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Vitamin D and Non-alcoholic Fatty Liver Disease: Explaining Molecular Connections - A Review

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Abstract

Non-alcoholic fatty liver disease (NAFLD) has become the furthermost recurrent chronic liver disorder worldwide, meticulously linked to elements of metabolic syndrome such as obesity, insulin resistance and diabetes mellitus. Recent studies indicate that Vitamin D in adding to its traditional role in calcium regulation, has a complex role in liver health. This review thoroughly investigates the association among Vitamin D levels and the development of NAFLD, emphasizing molecular, clinical and translational viewpoints. We critically evaluate results from cross-sectional and case-control studies carried out in various populations, including data from tertiary care centres in India and Egypt, which consistently reveal a negative association amongst serum Vitamin D concentrations and the severity of NAFLD. Experimental research in rodent models further corroborates the liver-protective properties of Vitamin D through its effects on lipid metabolism, inflammatory signalling, oxidative stress, and insulin sensitivity. Mechanistic insights reveal the modulation of crucial pathways like Sterol Regulatory Element-binding Protein-1c (SREBP-1c) PPARα (Peroxisome Proliferator-activated Receptor alpha), Nuclear factor kaapa B (NF-kB) and Insulin Receptor Substrate 2 (IRS-2) by Vitamin D. The therapeutic implications of these findings feature the efficacy of Vitamin D administration as a complementary approach in the NAFLD management. Despite encouraging data, uncertainties persist regarding causality, optimal dosing, and long-term effectiveness, necessitating further investigation. This review pursues to establish a complete framework for interpreting the emerging significance of Vitamin D in NAFLD, thereby guiding both clinical practice and future research initiatives.

Keywords: Epigenetics, Molecular Interaction, NAFLD, Vitamin-D.

Introduction

NAFLD characterizes a series of liver disorders expanded from simple and normal steatosis to NASH (non-alcoholic steatohepatitis), advanced fibrosis, cirrhosis and HCC (hepatocellular carcinoma) (1). With a worldwide occurrence projected at around 25%, NAFLD has appeared as the most general chronic hepatic disease globally, exceeding hepatitis by viral and alcohol associated liver dysfunction (2). The problem is predominantly observed in low income and moderate-income countries experiencing immediate epidemiological changeover. South Asian country like India, experience an inconsistent increase in NAFLD because of increasing obesity condition, sedentary lifestyle and following western diets (3). Epidemiologic studies from developing country like India gives a prevalence statement from 16% to 32% in developing urban inhabitants, with a noteworthy incidence even between non-obese personalities, which highlights an abnormal BMI (body muscle index) NAFLD phenotype (4). This NAFLD is very closely connected with components of metabolic disorder, which includes complex obesity, insulin resistance, dyslipidaemia and T2DM (Type 2 Diabetes Mellitus), that pinpoint it as a hepatic indication of comprehensive metabolic disorder (5).

The disease condition of NAFLD is multifaceted and complex, which connects inflammation with metabolic activity and oxidative stress pathways. Insulin resistance act as a vital role by validating liver de novo lipogenesis whereas preventing β-oxidation of free fatty acids, that guides to extreme triglyceride accumulation in hepatocytes (6). Determined lipotoxicity sequentially triggers

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oxidative stress, mitochondrial disturbances and pressure in endoplasmic reticulum, that concludes in hepatocellular or liver injury. Development as of simple steatosis to NASH is motivated by long-lasting low-level inflammation, initiation of Kupffer cells and fibrotic signals intermediated by liver stellate cells. Further pro-inflammatory cytokines like TNF-α (Tumour Necrosis Factor), NF-κB and Interleukin 6 (IL-6) stimulation of further intensified fibrosis and liver injury (7). In spite of widespread research, at present there is no proper pharmacological treatment for NAFLD mainly depend on lifestyle change, highlighting the necessity for new precautionary and adjunctive healing approaches (8). Vitamin D is a fat-soluble secosteroid hormone produced in the skin over exposure to Ultraviolet B (UVB) radiation and achieved from nutritional sources and enhancements. It undertakes liver hydroxylation to produce 25-hydroxyvitamin D [25(OH)D], the main circulating arrangement, followed by renal modification to the organically dynamic metabolic byproduct called 1,25-dihydroxyvitamin D (9). This active state employs its efficiency by attachment with VDR (Vitamin D receptor), a nuclear receptor extensively expressed in metabolic tissue matters, like adipose, pancreas, liver and immune cells.

As demonstrated in Figure 1, Vitamin D liver connections integrate molecular regulation of lipid metabolism and inflammation signalling with clinical disease brutality in NAFLD. Epidemiological studies steadily validate a contrary association among serum 25(OH)D levels and its occurrence and brutality of NAFLD. Studies based on population from India and other Middle East countries states that significantly increased rates of deficiency of Vitamin D amongst NAFLD individuals when compare to healthy population, independent of obesity condition (10, 11). These remarks propose that Vitamin D deficit might be complicatedly connected to NAFLD disease condition slightly than being a simple byproduct. Developing mechanistic indication shows a direct involvement of Vitamin D in controlling inflammation, liver lipid biodegradation and insulin signals. Vitamin D downregulates lipogenesis by suppressing SREBP-1c (Sterol Regulatory Element-Binding Protein-1c) whereas improving PPAR-α (Peroxisome Proliferator-Activated Receptor-α) intermediated fatty acid oxidation, thus reestablishing homeostasis of hepatic lipid (12). Moreover, Vitamin D displays effective anti-inflammatory properties by hindering NF-κB signals and encouraging crucial anti-inflammatory cytokines mechanisms like IL-10 (Interleukin-10) in preventing NASH development (13). Vitamin D as well as augments insulin sensitivity by modulating IRS-2 (Insulin Receptor Substrate-2) signalling and reduces oxidative stress by increasing antioxidant enzymes, such as catalase and superoxide dismutase (14).

