

The Effect of Vitamin D Deficiency on Liver Transplant Recipients

Shiva Rezaeian Deloei, Shahabaddin Sorouri¹, Iman Nikkhoo², Ghazaleh Elahabadi³, Benyamin Fazli*

Department of Anesthesiology, Mashhad University of Medical Sciences, ¹Department of Internal Medicine and Anesthesiology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, ²Department of Anesthesiology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, ³Department of Clinical Pharmacy, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran

Abstract

Liver disease, which leads to end-stage organ dysfunction, is becoming one of the top causes of death worldwide. Many molecular and cellular pathways affect liver transplant such as tissue maintenance or rejection. Low 25-dihydroxyvitamin D levels are linked to numerous chronic disorders, including end-stage liver disease. We conducted a thorough search of five major academic databases (ScienceDirect, PubMed, Medline, Google Scholar, and Scopus) for articles published by November 4, 2023. The research was carried out utilizing the seven processes delineated in the Cochrane Handbook. The search for studies involved the use of different keywords, including “Vitamin D,” “deficiency,” and “liver transplantation.” This study analyzed 14 papers that examined Vitamin D levels after liver donation (among the liver’s recipients). The research’s findings revealed that patients with normal Vitamin D levels had a greater rate of recovery after surgery, a stronger immune system, and a lower severity of the risk of transplant rejection than those with Vitamin D deficiency. In general, Vitamin D supplementation before or after liver transplantation can reduce the risk of infection and increase the survival rate in these patients without any toxic effects at standard doses.

Keywords: 1, 25-dihydroxyvitamin D3, calciferol, deficiency, liver transplantation, Vitamin D

INTRODUCTION

The prevalence of liver illness leading to end-stage organ dysfunction is increasing as a significant cause of death in the world.^[1] Liver transplantation is typically the major therapeutic option in most cases. Nevertheless, liver transplantation is a multifaceted activity, and its efficacy depends on various aspects.^[1] Researchers identified a variety of molecular and cellular mechanisms that have a role in maintaining or rejecting transplanted tissue following liver transplantation.

Documents consider that many chronic diseases, such as end-stage liver disease, are associated with low levels of 25-dihydroxy Vitamin D3 (25(OH)D3).^[2] For example, children with end-stage liver failure often experience bone discomfort, fractures, and growth retardation due to deficiencies in Vitamin D3 and hepatic osteodystrophy.^[3] As mentioned in the literature, in addition to the natural role of Vitamin D in controlling calcium and phosphate levels, the active metabolite of Vitamin D, 1 α ,25-dihydroxyvitamin D3 (1 α ,25(OH)2D3), also plays an effective role in balancing the innate and adaptive

immune systems.^[4] According to research, this is highly related to liver allograft function, including the occurrence of acute rejection and infection within the 1st month following transplantation.^[5] Evidently, the activation of neutrophils and macrophages is triggered by the release of inflammatory cytokines and chemokines, leading to tissue damage. After hepatocyte injury, the process of lipid peroxidation, the production of reactive oxygen species, and the production of damage-associated molecular patterns all make neutrophils and macrophages more destructive.^[6,7] Binding of 1,25(OH)2D3 to its specific receptor induces a variety of immunomodulatory

Corresponding Author: Dr. Benyamin Fazli,

Department of Anesthesiology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.
E-mail: fazlib@mums.ac.ir

Received: 15 December 2023; **Revised:** 15 June 2024;
Accepted: 04 August 2024; **Published:** 28 March 2025

Access this article online

Quick Response Code:



Website:
<https://journals.lww.com/ijjt>

DOI:
10.4103/ijot.ijot_148_23

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How to cite this article: Deloei SR, Sorouri S, Nikkhoo I, Elahabadi G, Fazli B. The effect of Vitamin D deficiency on liver transplant recipients. *Indian J Transplant* 2025;19:10-20.

functions, including suppression of Th1 helper lymphocytes both *in vitro* and *in vivo*,^[8,9] downregulation of the generation of cytokines, including interleukin 2 (IL-2) and interferon-gamma,^[10-18] and inhibiting T-lymphocyte proliferation.^[10,19,20] Deficiency or insufficiency of Vitamin D results in metabolic bone diseases (MBD) (such as rickets, osteomalacia, fractures, and bone pain) that are associated with liver transplantation. It can also cause problems in the immune system (such as impaired proliferation and differentiation of immune cells), metabolism (such as insulin resistance),^[3] and cardiovascular disease (such as hypertension).^[3] As a result, researchers are attempting to play a critical role by diagnosing and treating Vitamin D insufficiency in posttransplant patients to alleviate transplant-related complications.^[3] On the other hand, the use of immunosuppressant medications, such as steroids, following transplantation is assumed to be responsible for the delay in recovery of MBD.^[21] Corticosteroids cause an elevation in the breakdown of Vitamin D3, resulting in a deficit of Vitamin D3 and the beginnings of MBD.^[22]

It could be mentioned that the best way to determine one's Vitamin D status is to use cholecalciferol (25(OH)D3), which is the precursor to the active type of Vitamin D, Calcitriol. Vitamin D, in the form of either D2 (ergocalciferol) or D3, can be absorbed by the body through the intestine.^[23] After being attached to albumin or Vitamin D-binding protein (DBP), Vitamin D3 is transported to the liver, where 25-hydroxylation proceeds.^[24] DBP, a protein produced by the liver, binds to 88% of 25(OH)D, which is a form of Vitamin D.^[25] 25(OH)D is delivered to the kidney where it undergoes enzymatic hydroxylation to produce 1,25(OH)D3 or calcitriol, which is the biologically active form of Vitamin D3. The enzyme in the kidney's proximal tubule that is in charge of 1 α -hydroxylation is CYP27B1. Increasing levels of calcium and phosphorus in the bloodstream control the release of calcitriol.^[24] 1,25(OH)D is also well linked to DBP, and the Vitamin D receptor (VDR) is activated by this combination. Numerous human tissues, including the pancreas, liver, gastrointestinal tract, and immunological cells (such as T- and B-lymphocytes and natural killer cells), express VDR.^[26] 1- α -hydroxylase and 24- α -hydroxylase operate on 25(OH)D following separation to produce 1,25-dihydroxyvitamin D and 24, 25-dihydroxyvitamin D.

