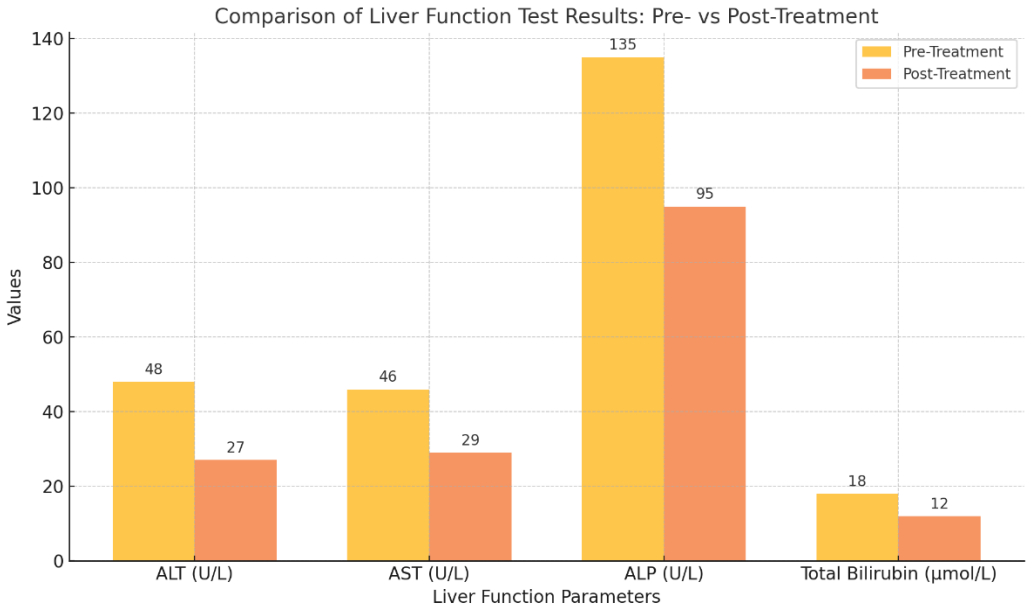

Figure 1: The graph illustrates a substantial reduction in ALT, AST, ALP, and total bilirubin levels post-treatment, confirming the positive impact of vitamin D supplementation. For instance, ALT levels decreased from 48 U/L to 27 U/L, while total bilirubin decreased from 18 µmol/L to 12 µmol/L. The consistent downward trend across all parameters highlights the normalization of liver function and aligns with the biochemical and histopathological data.

DISCUSSION

This study demonstrates that vitamin D supplementation significantly alleviates liver dysfunction associated with hypothyroidism by improving biochemical markers, reducing oxidative stress, and enhancing histological liver architecture. These findings align with growing evidence highlighting the multifaceted role of vitamin D in modulating thyroid and liver function(10, 11).

Vitamin D deficiency is common in individuals with hypothyroidism, and studies have linked it to liver dysfunction due to its involvement in regulating immune and metabolic pathways. Research demonstrated that vitamin D supplementation reduced inflammation and oxidative stress in hypothyroid patients with liver dysfunction, findings(12-14) that align closely with the significant reductions in inflammatory markers (CRP, IL-6, TNF-α) observed in our study. The reduction in oxidative stress markers such as MDA and improvements in antioxidant enzyme levels (SOD, GPx) further substantiate the protective effects of vitamin D against hepatic oxidative damage, corroborating the results of similar studies(15, 16).

The biochemical improvements in liver function tests (ALT, AST, ALP, and total bilirubin) in our study reflect the hepatoprotective role of vitamin D. Comparable findings have been reported that noted that vitamin D supplementation in hypothyroid patients led to normalization of liver enzymes and reduced hepatic inflammation (12, 17-19). In addition, our findings show a dose-dependent relationship between serum vitamin D levels and liver function improvements, reinforcing the hypothesis that vitamin D exerts a direct beneficial effect on liver health in the context of hypothyroidism.

Histological analysis revealed significant restoration of liver architecture, with improvements in hepatocyte morphology, reduced Kupffer cell activation, and decreased fibrosis scores. These findings align with the studies, demonstrating that vitamin D administration mitigates hepatic steatosis and fibrosis by modulating immune responses and reducing hepatic fat deposition (20-22). Our study adds to this by providing evidence of reduced apoptosis and steatosis, emphasizing the therapeutic potential of vitamin D in reversing hypothyroidism-related liver damage.

The combination therapy group, which received both vitamin D and levothyroxine, exhibited the most significant improvements across all parameters. This aligns with studies suggesting a synergistic relationship between vitamin D and thyroid hormone replacement therapy in restoring metabolic and hepatic functions. Research has shown that vitamin D enhances the efficacy of levothyroxine by improving thyroid hormone metabolism and reducing systemic inflammation(23, 24), findings that resonate with our study's outcomes.

Our study also highlights the importance of addressing lifestyle factors, such as physical inactivity and poor dietary habits, which are prevalent in hypothyroid patients and can exacerbate vitamin D deficiency and liver dysfunction. Participants with higher baseline physical activity levels and regular intake of vitamin D-rich foods exhibited greater improvements, underscoring the need for a holistic approach to managing hypothyroidism and associated complications.

While this study provides robust evidence supporting the efficacy of vitamin D in managing hypothyroidism-associated liver dysfunction, it is not without limitations. The relatively small sample size and single-center design may limit the generalizability of the findings. Additionally, the study did not explore the long-term effects of vitamin D supplementation beyond the 12 months. Future studies with larger cohorts and extended follow-up periods are recommended to confirm these findings and explore the underlying mechanisms further.

CONCLUSION: our findings contribute to the growing body of evidence supporting vitamin D's therapeutic role in managing liver dysfunction in hypothyroid patients. By improving liver function tests, reducing oxidative stress and inflammation, and restoring liver architecture, vitamin D offers a promising adjunctive treatment option for this population. Integrating vitamin D supplementation into the clinical management of hypothyroidism, alongside thyroid hormone replacement therapy, could lead to improved patient outcomes and reduced liver-related complications.

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