Preclinical investigations further validate this defensive efficiency. Few animal models of diet mediated NAFLD illustrate that Vitamin D administration mitigate hepatic steatosis, lessens oxidative stress, regularizes enzyme levels of liver and modifies gene expression connected with lipid and glucose metabolism (15). In spite of increasing evidence connecting Vitamin D deficit with NAFLD numerous crucial questions continue unresolved. It is undefined whether Vitamin D deficiency is an underlying factor or an outcome of hepatic steatosis. Moreover, optimum dosing approaches, time interval of supplementation and patient subcategories most probable to get positive results. Randomized controlled trials (RCT) have produced heterogeneous or varied outcomes, which highlights the necessity for mechanistic precision and uniform endpoints clinical trial (16). In this situation, the present review intent to broadly scrutinize the metabolic, molecular and immunological association among NAFLD and Vitamin D. By correlating epidemiological facts, mechanistic perceptions and experimental indication, this review simplifies the therapeutic efficiency of Vitamin D in NAFLD and recognize future directions for clinical and translational research.

Methodology

This rendering review was carried out by following conventional methodological direction for crystal clear and repeatable literature assessments in biomedical study, which includes PRISMA 2020 references where appropriate to random reviews (17, 18).

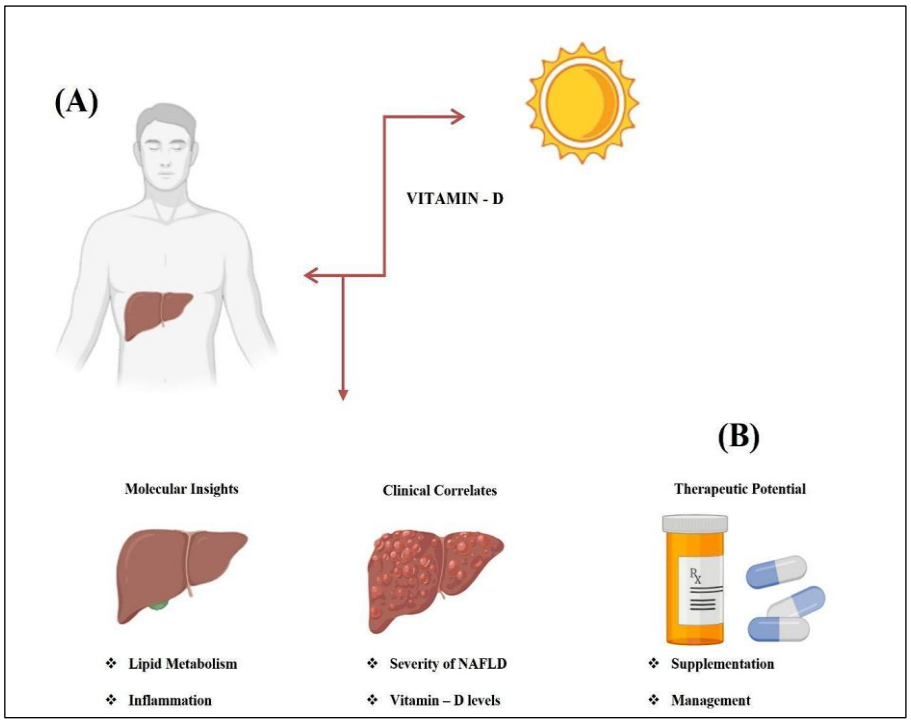

Figure 1: Probable Vitamin D Associated Mechanisms of NAFLD Pathogenesis and its Significance to Clinical Consequences and Therapeutic Approaches - (A) Diagrammatic illustrations of the Vitamin D hepatic axis demonstrating cutaneous amalgamation, hepatic participation and its impact on molecular pathways adapting lipid metabolism and inflammation, (B) Combined overview connecting molecular perceptions and clinical associates of NAFLD with the beneficial potential of Vitamin D administration in disease management

Strategy of Literature Search and Information Bases

A complete literature hunt was accomplished among four main electronic catalogues or databases: PubMed or MEDLINE, Scopus, Web of Science and Google Scholar. The search enclosed research issued from January 1, 2000 to May 30, 2024, mediating the time during which systematic and clinical indication connecting Vitamin D to NAFLD has considerably progressed. The search approach united MeSH (Medical Subject Headings) and keywords with free-text. The main MeSH details and search terms includes: 25-hydroxyvitamin D", "Vitamin D", "Cholecalciferol" "NAFLD", "Non-alcoholic fatty liver disease", "non-alcoholic steatohepatitis" "Liver Inflammation" "Liver Fibrosis", "Hepatic Steatosis" "Hepatic Cells", "Insulin Shock", "Metabolism of Lipids". Boolean operatives were used analytically. Illustrative search terms include: "Vitamin D" AND "NAFLD" "NASH" "Vitamin D" AND ("Resistance of Insulin" OR "Lipid Biodegradation") AND Hepatic OR Liver. Database precise filters were utilized to control outcomes to English-language based articles and scholarly peer-reviewed journals. No limitations were positioned on geographical place or study strategy at the search platform.

Grey Literature and Google Scholar

Specifying the restrictions of Google Scholar on reproducible grading, a structured method was implemented. Searches were carried out by identical or matching terminology combinations and first 200 results grouped by significance were analysed, compatible with methodological guidance (19). Furthermore, grey literature was specifically incorporated by assessing reference lists of related review papers and meta-analyses by snowballing, since unpublished research thesis, certain preprints and non-indexed publication sources were omitted to sustain scientific accuracy.