This systematic review aims to assess the literature on Vitamin D insufficiency following liver transplantation and its potential impact on transplant acceptance or rejection.

MATERIALS AND METHODS

This study investigates the consequences of Vitamin D deficiency after liver transplantation, following the criteria outlined in the Cochrane Handbook for Systematic Reviews.^[27] During our investigation, we did a thorough search across several databases, following both inclusion and exclusion criteria. Studies that were not relevant were removed, and we assessed the scientific accuracy of the included papers.

Subsequently, we analyzed the outcomes of our investigation. We searched the databases ScienceDirect, PubMed, Medline, Google Scholar, and Scopus for relevant papers published up to November 4, 2023.

Process literature search

Between October 30 and November 4, 2023, an extensive search was conducted across five databases: ScienceDirect, Medline, PubMed, Google Scholar, and Scopus, for the present study. This search used specific words like "Vitamin D," AND "deficiency," AND "liver transplantation" to find all relevant research articles published within these databases.

Study selection criteria

Vitamin D deficiency postliver transplantation was included as a criterion. Studies focusing on or recommending Vitamin D supplementation before liver transplantation were excluded from the study. The selected papers were limited to clinical studies written in English. This review specifically omits narrative or systematic review articles, meta-analyses, books, animal research, letters to the editor, qualitative studies, dissertations, or conference papers.

Extraction of data and study planning

We conducted an extensive search across five widely used English databases (as mentioned). Our goal was to identify relevant papers for the current research. Subsequently, titles and abstracts underwent a rigorous screening process based on predefined eligibility criteria. Full versions of the selected papers were then obtained for a final assessment. Duplicates, irrelevant articles, those published in a non-English language, or lacking sufficient data were excluded from further consideration. Two researchers independently evaluated the titles and abstracts, consistently exchanging key observations. Relevant details pertaining to the study aims were meticulously gathered, and a checklist was created using the collected data. Figure 1 illustrates the Preferred Reporting Items for Systematic Reviews and Meta-analyses flow chart detailing the selected articles and their respective procedures.

Quality

Each paper underwent a quality assessment using the Cochrane risk of bias tool, which evaluates clinical studies on random sequence generation, allocation concealment, blinding of participants and staff, blinding of results assessment, attrition bias, insufficient outcome data, selective reporting, and other biases.^[27] The data collection involved categorizing responses as "Yes," "No," and "Unclear," corresponding to low, high, and uncertain risks of bias, respectively.

Overview of the results and conclusions of the study

At last, as demonstrated in Figure 1, a total of 539 articles were discovered in the databases, as determined by the specified keywords. Initially, duplicate articles were eliminated after the titles were examined ($n = 63$). Subsequently, 9 systematic review and narrative review publications were eliminated from the study. Out of the remaining articles, 62 of them

