HNSJ Humanities & Natural Sciences Journal
ISSN: (e) 2709-0833
www.hnjournal.net

Peer-Reviewed Journal
Indexed at: NSP - SJIF
Impact Factor 2022 = 4.91

RESEARCH TITLE

Viral Hepatitis and Vitamin D Deficiency

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HNSJ, 2024, 5(8); https://doi.org/10.53796/hnsj58/13

Published at 01/08/2024 **Accepted at 22/07/2024**

Abstract

This review aims to determine whether vitamin D levels were correlated with viral Hepatitis. Chronic liver disorders brought on by hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are frequently linked to vitamin D deficiency. According to studies, low vitamin D levels probably don't stop HBV replication and are a factor in chronic HBV infection's poor clinical results. Higher levels of vitamin D or vitamin D supplementation have been linked in meta-analyses to better sustained virological response (SVR) to interferon-based therapy in individuals with long-term HCV infection. For individuals with vitamin D levels more than 30 ng/mL, the odds ratio for reaching SVR was 1.57 (95% CI: 1.12-2.2) in comparison to those with lower levels. Furthermore, compared to healthy controls, individuals with chronic hepatitis B (CHB) had considerably decreased vitamin D levels, according to a systematic review and meta-analysis. Serum vitamin D levels and HBV viral loads were found to be inversely correlated. Patients with chronic viral hepatitis B and C are frequently found to be vitamin D deficient, and increasing vitamin D levels or supplementation may enhance treatment outcomes, especially for HCV infection. In summary, vitamin D deficiency was found to be strongly correlated with poor clinical outcomes in individuals with HBV and HCV, such as the development of liver cirrhosis and hepatocellular carcinoma.

Key Words: 25(OH)D3; chronic liver disease; hepatitis infection; vitamin D; vitamin D deficiency; Liver cirrhosis;

Introduction

The phrase "vitamin D" refers to a group of related substances. When exposed to UVB rays from the sun, 7-dehydrocholesterol is converted to previtamin D in the skin, which is then isomerized to become vitamin D. This process is part of the metabolism of vitamin D. Additionally, vitamin D is consumed with food in the form of cholecalciferol (vitamin D3) from animals and ergocalciferol (vitamin D2) from plants.[1].

Vitamin D metabolism and function

In the early 1900s, vitamin D was originally recognized as a prohormone. It controls both skeletal and non-skeletal processes and is a fat-soluble secosteroid [1]. For osteoblasts and osteoclasts to rebuild osseous structures and prevent osteoporosis, adequate amounts of vitamin D are necessary[1,2]. In order to support proper bone mineralization and prevent hypocalcaemia, vitamin D maintains vital blood calcium and phosphate concentrations and facilitates the absorption of calcium, magnesium, phosphate, iron, and zinc from the gut. The non-skeletal activities of vitamin D have drawn more interest with the identification of the vitamin D receptor (VDR). VDR is a transcription factor that belongs to the nuclear receptor family and is expressed on over 35 different types of solid tissues, macrophages, T cells, and B cells [3, 4, 5]. Through VDR activation, vitamin D is implicated in physiological processes such as immune response control, cell proliferation, and differentiation[6,7, 8]. As a result, vitamin D is thought to be an effective regulator of pathophysiological pathways in a number of malignancies, metabolic illnesses, and infectious diseases[9, 10]. There are two forms of vitamin D: vitamin D2 (25(OH)D2; ergocalciferol) and vitamin D3 (25(OH)D3; cholecalciferol). Over 90% of vitamin D3, the most common form of vitamin D, is created in the skin by exposure to sunshine; the remaining 10% is obtained from food[1]. Little quantities of vitamin D2 are obtained from plants, and it is not dependent on sunlight[11]. Vitamins D2 and D3 are both inactive. They must be hydroxylated in the liver and kidney in order to be successively transformed into their intermediate metabolite, calcidiol, 25(OH)D, and their final active form, calcitriol, 1,25(OH)2D, in order for them to become biologically active. The process of hydroxylation involves adding a hydroxyl group (-OH) to vitamin D2 and D3 in the liver, resulting in the formation of 25-hydroxyvitamin D [25(OH)D]. In the kidney, the metabolites undergo further hydroxylation to yield calcitriol, which is the active form. The active form functions as a hormone in the bloodstream to control calcium and phosphate levels and to encourage normal bone growth and remodeling[12]. The short half-life of calcitriol and its 1000-fold lower serum concentration than that of 25(OH)D make precise quantification of the substance difficult. However, because 25(OH)D has a half-life of roughly three weeks, it can be used as a suitable and generally accurate predictor of a person's vitamin D status[13].