Eligibility and Study Selection Guidelines

The Inclusion criteria include: Original investigation (Databased studies, random or non-random clinical context, cell line and animal studies). Studies clearly examine Vitamin D level, administration, its crucial signalling or molecular

mechanisms in connection to liver steatosis, insulin shock or resistance NAFLD, inflammation, fibrosis and metabolism of lipid. Meta-analyses and systematic reviews addressing Vitamin D and NAFLD, included for contextual and background synthesis. Articles published in peer-reviewed journals and available as full text in English. Exclusion criteria include: Research work concentrating on liver pathogenesis related to alcoholic, virus, drug-mediated causative and autoimmune disorders. Case studies, abstracts from conference, editorial viewpoints, comments and judgement opinions missing basic data. Research works without acceptable methodological explanation or unreachable full text.

Data Extraction and Screening

All recovered records were introduced into a reference manager tool like Mendeley and duplicates were deleted. Heading and abstract selection were self-sufficiently directed by two reviewers, tracked by full-text evaluation of possibly qualified research articles. Variations were determined through debate, with mediation by a third referee when needed (20, 21). Data mining was executed by means of standardized method apprehending: study strategy, inhabitants or prototypical model, Vitamin D evaluation parameters (serum 25(OH)D levels, dose, time), NAFLD analytical measures (like imaging technique, histopathology, biochemical parameters) metabolism and inflammatory consequences and vital signalling pathways insulin, VDR and mitochondrial).

Quality Valuation and Data Combination

Procedural excellence and risk of predisposition were evaluated using suitable tools which is based on study type, that includes conventional measures for empirical and experimental findings (22). Due to diversity in study plans and conclusions, measurable meta-analysis is not achievable. In its place, discoveries were produced narratively beneath theme-based realm like resistance of insulin, immune alterations, lipid breakdown and fibrosis development, consistent with suggested performance for narrative analyses (23).

Results

Vitamin D deficit is progressively recognized as a prevalent comorbidity among individuals with NAFLD, with emerging evidence suggesting both regional variations and global consistency. Approximately 30-60% of individuals worldwide diagnosed with NAFLD exhibit Vitamin D deficiency, representing a significant overlap among these two conditions. This association is particularly pronounced in populations with high rates of obesity and insulin shock, which are autonomous risk factors for both NAFLD and lack of Vitamin D. In India, a cross-sectional analysis carried at a high-care facility in the northern region exposed that 45% of NAFLD individuals were Vitamin D deficient, with an extra 16% categorized as inadequate. Particularly, Vitamin D deficit was common among individuals aged 41-50 years and those classified as obese (24). In Egypt, a study concentrating on cruelly obese individuals indicated that only 34% of NAFLD individuals had satisfactory Vitamin D levels, compared to 76.7% of normal individuals, underscoring a significant difference (25). These provincial studies align with global systematic reviews that reveal lower serum concentrations in persons with NAFLD across various cultural groups and sections (26). Collectively, the indication suggests that Vitamin D deficit might not only coincide with NAFLD, but also contribute to its pathogenesis. Considering these inclinations is crucial for guiding public health advantage and developing targeted observation and supplementation approaches personalized to precise regions.

Deficiency of Vitamin D in individuals with NAFLD is closely associated with several clinical factors, including BMI (body mass index), enzyme levels in liver, and the ultrasonic categorization of fatty liver. A study carried out in India revealed that 91.7% of obese NAFLD patients experienced Vitamin D deficit, compared to only 39.1% of individuals with a regular BMI, highlighting a significant link between fatness and low vitamin (27). Furthermore, increased enzyme levels in the liver, predominantly alanine aminotransferase and aspartate aminotransferase, were common among individuals with Vitamin D shortage, indicating potential hepatocellular injury (28).

Additionally, ultrasonic scoring demonstrated a significant contrary relationship between Vitamin D and the harshness of fatty liver, low Vitamin D observed in individuals classified with steatosis of Grade 2 and Grade 3 (29). These clinical associations highlight the efficacy of Vit-D as a non-invasive biomarker for evaluating the severity of NAFLD.

Vitamin D has taken place as a critical regulator in the disease circumstances of NAFLD, expanding its role in the outermost calcium balance to contain anti-inflammatory, lipid regulation, sensibilizing insulin. Many intermixed placebos evaluated trials have exposed the possessions of vitamin D management on control individuals and NAFLD adults, revealing a stable form of increased serum concentrations followed by administration of vitamins. Similarly, previous research confirmed a noteworthy advancement from 20.1 ± 5.2 ng/mL to 45.2 ± 8.1 ng/mL with weekly 50,000 IU administration over 12 weeks (30). These outcomes were further recorded by previous research work which remunerated a stimulated yogurt beverage to dispense 1000IU/day, that guides to detectable improvement in 25(OH)D and marking dietary agents as possible transmission options (31). Investigation done by many preceding research teams as well approve that varying treatments of vitamin D are effective in purifying levels of serum in NAFLD and control individuals. The observed precisions in vitamin D levels are clinically connected, assuming the contrary association amongst serum 25(OH)D and liver steatosis, battle of insulin and usual inflammation, these are the stamps of NAFLD expansion (32-35). These results reinforce the beneficial efficacy of Vitamin D not only as an indicator of disease severity but also as an adaptable characteristic in NAFLD management.