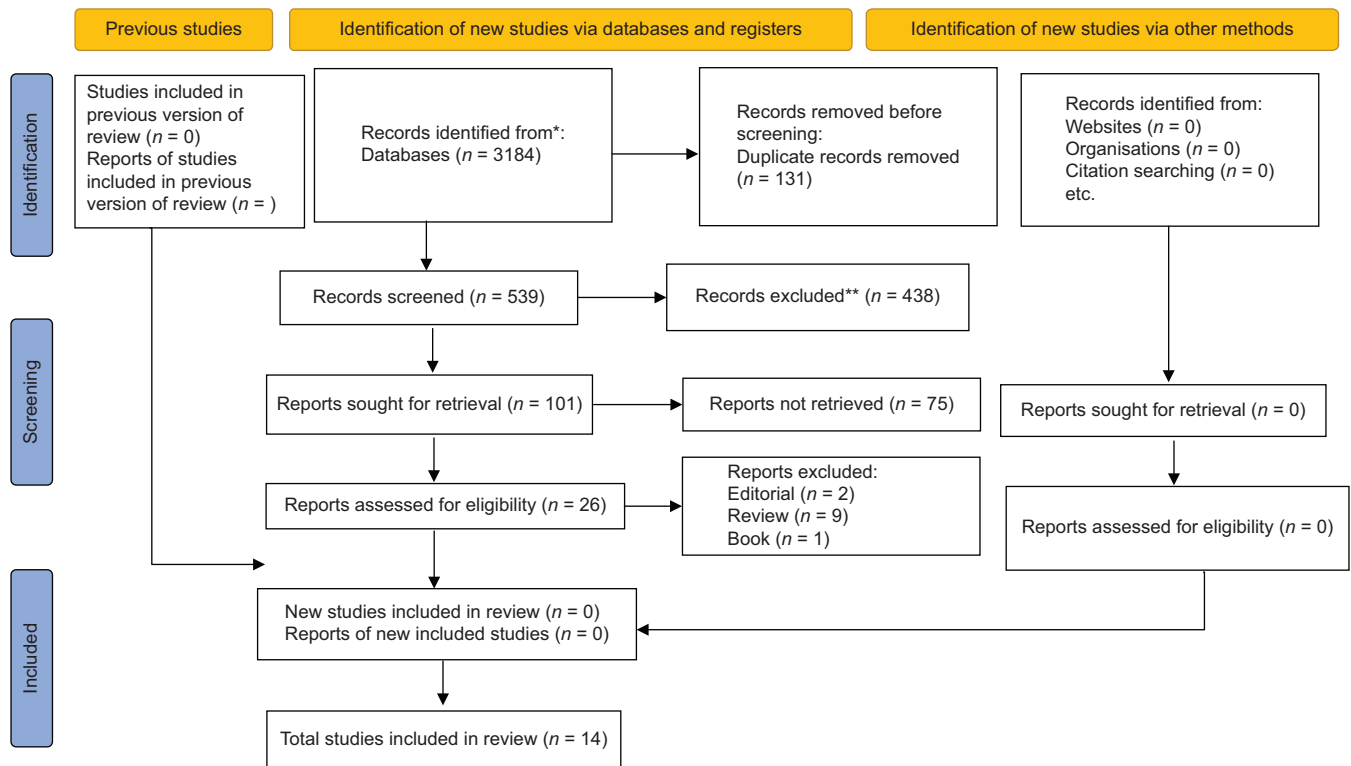


Figure 1: The preferred reporting items for systematic reviews and meta-analyses flowchart depicts the procedure for selecting studies

had titles or purposes that were not relevant to the aim of this study. In addition, there were 2 letters to the editor and 1 book. Ultimately, there were 14 articles left for evaluation and analysis.

A total of 14 papers were concluded on a cohort of 1755 liver transplant recipients. Approximately 61% of the participants were male. Research was carried out in various countries, including Asia (China = 1, Japan = 1, and Turkey = 2), Europe (Switzerland = 2, UK = 1, and Italy = 3), and the USA = 4. Out of the total number of publications, 6 were conducted retrospectively (42.86%). In addition, 4 articles were conducted prospectively (28.57%). Another 4 articles were clinical trials (28.57%).

The research employed several techniques to measure the concentration of Vitamin D including high-performance liquid chromatography (LC) ($n = 3$), LC-tandem mass spectrometry (LC-MS/MS), MS/MS, competitive protein binding assay and radioreceptor assay, and chemoluminescent immunoassay.

The following maintenance drugs were used: Tacrolimus ($n = 9$), cyclosporine ($n = 6$), mycophenolate mofetil ($n = 6$), azathioprine ($n = 2$), and corticosteroids/steroids ($n = 9$), etc.

The outcomes from 8 research articles indicate a clear correlation between Vitamin D deficiency and higher infection rates, as well as lower rates of recovery and survival.^[5,28-33] Vitamin D insufficiency frequently arises as a consequence of liver disorders, leading to liver transplant surgery. Patients with Vitamin D insufficiency were shown to have transplant rejection.^[5]

Table 1 presents the information about the patients and the reports extracted from the studies.

Assessment of methodological approaches for their quality

According to the findings, five of the studies analyzed in this review had a moderate level of bias, whereas the other studies had a low level of bias. The evaluation of the articles' quality is illustrated in Table 2 and Figure 2.

DISCUSSION

The only long-term treatment available for end-stage liver disease is liver transplantation. As previous studies showed, Vitamin D levels are inversely related to the progression of invasive infections as well as acute cellular rejection.^[5,41,42] Studies also suggest that the amount of Vitamin D in liver recipients is a predictor of the severity of the disease (i.e., the Model for End-Stage Liver Disease [MELD] score).^[43]

The relation between Vitamin D and liver transplantation

It is unclear if liver transplantation by itself, along with the graft and functioning of the liver recovery that follows, can raise Vitamin D levels following transplantation.^[30] In addition, it is important to highlight that a variety of factors, such as hemodilution, decreased hepatic production and conversion, decreased synthesis of DBP, increased consumption during the acute phase of the disease and systemic inflammation, increased tissue demand, and enhanced metabolite catabolism, all contribute to diminished levels of Vitamin D in patients with liver disease and, more specifically, acute liver failure.^[44]

Table 1: Extraction and analysis of data from the articles published

Author/year	Type of study	No (male/female)	Group	Age	Follow up	MELD score	Treatment
Rabinovitz <i>et al.</i> , 1992 ^[34] USA	Clinical trial	30 (17/13)	-	46±10 (20–61)	30 days	-	Cyclosporine, glucocorticoids
Argao <i>et al.</i> , 1994 ^[35] USA	Clinical trial	9 (4/5)	-	6–21 months	>4 months	-	Prednisone, cyclosporine, AZA, and VD before transplant
Okajima <i>et al.</i> , 2003 ^[36] Japan	Prospective study	30 (15/15)	-	34 (7–181) months	24 months	-	TAC, steroids, 1-hydroxyvitamin D3 (before the transplant surgery and it was stopped at least one month before transplanting)
Bitetto <i>et al.</i> , 2010 ^[37] Italy	Retrospective study	133 (100/33)	-	55 (23–67)	0–2 months after transplant operation and 3–8 months of post-LT	>15	Cyclosporine- or TAC, corticosteroids, 79 patients received oral Vitamin D3 supplementation before transplant, 53 participants were started during the 1 st month following surgery
Legarda <i>et al.</i> , 2013 ^[32] UK	Retrospective study	199 (106/93)	White ethnicity (<i>n</i> =163), Asian Ethnicity (<i>n</i> =27), and black ethnicity (<i>n</i> =9)	7 (1–18)	1 year	-	Steroids, prednisolone, TAC, CYA, MMF, AZA, SRL, VD supplementation (<i>n</i> =20)
Chaney <i>et al.</i> , 2015 ^[33] USA	Retrospective study	127 (79/48)	Not given VD ≤400,000 VD supplementation >400,000 VD supplementation	57 (21–74)	6 months	23 (12–48)	MMF, prednisone, TAC, basiliximab
Schreiber <i>et al.</i> , 2018 ^[38] Switzerland	Prospective, nested project	140 Kidney transplant=70 (42/28), liver transplant=70 (47/23)	Kidney transplant (<i>n</i> =70), liver transplant (<i>n</i> =70)	55 (43–62)	4.9 years	-	-
Schreiber <i>et al.</i> ^[29] Switzerland	Prospective cohort study	135 (87/48)	-	54 (45–61)	6–30 months posttransplant	20 (14–28)	Basiliximab, rituximab, TAC, MMF, steroids, cyclosporine A, peritransplant cholecalciferol (<i>n</i> =24): 1, 25-dihydroxycholecalciferol (<i>n</i> =2) or posttransplant cholecalciferol (<i>n</i> =55): 1, 25-dihydroxycholecalciferol (<i>n</i> =2)
Zhou <i>et al.</i> , 2019 ^[5] China	Retrospective Cohort Clinical Study	141 (100/41)	VD supplementation group (<i>n</i> =71), non-VD supplementation group (<i>n</i> =70)	49.7 (10.1)	Until June 30, 2018 or until the patient's death	13.5	IL-2 receptor antibody therapy, methylprednisolone, prednisone, TAC, MMF, calcitriol (for VD supplementation group)
Veraldi <i>et al.</i> , 2020 ^[39] Italy	Retrospective study	166 (81/85)	VD deficient (<i>n</i> =56), VD normal (<i>n</i> =98)	15.7	12 months	PELD score: 19.5	-
Doi <i>et al.</i> , 2020 ^[31] USA	Retrospective cohort study	528 (350/178)	No VD supplement (<i>n</i> =131), received VD pretransplant (<i>n</i> =47), received VD posttransplant (<i>n</i> =41), and received VD during both pre- and post-transplant (<i>n</i> =309)	58 (52–64)	<1 year	19 (13–28)	TAC, corticosteroids, MMF
Martucci <i>et al.</i> , 2021 ^[30] Italy	Prospective observational study	67 (55/12)	Severe deficiency (<i>n</i> =47), no severe deficiency (<i>n</i> =20)	58 (52–63)	0–1 year	14 (9–19)	OLT recipients were not routinely supplemented with VD

Contd...

Table 1: Contd...

Author/year	Type of study	No (male/female)	Group	Age	Follow up	MELD score	Treatment
Yuksel <i>et al.</i> , 2021 ^[28] Turkey	Clinical trial	135 (74/61)	-	22 (8–60)	24 months	20 (–10–52)	TAC, steroids, trimethoprim, sulfamethoxazole, acyclovir/ganciclovir, when VD was <20 ng/mL, all patients received 300,000 IU IM stoss VD therapy. Posttransplant stoss dosage was repeated on days 2 and 5 if VD was <20 ng/mL VD supplementation continued at 1000 IU/day on day 7 If serum VD maintained inadequate in the 1 st month posttransplant, the next stoss dosage was given To avoid false high VD levels in the weekly regimen, VD levels were measured at least a week (up to 4 weeks) following the last stoss dose
Arif <i>et al.</i> , 2023 ^[40] Turkey	Clinical trial	118 (99/19)	-	42.4 (0.7–66)	9 months (1–78)	-	TAC, cyclosporine, everolimus, MMF, steroid
Author/year	Serum level of VD	Donor data	Serum VD measurement	Outcome			
Rabinovitz <i>et al.</i> , 1991 ^[34] USA	-	-	HPLC	Prior to OLTx, patient's plasma concentrations of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D were considerably greater than those following OLTx The corticosteroid medication administered after surgery most likely contributed to the decrease in VD levels recorded after OLTx			
Argao <i>et al.</i> , 1994 ^[35] USA	15–50 ng/mL: Normal range of VD, <15 ng/mL: VD deficiency, 25 to 50 pg/mL: Normal range of 1,25(OH) ₂ D	-	HPLC	In seven patient's long-term follow-up (>4 months), bone mineral content returned to normal Serum 25(OH) D levels in six patients who had normal levels prior to orthotopic liver transplantation showed a noticeable fall 1–2 months after the transplant, and then returned to normal by 3–6 months. Before orthotopic liver transplantation, three patients had low serum 25(OH) D levels (<15 ng/mL), which normalized following the procedure In the seven patients who were available for long-term follow-up, sustained normal serum 25(OH) D and 1,25(OH) ₂ D levels preceded or accompanied normalization of bone mineral content, despite the fact that there was no association between serum 25(OH) D level and bone mineral content before transplant While initially low blood 25(OH) D levels eventually normalize within 2–4 months following orthotopic liver transplantation, normal baseline serum 25(OH) D levels decrease 1–2 months after the procedure and then return to normal			
Okajima <i>et al.</i> , 2003 ^[36] Japan	Normal ranges for 25(OH) D ₃ : 15–40 ng/mL and for 1,25(OH) ₂ D ₃ : 20–70 pg/mL	-	Competitive protein binding assay and radio receptor assay	Before transplantation, most had serum levels of 25(OH) D ₃ that spread under the average standard range Serum 25(OH) D ₃ levels were quickly and consistently elevated upon transplantation; liver transplantation may raise low BMD states and 25(OH) D ₃ levels			
Bitetto <i>et al.</i> , 2010 ^[37] Italy	<10–15 ng/mL determined insufficient	Donor age: >45 Donor gender: 71.42% male	Chemo-luminescent immunoassay	A lack of transplant cellular rejection was found to be independently correlated with early Vitamin D ₃ administration ($P<0.05$) The findings imply that VD may support immunological tolerance to the liver allograft			
Legarda <i>et al.</i> , 2013 ^[32] UK	<12 ng/mL: VD deficiency, 12–19 ng/mL: VD insufficiency	-	Tandem mass spectrometry	28 children (14%) had VD deficiency, and 105 children (53%) had inadequate VD levels overall Deficit in VD was more common in the 1 st year following transplant VD levels were not found to be significantly correlated with graft function or any other immunological or metabolic problems			

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Table 1: Contd...