Table 1: Key Statistical Verdicts Connecting Vitamin D and NAFLD

Population Studied	Key Findings	Statistical Significance	References
262 Italian adults (with and without NAFLD)	NAFLD patients had significantly lower 25(OH)D levels (17.5 ± 6.2ng/mL) compared to controls (24.8 ± 7.1ng/mL)	$p < 0.001$	(11)
21 studies, ~12,000 subjects	Vitamin D deficiency increased NAFLD risk (OR (Odds Ratio) = 1.50, 95% CI (Confidence Interval): 1.28-1.76)	Highly significant	(35)
60 NAFLD patients	Low 25(OH)D levels associated with greater hepatic steatosis severity on imaging	$p < 0.01$	(10)
50 NAFLD patients (Vitamin D vs placebo)	Vitamin D supplementation (50,000 IU (International Unit) per week for 8 weeks) reduced ALT, AST, and hepatic fat	$p < 0.05$	(30)
~6,000 UK adults	Low serum Vitamin D linked to increased insulin resistance (HOMA-IR (Homeostatic Model Assessment for Insulin Resistance)) and liver enzyme levels.	$p < 0.01$	(36)
237 T2DM patients with NAFLD	Serum Vitamin D inversely correlated with NAFLD grade ($r = -0.38$)	$p < 0.01$	(37)
75 NAFLD patients	Low Vitamin D associated with increased pro-inflammatory cytokines (TNF-α, IL-6)	$p < 0.01$	(11)
316 NAFLD patients	Vitamin D deficiency associated with higher cardiovascular risk score	$p < 0.001$	(38)
60 obese adults with NAFLD	Vitamin D improved hepatic insulin sensitivity and reduced fat score	$p < 0.05$	(39)

Statistical conclusions concerning Vitamin D with NAFLD. Table 1 illustrates, the summarized studies determine a steady inverse integration among serum 25(OH)D levels and NAFLD existence, severity and disorder in metabolism among diverse populations. Vitamin D deficiency is suggestively linked to augmented steatosis, inflammation, insulin confrontation, and cardiometabolic risk, at the same time Vitamin D supplementation works specify measurable advancements in hepatic enzymes, fat content and insulin accuracy. Altogether these significant robust outcomes support an influential role of Vitamin D in NAFLD disease development. In interventional trials, Vitamin D supplement established noteworthy enhancements in liver enzymes, insulin and scores of hepatic fats. Vitamin D is indispensable for the pronunciation of hepatic metabolism, particularly regarding NAFLD. At the microenvironment cellular level, Vitamin D functions by the VDR, which is formed in hepatic cells and stellate cells of liver, to disturb expression of genes related with inflammation and phospholipid metabolism (40). Studies directed on rodents with NAFLD have established that Vitamin D administration leads to a decreased SREBP-1c, a noteworthy transcription feature that leads to lipogenesis, therefore reducing triglyceride accumulation in the liver. Simultaneously, Vitamin D enables the upregulation of peroxisome

multiplied activation receptors that improves fatty acid β-oxidation and alleviates steatosis. Additionally, Vitamin D upregulates insulin sensitivity by activating IRS-2, therefore enhancing glucose metabolism in liver (41). Its anti-inflammatory properties, which are interceded by the interference of NF-κB, also promote the decline of hepatocellular damage. Cooperatively, this emphasizes the noteworthy role of Vitamin D in preserving a balance in hepatic metabolic and labelling the improvement of NAFLD. Table 1 displays the substantial connotation of NAFLD and Vitamin-D.

Insulin Resistance is a central characteristic in the development of NAFLD, with Vitamin D documented as a vital controller of the insulin pathway. Vitamin D improves insulin response by attaching to the VDR situated in liver tissues and pancreatic β-cells, thus regulating genes connected with glucose breakdown (42). A distinguished pathway determined by Vitamin D is the IRS pathway, mainly IRS-2, that enable the subsequent commencement of the PI3K/Akt (Phosphoinositide 3-kinase/Protein Kinase B) cascade important for glucose acquiring and glycogen incorporation in liver (43). One more study display in rodents' diet based NAFLD and Vitamin-D has exposed the capability to reinstate IRS-2, and progress glucose tolerance and decrease equilibrium conventional assessment of insulin resistance standards. Moreover, Vitamin D disturbs calcium homeostasis, which plays a secondary and active role in insulin liberation and functioning of β-cells (44). These conclusions specify that Vitamin D scarcity worsens insulin confrontation and might quicken the progress of NAFLD, whereas its enhancement might propose a metabolic benefit in management of NAFLD.

Oxidative stress plays a dynamic role in the development of NAFLD, mainly in the changeover from moderate steatosis to NASH (Non-alcoholic steatohepatitis). This condition mostly ascends from the life-threatening accretion of reactive oxygen species (ROS) due to deterioration of mitochondria, lipid peroxidation and persisted inflammation (45). Vitamin D exposed to display antioxidant possessions that aid to uphold liver oxidation-reduction equilibrium. It diminishes oxidative stress by improving the shifting of endogenous antioxidant enzymes like CAT (Catalase) and Superoxide Dismutase (SOD), although lessening the lipid peroxidation marker malondialdehyde (MDA) (46). Impending to animal studies it includes NAFLD persuaded by elevated fat and fructose control, Vitamin D encouragingly dropped hepatic MDA levels and reimbursed SOD and CAT level, that leads to enhanced hepatic complete structure and biological parameters (47). Additionally, Vitamin D might indirectly lessen oxidative stress by controlling pathways like inflammation, such as NF-κB, which are precisely connected to ROS production (48). These verdicts postulate that Vitamin D assists a dual role, operative as an anti-inflammatory factor and as a regulator of oxidative stress, therefore provides defence against the progress of NAFLD. Table 2 depicts RCT tangled in present meta-analyses of vitamin D management in NAFLD cohorts.