Author/year	Serum level of VD	Donor data	Serum VD measurement	Outcome
Chaney <i>et al.</i> , 2015 ^[33] USA	>30 ng/mL: No VD deficiency, 20–30 ng/mL: Mild VD deficiency, 15–19.9 ng/mL: Moderate VD deficiency, <15 ng/mL: Severe VD deficiency	-	Liquid chromatography-tandem mass spectrometry	Following liver transplantation, VD deficiency and insufficiency are common in children, particularly in the winter and spring and in patients who are not white The early posttransplant phase and elevated PTH have a substantial correlation with deficiency of VD 74% of the 107 patients who were evaluated at LT still lacked VD Prior to LT, only 62% of patients took VD supplements Severe and moderate deficits were rare 4 months after LT and less common at LT A correlation was seen between the improvement in the VD deficient category at LT and the increasing intake of VD (>400,000 IU total) ($P=0.004$) Data revealed no correlation between functional status, fractures, or readmissions after LT and VD inadequacy at LT
Schreiber <i>et al.</i> , 2018 ^[38] Switzerland	<25 nmol/L: Severe VD deficiency, ≥25 and <50 nmol/L: VD deficiency, ≤50 nmol/L: No VD deficiency	DBD, living related, living unrelated	Immunodiagnostic systems	Most liver transplant recipients had extremely inadequate or deficient 25-OHD levels. Most liver recipients showed severe 25-OHD deficient ($n=27$, 38.6%) or deficiency ($n=23$, 32.9%) 6 months after transplantation. Twenty patients had 25-OHD levels of at least 50 nmol/L found in them. 25-OHD levels were steady peri- and 6-month posttransplant ($P=0.414$) 6 months posttransplant 1, 25-(OH) 2D levels were similar to peri-transplant levels ($P=0.179$)
Schreiber <i>et al.</i> ^[29] Switzerland	<50 nmol/L (20 ng/mL): VD deficiency, ≥50 nmol/L no VD deficiency	Deceased donor ($n=126$), living donor ($n=9$)	Roche diagnostics VD total assay	At the time of transplantation and 6 months later, VD deficiency was prevalent, although there was no discernible shift in the median 25-OHD levels VD deficiency was found to be a risk factor in univariable analyses for incident infections that occurred within the first 6 months of transplantation and for bacterial infections that developed between 6 and 30 months of transplantation After multiple confounders were taken into account in a multivariable analysis, these associations were not found
Zhou <i>et al.</i> , 2019 ^[5] China	>50 nmol/L: VD sufficiency, 25–50 nmol/L: VD insufficiency, <25 nmol/L: severe VD deficiency	After cardiac death, donor's livers were used for transplants	Chemo-luminescent immunoassay	One significant independent risk factor for ACR was a VD deficiency In patients receiving VD supplements, the incidence of bacterial and fungal infections as well as ACR was decreased The level of VD was strongly correlated with death VD supplementation may enhance immune tolerance to liver allografts because it is linked to a decreased risk of infection and ACR
Veraldi <i>et al.</i> , 2020 ^[39] Italy	<20 ng/mL: VD deficiency	-	HPLC	No correlation was found between vitamin status and the risk of acute rejection or the severity of liver fibrosis. The prevalence of VD deficiency after transplantation has not changed
Doi <i>et al.</i> , 2020 ^[31] USA	<20 ng/mL it was considered low	Donor age: 42 (30–54) Donor gender: 59.9%	-	Lower survival following LT was linked to VD deficiency during the posttransplant period, and a lower risk of ACR was linked to VD supplementation after transplantation The pretransplant period's VD levels might play a significant role in ACR 5-year OS was correlated with older age (>60) and posttransplant VD sufficiency VD supplementation as nutritional support may be helping to improve long-term effects
Martucci <i>et al.</i> , 2021 ^[30] Italy	<20 ng/mL: VD deficiency, and <12 ng/mL: Severe VD deficiency	Donor age: 61.7±17.2	HPLC	In the first 28 postoperative days, preoperative VD was strongly linked to invasive infection and is correlated with disease severity Following OLT, there was a strong correlation between the value on postoperative day 28 and graft function
Yuksel <i>et al.</i> , 2021 ^[28] Turkey	<30–21 ng/mL: Insufficient, 20–10 ng/mL: Deficiency,		Chemiluminescence microparticle immunoassay	In 98% of patients, the VD status had increased to >30 ng/mL after 6 months The severe VD deficiencies group showed a greater infection rate (18.7%) than the VD deficiency group, but only at pre-LT

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Table 1: Contd...