Table 2: Individual RCT Comprised in Contemporary Meta-analyses of Vitamin D Administration in NAFLD Individuals

Intervention (No's)	Control (No's)	Dosage	Duration (weeks)	Vehicle	Intervention Type	Mean Age (Intervention)	Mean Age (Placebo)	References
26	29	2,000 IU/day Vitamin D_3	24	Oral Capsule	Vitamin D_3 daily oral	49-69	49-69	(49)
~31	~28–32	50,000 IU/week Vitamin D_3 or 25 µg calcitriol	12	Oral Syrup/Tablet	Vitamin D_3 or Calcitriol orally	20-75	20-75	(50)
30	30	50,000 IU/week Vitamin D_3	10	Oral Capsule	Vitamin D_3 weekly oral	30-70	30-70	(51)
8	10	2,100 IU/day VD_3	48	Oral capsule	Vitamin D_3 daily oral	23-63	23-63	(52)
37	37–36	25 µg Calcitriol/day	12	Oral Capsule	Active Vitamin D (Calcitriol)	18-65	18-65	(53)
~37	~38	600,000 IU Injection Vitamin D_3 Once	4	Intramuscular Injection	Single Bolus Injection	29-41	29-41	(54)
51	30	600,000 IU injection Vitamin D_3 once	24	Intramuscular Injection	Single bolus injection	~37-40	~37-40	(27)
27	26	50,000 IU Vitamin D_3 Biweekly	16	Oral Capsule	Vitamin D_3 Every Other Week	18-70	18-70	(30)

Summary of RCTs assessing Vitamin D administration in individuals identified with NAFLD. Table 2 illustrates the equivalence of intervention and normal groups in relations to dose, period, distribution vehicle and modality of intervention. Jointly, these RCTs validate that beneficial Vitamin D supplementation differs widely across experimental situations, supportive in growing deliberation as an adjunct tactic in NAFLD management. Persistent mild inflammation is a key feature of NAFLD, particularly in its progressive form known as NASH. Increased levels of inflammatory cytokines, like monocyte chemoattractant protein-1, IL-6 and TNF-α, were present in NAFLD and subsidize hepatocellular fibrosis and damage (55). In this context, Vitamin D plays an indispensable immunomodulation role by weakening the outcomes of pro-inflammatory cytokines whereas encouraging anti-inflammatory responses. Mechanically, Vitamin D inhibits the NF-κB pathway, a key regulator of inflammation, thus dropping hepatic concentrations of IL-6 and TNF-α (56). Exploration studies applying NAFLD animal models have established that Vitamin D supplementation encouragingly decreased hepatic NF-κB whereas upregulating IL-10, additionally anti-inflammatory cytokine that inhibits macrophage commencement and the diffusion of cell connected to inflammation. This modification in cytokine homeostasis to an anti-inflammatory status supports to diminish hepatic inflammation and avert additional liver damage. These results reinforce the concept that Vitamin D distresses metabolic pathways but also has a straight effect on immune reply, thus placing it as a probable helpful remedy to lessen hepatic inflammation in NAFLD patients. Figure 2 explains a combined conceptual model demonstrating how Vitamin D status impacts the mechanisms beneath NAFLD, which includes disordered lipid metabolism, inflammation, fibrogenesis, oxidative pressure and insulin sensitivity. In addition, it connects these critical pathways to clinical associations such as obesity, cardiometabolic issues, liver enzyme irregularities and disease development. Moreover, the diagram highlights the global problem of Vitamin D deficit and its supplementation as a possible regulation strategy to progress liver and metabolic consequences in NAFLD.

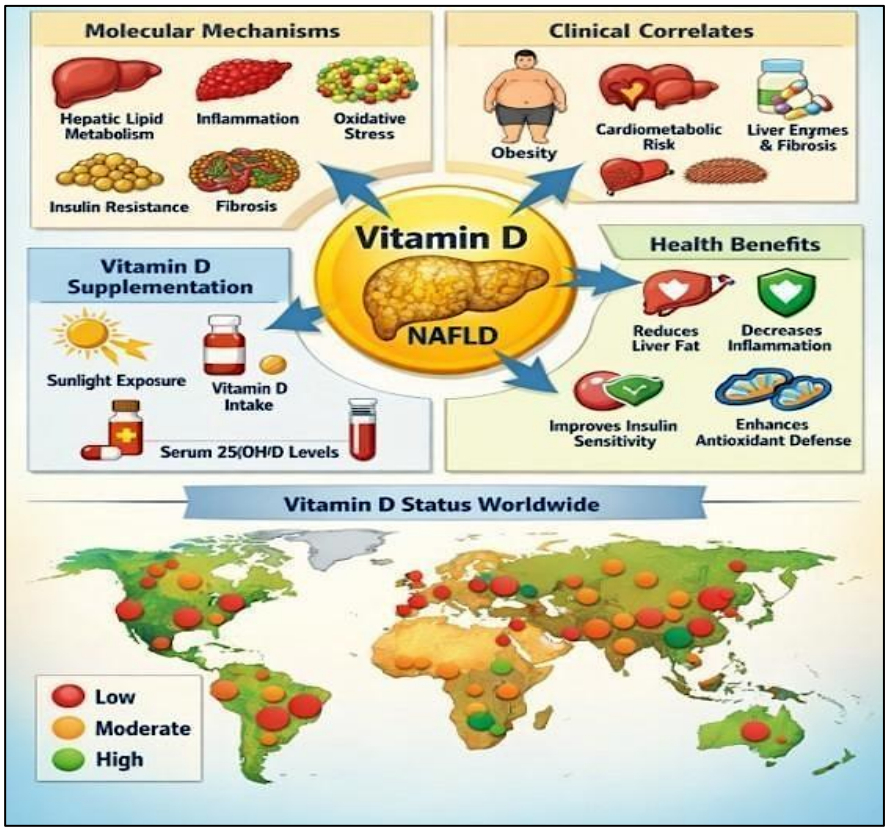

Figure 2: Comprehensive and Mechanical Indication of Vitamin D in Pathogenesis, Clinical Indexes and Therapeutic Variation of NAFLD

The multilayered role of Vitamin D in NAFLD, amalgamating mechanisms like hepatic metabolism, insulin accuracy, inflammation, reactive oxygen species (ROS) and fibrosis with important clinical connections like cardiac problem, obesity, fluctuations in liver enzymes and development of fibrosis.

Summary of placebo measured randomized trials assessing variations in serum Vitamin D meditations earlier and after administration in normal and NAFLD individuals explained in Table 3. Results compare starting point and ultimate Vitamin D (mean ± SD) among interposition and placebo clusters across varied medicating regimens and duration of studies. Overall, a reliable post-intervention increase in serum 25(OH)D levels is detected in dealing groups, representing the efficiency of Vitamin D administration across cohorts. Animal models have significantly improved our understanding of the biomolecular mechanisms that underlie the beneficial effects of Vitamin D in NAFLD. Investigational studies involving high-fat, fructose-based diets in NAFLD rats have constantly indicated that Vitamin D administration offers hepatoprotective advantages.

Table 3: Summary of Interventions and Vitamin-D Concentrations in Randomized Placebo-Controlled Trials Involving Healthy Adults and NAFLD Patients

Type of Intervention	Mean Vitamin-D Baseline (Intervention) (ng/mL)	SD Baseline (Intervention)	Mean Vitamin-D Baseline (Placebo) (ng/mL)	SD Baseline (Placebo)	Mean Vitamin-D Final (Intervention) (ng/mL)	SD Final (Intervention)	Mean Vitamin-D Final (Placebo) (ng/mL)	SD Final (Placebo)	References
2000 IU/day Cholecalciferol for 24 Weeks	18.9	4.5	19.2	4.7	32.1	6.8	19.5	5.0	(49)
50,000 IU/week Cholecalciferol for 12 weeks	20.1	5.2	20.6	5.0	45.2	8.1	22.4	5.6	(30)
Vitamin D fortified yogurt drink (1000 IU/day) for 12 weeks	21.3	4.6	20.8	4.9	31.6	5.7	22.1	5.0	(26)
50,000 IU/week Cholecalciferol for 8 weeks	17.5	3.9	18.0	4.1	39.8	7.3	18.6	4.5	(57)
4000 IU/day Vitamin D for 12 weeks	19.6	4.8	19.4	4.7	35.4	6.2	20.1	5.1	(50)
50,000 IU every 2 weeks for 4 months	21.2	4.4	20.9	4.5	38.5	7.0	21.4	4.8	(53)

A pivotal study by an expert research team revealed that administering Vitamin D3 to NAFLD animals leads to marked enhancements in liver histopathology, reductions in hepatic steatosis, hepatolobular inflammation and swelling deterioration (58). These enhancements were linked to the regularization of enzymes such as ALT (Alanine Aminotransferase) and Aspartate Aminotransferase (AST). At the molecular level, Vitamin D had a significant impact on metabolic and signalling pathways related to inflammation. It downregulated the expression of the lipogenic transcription factor SREBP-1c, upregulated fatty acid oxidation through PPAR-α, and enhanced insulin signalling via IRS-2 activation. Furthermore, Vitamin D diminished oxidative stress markers such as MDA and restored the activity of antioxidant enzymes. Crucially, anti-inflammatory outcome attained through the conquest of NF-κB signalling and the elevation of IL-10 expression. These translational findings offer mechanistic support for clinical observations and indicate that Vit-D supplement may decelerate the progression of NAFLD by targeting various pathogenic pathways. Figure 3 illustrates the integrative hypothesized novel, non-canonical pathways by which Vitamin D affects liver diseases apart from standard metabolic regulation. It correlates ferroptosis inflection, circadian control and microbiota regulated Vitamin D metabolism as significant factors of hepatic damage and inflammation. This figure highlights emerging chrono-biological and immunometabolism mechanisms that might expose novel translational roads for précised targets for NAFLD treatments.