Author/year	Serum level of VD	Donor data	Serum VD measurement	Outcome
Yuksel <i>et al.</i> , 2021 ^[28] Turkey	<10 ng/mL: Severe deficiency as	-	-	Serum VD levels had no effect on survival After LT, VD levels significantly decreased The only factor correlated with the VD status was the infection rate
Arif <i>et al.</i> , 2023 ^[40] Turkey	>20 ng/mL: VD deficiency, ≤20 ng/mL	Donors for 18 patients were dead bodies	-	A deficit of 25(OH) D3 is probably present in over 50% of patients who get transplants The initial year following transplantation and the time duration during which corticosteroid-based immunosuppressive medication is utilized to avoid tissue rejection are particularly significant risk factors for 25(OH) D3 deficiency

MELD: Model of end-stage liver disease, TAC: Tacrolimus, CYA: Cyclosporine, MMF: Mycophenolate mofetil, AZA: Azathioprine, SRL: Sirolimus, HPLC: High performance liquid chromatography, ACR: Acute cellular rejection, OS: Overall survival, OLT: Orthotopic liver transplantation, PELD: Pediatric end-stage liver disease, DBD: Donation after brain death, VD: Vitamin D, BMD: Bone mineral density, PTH: Parathyroid hormone, LT: liver transplantation, OLTx: orthotopic liver transplantation

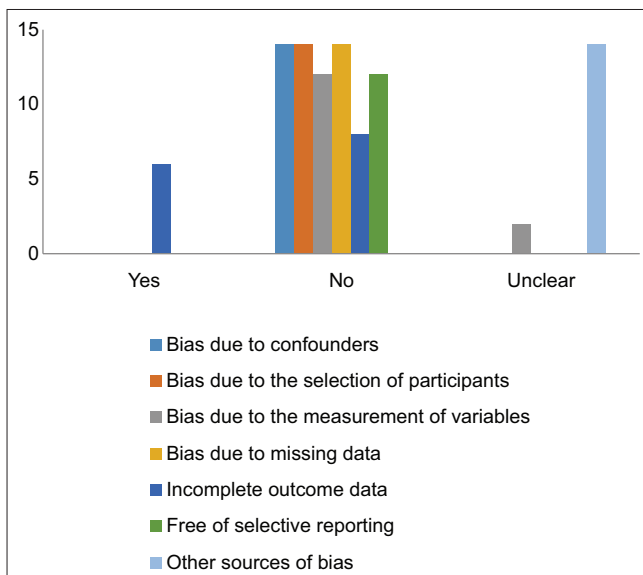


Figure 2: Analysis of the provided papers for quality control

Evidence declared that Vitamin D analogs exhibit superior binding affinity to the VDR, leading to impressive biological effects in transplant conditions.^[45]

Therefore, in experimental transplantation setups, Vitamin D and numerous substitutes for it have been examined. Martucci *et al.* studied the change in Vitamin D levels in orthotopic liver transplantation (OLT) recipients at the start and throughout the first 28 days following transplantation. Severe Vitamin D deficiency was present in most of the population, and this condition was linked with the severity of pre-OLT disease. Regarding additional results, they discovered that lower Vitamin D levels on postoperative day (POD) 28 were linked to a higher incidence of incomplete graft recovery and that preoperative Vitamin D levels were connected with infections in the first 28 days following OLT. In addition, they discovered that also in hepatocellular carcinoma recipients, there was a definite inverse relationship between Vitamin D and MELD and Child–Pugh scores.^[30] According to Redaelli *et al.*, giving rats 1,25(OH)2D3 inhibits acute hepatic allograft rejection and increases the rats' chances of surviving after

transplant. Furthermore, they noted that using 1,25(OH)2D3 in combination with other immunosuppressive medications at lower doses might be another method to benefit from its immunosuppressive impact.^[46]

It could be noted that Vitamin D undergoes two continuous hydroxylation processes to convert into the biologically active metabolite 1,25-dihydroxyvitamin D3 (1,25(OH)2D3), also known as calcitriol. Renal cytochrome P450 (CYP)27B1 activity is the primary determinant of systemic 1,25(OH)2D3 levels. Controlling systemic levels of 1,25(OH)2D3 is a complex balancing act between CYP27B1 and CYP24A1, which is mediated by parathyroid hormone (PTH) and the phosphaturic hormone fibroblast growth factor 23.^[4]

25-hydroxylases such as CYP2R1, CYP2D11, CYP2D25, and CYP3A4 in the liver convert Vitamin D to 25-hydroxyvitamin D3 (25(OH)D3). The 25(OH)D3 level is taken into account because it is the most common circulating form of Vitamin D. An important immunomodulatory function for 1,25(OH)2D3 is suggested by the extensive expression of the nuclear receptor VDR and Vitamin D-metabolizing enzymes in almost all cells of the innate and adaptive immune system, including macrophages, dendritic cells (DCs), and activated B- and T-cells.^[47-49]

Bitetto *et al.* studied the risk of acute allograft rejection after human liver transplantation, as well as the influence of Vitamin D. Data demonstrated that Vitamin D may promote immunological tolerance to liver transplantation, and pretransplant blood Vitamin D concentration is associated with rejection events. As a result, they concluded that early Vitamin D intake is related to a lower risk of rejection.^[37] There are some evidence including in recipients of cardiac transplants, administering calcitriol had a positive effect that reduced the need for immunosuppressant medication.^[50] In the context of kidney transplantation, Vitamin D administration has been positively linked to acute rejection rates as well as a slowdown in the deterioration of graft function.^[51]

The level of Vitamin D serum concentrations

Although there is currently inadequate data to support this claim, it is probable that larger Vitamin D consumption in large populations may raise the risk of overdose in specific

Table 2: Assessment of research quality using Cochrane's risk-of-bias methodologies