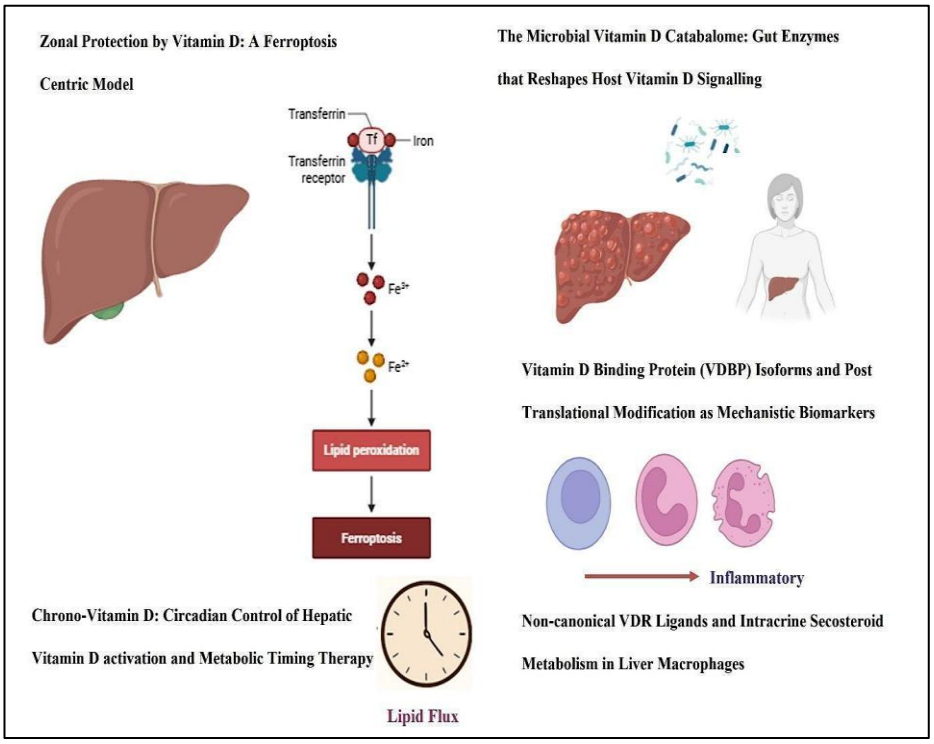

Figure 3: Evolving Paradigms of Vitamin D Signal in Liver Pathophysiology: Ferroptosis Controller, Catabolism of Microbes and Circadian Immune Integration Crosstalk

This portrays progressive, non-classical mechanisms in which Vitamin D legalizes hepatic equilibrium, highlights ferroptosis regulation by modulating metabolism of iron, lipid peroxidation and regulates circadian pattern of liver Vitamin D initiation. Further shows are evolving. controlling axes connecting gut microbiota intermediated catabolism of Vitamin D, VDBP homologs diversity as inflammatory biomarkers and non-canonical VDR signalling in liver macrophages that jointly impact liver inflammation and disorder in metabolism.

Discussion

The increasing amount of evidence connecting Vitamin D deficiency to NAFLD carries significant diagnostic and prognostic consequences. Serum 25-hydroxyvitamin D levels could act as a non-invasive bioindicator for evaluating the risk and severity of NAFLD. Research conducted by the previous research team illustrates that a Vitamin D cutoff value of 27.75 ng/mL was found to effectively predict NAFLD, achieving a sensitivity of 64% and a specificity of 90%, indicating its potential in identifying individuals at high risk, especially within obese populations. In similar vein research, it discovered a significant correlation between Vitamin D deficiency and the ultrasonographic grading of fatty liver, as well as elevated liver enzymes, which are critical indicators of disease severity (59). From a prognostic perspective, lower levels of Vitamin D have been linked to advanced histological characteristics of NAFLD, such as inflammation and fibrosis (60). Considering its influence on insulin confrontation, soreness, and oxidative trauma, essential elements in the progression of NAFLD - Vitamin D status may assist in forecasting long-term outcomes and informing therapeutic approaches. Although additional longitudinal studies are necessary, these results advocate for the incorporation of Vitamin D evaluation in standard assessment and risk stratification protocols for patients with NAFLD. The efficacy of Vitamin D as a beneficial agent for NAFLD has reaped attention due to its involvement in controlling metabolic, inflammatory, and oxidative stress pathways. Evidence from both animal studies and human observational research indicates that Vitamin D supplementation yields positive results. In studies involving NAFLD-induced rats, the administration of Vitamin D3 led to improvements in liver histopathology, normalization of liver enzyme levels, and a significant decrease in markers of inflammation and oxidative stress through the modulation of the

SREBP-1c, PPAR-α, NF-κB, and IRS-2 signalling pathways (61). These mechanistic findings underscore Vitamin D's capacity to affect critical regulators of hepatic lipid metabolism and insulin sensitivity. Medically, a growing body of research suggests that restoring sufficient Vitamin D could potentially slow the advancement of NAFLD. Nevertheless, the ideal dosage, frequency, and duration of Vitamin D supplementation for NAFLD have yet to be clearly defined. While standard guidelines suggest maintaining specific serum levels above 30ng/mL, it is suggested that dosing be tailored to individual baseline levels and existing comorbidities. To regulate efficiency, protection and consistent treatment procedures for NAFLD management, large-scale RCT are compulsory. Ferroptosis, a cellular demise pattern characterized by iron-dependent lipid peroxidation, has been documented as a significant characteristic in hepatocyte injury throughout the progression of NAFLD; the inhibition of ferroptosis has been displaced to the development the disease in presymptomatic form (62). Vitamin D signalling by means of VDR plays a critical role in managing redox and metabolic genes in liver cells and has been established to impact oxidative stress and functions of mitochondrial (63). Small gradients of vitamin D catalyst (CYP27B1) and its catabolism breakdown (CYP24A1) through different hepatic regions generate variable levels of predisposition and flexibility to ferroptosis (for example, portal hepatocytes display better defence in comparison to cells in pericentral when limited initiation is sustained). Testable substances comprise: (a) three-dimensional transcriptomics and immunofluorescence for CYP27B1, VDR, CYP24A1, ACSL4, SLC7A11 and GPX4 on NAFLD biopsies of humans (b) accurate liver slice ferroptosis analyse without or with ferrostatin-1 and 1,25-dihydroxycholecalciferol to establish possible release; (c) associating regional vitamin D initiation guides with clinical markers and visualising of disease progression. The microbiota in the gut plays a central role in modifying bile acids and numerous host metabolites that disturb inflammation and liver metabolism; the communications among the liver and gut are important to the disease development of metabolic associated fatty liver disease (MAFLD) (64). Vitamin D levels are connected with characteristics of NAFLD in extensive studies like wide-ranging meta-analyses specify unpredictable properties of enhancement on metabolic consequences (65). An innovative suggestion and detailed opinions: it is projected that convinced microbial taxonomic group hold enzymatic role that chemically modify host cholecalciferol (Vitamin-D/calcitriol) or bring out VDR bile acid byproducts either in active or inactive form, that might decrease the bioavailability of Vitamin D level once levels of serum 25(OH)D is regular, subsequently varying enterohepatic VDR signal that guides to fibrosis. Recommended investigational tactics include: (a) directing shotgun meta-genomics on fine categorized NAFLD cohorts to recognize possible microbial dehydrogenases and hydroxylases, associating these verdicts with faecal vitamin D breakdown products and serum calcitriol; (b) incorporating bile acid metabolomics to determine microbially resulting VDR ligands; (c) capturing germ-free mice through possible taxa to begin interconnection. From a beneficial viewpoint, probiotics intended to uphold host secosteroids and hinder microbial defusing enzymes might aid as adjuncts to vitamin D supplement (66).