Author/year	Bias due to confounders	Bias due to the selection of participants	Bias due to the measurement of variables	Bias due to missing data	Incomplete outcome data	Free of selective reporting	Other sources of bias	Risk of bias
Rabinovitz <i>et al.</i> , 1992 ^[34] USA	No	No	No	No	Yes	No	Unclear	Intermediate
Argao <i>et al.</i> , 1994 ^[35] USA	No	No	No	No	Yes	No	Unclear	Intermediate
Okajima <i>et al.</i> , 2003 ^[36] Japan	No	No	No	No	Yes	No	Unclear	Intermediate
Bitetto <i>et al.</i> , 2010 ^[37] Italy	No	No	No	No	No	No	Unclear	Low
Legarda <i>et al.</i> , 2013 ^[32] UK	No	No	No	No	No	No	Unclear	Low
Chaney <i>et al.</i> , 2015 ^[33] USA	No	No	No	No	No	No	Unclear	Low
Schreiber <i>et al.</i> , 2018 ^[38] Switzerland	No	No	No	No	Yes	No	Unclear	Intermediate
Schreiber <i>et al.</i> ^[29] Switzerland	No	No	No	No	No	No	Unclear	Low
Zhou <i>et al.</i> , 2019 ^[5] China	No	No	No	No	No	No	Unclear	Low
Veraldi <i>et al.</i> , 2020 ^[39] Italy	No	No	No	No	Yes	No	Unclear	Intermediate
Doi <i>et al.</i> , 2020 ^[31] USA	No	No	Unclear	No	No	No	Unclear	Low
Martucci <i>et al.</i> , 2021 ^[30] Italy	No	No	No	No	No	No	Unclear	Low
Yuksel <i>et al.</i> , 2021 ^[28] Turkey	No	No	No	No	No	No	Unclear	Low
Arif <i>et al.</i> , 2023 ^[40] Turkey	No	No	Unclear	No	Yes	No	Unclear	Low

patient groups. The hypercalcemic toxicity of Vitamin D and its bioactive derivative 1,25(OH)₂D₃ restricts their therapeutic consumption since supraphysiologic doses are necessary to modify the dysregulated immune responses. However, no adverse effects have been identified in people with dosages of up to 50,000 IU Vitamin D per week for 12 weeks, or 100,000 IU per week for 1 month following 100,000 IU monthly for a duration of 5 months.^[52,53] Documents showed Vitamin D serum concentrations of 20 ng/mL (50 nmol/L) are sufficient for calcium homeostasis and bone health, but Vitamin D serum values of 40–80 ng/mL (100–200 nmol/L) are likely to be necessary for most of the immunomodulatory advantages.^[54] Moreover, lowering 25OHD levels to <30 ng/mL is directly related to the reduction of active absorption of intestinal calcium and the increase in secretion of serum PTH, which plays a role in maintaining normal serum calcium levels.^[55,56] Evidence from non-obese diabetic mice suggests that 25(OH)D concentrations above 90 ng/mL (225 nmol/L) would be necessary to control immunological dysregulation; however, such high dosages are likely to cause calcemic adverse effects when used routinely. Moreover, Vitamin D insufficiency (<20 ng/mL or 50 nmol/L) can result in various clinical disorders, with the most notable one being rickets, a musculoskeletal condition characterized by bow-leggedness.^[26] Newer studies detail links to additional conditions, including cardiovascular disease, cancer, autoimmune symptoms, and compromised antimicrobial defenses.^[57]

Association between Vitamin D and Immunological Processes

The effects of Vitamin D deficiency on various inflammatory immunological processes have been a source of concern, and previous studies have shown that inflammation is a reason for a wide range of chronic diseases. Infections, inflammation, and autoimmune diseases all have a close relationship with one another. Aside from hereditary reasons, autoimmune disorders

are assumed to be influenced significantly by environmental triggers, including viruses, bacteria, and other infectious pathogens.

Genetic research indicates a connection between variations in Vitamin D-related genes, such as the VDR and Vitamin D metabolism genes, and specific disorders. Furthermore, epidemiological evidence demonstrates a solid association between a lack of Vitamin D and the higher occurrence of autoimmune and chronic inflammatory disorders. These observations, along with the immunomodulatory effects of 1,25(OH)₂D₃ seen in laboratory and living organisms, support the idea that Vitamin D supplementation could potentially offer defense against certain immunological disorders.^[4]

For instance, the immunoregulatory actions of VDR agonists have been shown in models of allograft rejection, which has resulted in successful intervention in a variety of graft rejection models, including skin, small bowel, pancreatic islets, kidney, liver, and heart allografts. It has been demonstrated in experimental models that the combination of inadequate dosages of immunosuppressive drugs such as cyclosporine A (CsA) and VDR agonists can postpone acute rejection. It has been demonstrated in experimental models that the combination of VDR agonists with a suboptimal dose of CsA or other immunosuppressive agents can postpone acute rejection.^[58]

Association between Vitamin D deficiency and incidences of invasive infections following orthotopic liver transplantation

Studies have revealed that the level of Vitamin D before surgery is connected to the severity of the disease; for example, in Martucci's study, following OLT, the value of POD 28 had a significant correlation with graft function. Throughout the initial 28 days following OLT, 42 isolated or concurrent invasive

infections were identified in 41.8% of people, and 33% of them had been diagnosed with septic shock.^[30] Similarly, in Zhou's study,^[5] data found that the incidence of bacterial and fungal infections was higher in the group that did not receive Vitamin D treatment than in the group that did. The findings revealed that the control group had a higher risk of infection in the 1st month following transplantation than the Vitamin D supplement group. As a matter of fact, patients with sepsis had lower blood levels of Vitamin D and a higher death rate. Since it was discovered that both innate and adaptive immune system cells express the VDR, there has been an increase in interest in Vitamin D's role in infection. A crucial connection exists between the activation of toll-like receptors and antimicrobial responses through Vitamin D. It has been demonstrated that administering a high dose of cholecalciferol (400,000 IU) *in vivo* to patients experiencing early stages of sepsis and septic shock can safely and quickly raise blood levels of Vitamin D and cathelicidin, an endogenous peptide that binds endotoxins and is dependent on Vitamin D and is primarily present in human neutrophils.^[42]