VDBP (Vitamin D-Binding Protein) controls the distribution of vitamin D metabolites to nerves and tissues and disturbs the available hormone; blood serum of VDBP and its genetic constitution have been connected to liver disease, thus they aid inadequate prognostic understandings. Investigation in animals designates that a lack in VDBP modifies the harshness of liver damage (67). A new suggestion and exact points: it is recommended that several VDBP isoforms like glycoforms, corroded forms and proteolytic wreckages gather early in NAFLD and possess a straight influence on the initiation of liver stellate cells by means of receptor-mediated approval called Large, Multi-Ligand Receptor Protein (LRP2). Applied steps such as: (a) retaining selected mass spectrometry to outline VDBP proteoforms in individuals with NAFLD and associating isoform catalogues with elastography and fibrotic markers biopsy; (b) handling primary human hematopoietic stem cells with secluded isoforms to evaluate Transforming Growth Factor beta (TGF-β) signals and synthesis of collagen; (c) influencing that the VDBP isoform catalogue improves the guess of fibrotic alteration behind the usage of 25(OH)D separately. The probable influence of this investigation is the expansion of

an applied serum cohort biomarker to classify individuals appropriate for early antifibrotic handlings.

Circadian disturbance (shift slog, uneven feeding) upsurges NAFLD risk; liver clock genes control sequences of lipid formation and oxidation. Evolving information specifies vitamin D interrelates with circadian paths and that metabolic productivities might be time-dependent (68). Specific points to be considered: propose that irregular liver clock modifies daytime CYP24A1/YP27B1 rhythms, fluctuating time-of-day Vitamin-D bioavailability and upsetting feeding and fasting lipid fluctuation, thus endorsing steatosis. Examinations: (a) rodent chrono treatment examinations with timetabled active form of Vitamin-D (fasting vs feeding gaps) and calculating liver lipid fluctuation and clock genetic factor statement; (b) translational inspection in shift labours with 24hr sequential Calcidiol/Vitamin-D and exterior clock indicators to observe if time displaced vitamin D rhythms guess steatosis development; (c) assess whether scheduled vitamin D supplement progresses metabolic terminations vs non-timed dosage. This unlocks the likelihood of chrono-supplement to line up vitamin D signal pathways with liver metabolic sequences. VDR can be activated by several ligands outward regular calcitriol; intracrine (local) breakdown of secosteroids in immune cells that might fabricate vigorous VDR ligands that regulate soreness or inflammation. In NAFLD, liver monocytes and Kupffer cells are significant controllers of inflammation and fibrosis conditions. New points: propose that intramacrophage conversion of vitamin D precursors gives different, macrophage approved VDR ligands that shape inflammasome commencement and cytokine formation, influencing advancement from steatosis to NASH. Examining blueprint: single-cell metabolomics and single cell RNA sequencing of immune cells in liver to observe internal secosteroid constituent and subordinate with pro-inflammatory transcriptional outlines; pharmacological blockade of internal hydroxylases in innate immune models to inspect results on NLR family pyrin domain contains 3 (NLRP3) instigation and activation of paracrine hematopoietic stem cells.

Conclusion

Topical studies highlight a noteworthy association between Vitamin D deficiency and the commencement and development of NAFLD. By distressing liver lipid breakdown and insulin signal pathway, along with modifying inflammation and oxidative stress, Vitamin D appears as a probable balancing valuable target. Though, difficulties such as an absence of adequate fundamental indication, the absence of standardized administration procedures, and the requirement for long-term experimental trials inhibits its incorporation into clinical practice. Future studies should engage mapping RNA, proteins and metabolites, chrono approach like timing the pharmacological and gut-liver group culture models to dichotomize Vitamin D's zone specified and time-based schedules. Clinical authentication of Vitamin D binding protein and microbiota-associated Vitamin D metabolites might develop biomarker detection. Accuracy grounded Vitamin D variation compounding probiotic, ferroptosis-selection, and chrono-administration approaches might reanalyse NAFLD therapeutics.

Abbreviations

AKT: Protein Kinase B, HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, IU: International Unit, MDA: Malondialdehyde, MeSH: Medical Subject Headings, NAFLD: Non-alcoholic Fatty Liver Disease, NASH: Non-Alcoholic Steatohepatitis, ROS: Reactive Oxygen Species, UVB: Ultraviolet B.

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Author Contributions

Ramani G: provide research idea, conceptualization, Sudha R: data collection, review works, Senthil Kumar B: writing the manuscript, Jayashree S: assisted in manuscript, review works.

Conflict of Interest

The author declares no conflict of interest.

Data Availability

All the authors agreed to give data on request through mail, especially from the corresponding author.

Declaration of generative AI and AI assisted technologies in the writing process

All the authors declare that we did not rely on AI help. It is purely written by our own.

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