The mechanism of Vitamin D in the immune system

The active metabolite of Vitamin D3 (1α -25(OH)2D3) strongly influences the activity of some immune cells. Within DCs, the presence of 1α -25(OH)2D3 prompts the development of a tolerogenic phenotype. Therapeutic applications in autoimmune disorders and transplantation situations are promising for 1,25D3 – DCs due to their key function in maintaining a balance between immunogenicity and tolerance. 1α -25(OH)2D3 inhibits the differentiation and maturation processes of DCs,^[59] which are derived from bone marrow progenitors or peripheral blood monocytes. This causes the DCs to remain in a state of tolerance.^[60] DCs produced in the presence of 1α -25(OH)2D3 (1,25D3-DCs) retain CD14 expression, have low levels of CD1a expression, exhibit decreased levels of antigen-presenting molecules (such as human leukocyte antigen [HLA]-ABC and-DR), and costimulatory molecules (such as CD80 and CD86), and have reduced secretion of stimulatory cytokines (such as IL-12 and IL-23) that play a role in regulating the polarization of T effector cells.^[61-63] There is also an increase in the production of regulatory cytokines such as IL-10, transforming growth factor- β , and tumor necrosis factor- α , and the expression of inhibitory molecules such as programmed death-ligand (PD-L) 1, PD-L2, and immunoglobulin-like transcripts-3 and -4.^[61,64,65]

Therefore, 1,25D3-DCs affect T-cell behavior by generating hyporesponsiveness and changing T-cell polarization from T-helper (Th)1 and Th17-mediated inflammatory reactions into Treg responses.^[8-10] Furthermore, 1α -25(OH)2D3 significantly influences the ability of DCs to migrate by increasing the expression of the chemokine receptor CXCR3, which directs cells toward inflamed areas. Several microarray investigations have been conducted on various cell types, such as subsets of immune cells, to discover specific transcriptional targets of 1α -25(OH)2D3. Nevertheless, only the first time intervals are valuable for differentiating between major and secondary

target genes, as it is widely thought that the complete transcriptional pathway controlled by 1,25(OH)2D3 takes approximately 2–3 h.^[66]

In addition, at least one Vitamin D responsive element should be present in the promoter region of primary 1,25(OH)2D3 targets. As a result, the development of the chromatin immunoprecipitation sequencing (ChIP-seq) method allowed for a more in-depth examination of transcriptional regulation over the entire genome. For example, the CD14 gene expression has been observed to be early increased by 1α -25(OH)2D3 therapy. Furthermore, multiple VDR binding sites are located in the CD14 promoter region, demonstrating that CD14 is a direct target of active Vitamin D3.^[67,68]

In past years, research has demonstrated that 1α -25(OH)2D3 has the ability to quickly control the activity of many immunological genes in monocytes and DCs, such as CD274, CD40, CD80, and HLA-DR.^[67-70] Regarding the physiological effects of active Vitamin D, it is necessary to consider not only the major targets of 1α -25(OH)2D3 but also the secondary targets. 1α -25(OH)2D3 stimulates the activation of other transcription factors that have the potential to control the expression of secondary target genes.^[71] Another method of indirect regulation by 1α -25(OH)2D3 involves protein–protein interactions with other transcription factors, such as nuclear factor kappa B (NF- κ B), specifically in the case of IL-12.^[72] This contact prevents NF- κ B from binding to its genomic locations or causing epigenetic alterations.^[73] Moreover, Vanherwegen *et al.* confirmed the ability of 1α -25(OH)2D3 to stimulate tolerogenic DCs, which maintain their stability when exposed to pro-inflammatory signals in both laboratory settings and living organisms.

This finding enhances the potential application of these 1,25D3-DCs in promoting tolerance in autoimmune diseases and presents new ways for treating graft-versus-host disease. However, more combining ChIP-seq studies and investigations in human 1,25D3-DCs could provide additional knowledge into genomic VDR binding locations, allowing for improved distinction of primary and secondary targets.^[74]

Limitation and suggestion

Due to the retrospective nature of the majority of the studies, it was not possible to check the level of Vitamin D in patients before and after the transplant operation, as well as other side factors that play a role in getting an infection or increasing the speed of recovery, as well as the effect of underlying diseases, which were not thoroughly examined in all studies. Future research should look at the impacts of immunosuppressive drugs and their possible function in the absorption or blockage of vitamins like Vitamin D and their receptors at the cellular level.

CONCLUSION

Following liver transplantation surgery, individuals commonly experience a decline in their Vitamin D levels as a normal condition. Moreover, administering Vitamin D supplements

before or following liver transplantation can mitigate the risk of infection and enhance the survival rate among these patients, without inducing any detrimental effects when administered in the recommended dosages.

Acknowledgments

This work was funded by the Mashhad University of Medical Sciences and Health Services, Mashhad, Iran.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Vitamin D AND
Deficiency AND
Liver transplantation



14 papers



1755 liver transplant patients



Low Levels of vitamin D seen in post liver transplant patients



Low levels of Vitamin D associated with incomplete graft recovery and infection



Adequate Levels of vitamin D associated with graft tolerance



Vitamin D levels : 40 to 80 ng/ml is required for immunomodulatory advantages



Dendritic cells in the presence of active Vitamin D remains less immunogenic



Increased levels of regulatory cytokines



1,25 (OH)2D3 also has secondary targets



1,25 (OH)2D3 regulates protein protein interactions

Administering Vitamin D supplements before or following liver transplantation is associated with reduced infection rate and enhanced survival in liver transplant

Author,
Shiva Rezaeian Deloei, Shahabaddi
Sorouri, Iman Nikkhoo, Ghazaleh
Elahabadi, Benyamin Fazli
VA by Dr.Jithu Kurian,