Vitamin D Deficiency

There isn't a common definition for vitamin D insufficiency. In the past, the assessment of vitamin D level was done empirically, for example, by making a clear diagnosis of osteomalacia in adults and pediatric rickets[14, 15]. These days, the diagnosis of deficiency is based on measuring serum levels of vitamin D, which only reflects the available supply rather than functional activity and does not provide enough evidence to support a consensus definition of vitamin D deficiency. There is an inverse relationship between parathyroid hormone (PTH) levels and serum 25(OH)D levels. PTH production is stimulated by low vitamin D levels, and as a result, PTH may be used as a stand-in diagnostic for vitamin D deficiency. Nevertheless, lower PTH levels are not usually the result of elevated vitamin D levels. Serum PTH levels will be at a low, stable level if vitamin D levels are higher than

about 30 ng/mL[16,17]. Therefore, inadequacy (< 20 ng/mL), insufficiency (20–30 ng/mL), and sufficiency (> 30 ng/mL) are the current and commonly accepted criteria of vitamin D levels[15]. A deficit in vitamin D is linked to a variety of ailments, such as bone abnormalities, several infectious and autoimmune diseases, asthma, cancer, and mental health issues[15, 18, 19]. Both deficiency and insufficiency of vitamin D are involved in vitamin D inadequacy, which is a health concern that is often overlooked in many populations [20]. Nearly half of the population suffers from vitamin D insufficiency in affluent nations[15]. Furthermore, an international evaluation of the vitamin D status in postmenopausal women with osteoporosis revealed that 24% of them had a severe deficit (< 10 ng/mL), with central and southern Europe reporting the greatest prevalences[13]. A cross-sectional, observational study conducted at 61 sites across the United States revealed a similar pattern, showing that among 1536 postmenopausal women getting osteoporosis therapy, 52% and 18%, respectively, had 25(OH)D levels of less than 30 ng/mL and 20 ng/mL[16]. In addition to Asia and Africa, western and northern nations also frequently suffer from vitamin D deficiency[21–25]. Three sizable cross-sectional studies were conducted in China (n = 3262)[23], South Korea (n = 6925)[22], and Thailand (n = 2641)[21] to evaluate serum levels in Asian populations. These investigations showed that the largest prevalences of deficiency were seen in South Korea (males 47%; females 65%) and China (69%), where deficiency was defined as levels of less than 20 ng/mL[22]. In Thailand, however, the prevalence of insufficiency was just 6%, a much lower prevalence[21]. Its proximity to the equator is most likely the cause of this. However, smaller sample sizes in subsequent studies conducted in Vietnam revealed that the prevalence of vitamin D insufficiency ranges from 16 to 63%[26, 27]. African communities are known to have low levels of vitamin D due to skin pigmentation, traditional full-length clothing, and the prevalence of infectious diseases such as malaria, HIV/AIDS, and tuberculosis, which are linked to vitamin D insufficiency [28–32]. According to a cross-sectional study of adults participating in the National Health and Nutrition Examination Survey (n = 8415), vitamin D deficiency was found in as much as 81% of African Americans but only 28% of people of European ancestry[33]. Studies have consistently shown that immigrants from Africa to the United States and Europe are more likely to be deficient in vitamin D[34, 35]. These studies highlight the significant role that skin pigmentation plays in lowering vitamin D synthesis. Many infectious diseases are prevalent in Sub-Saharan Africa and some regions of Asia, and these illnesses may have an impact on vitamin D levels. Numerous research looked at the relationship between vitamin D insufficiency and the severity and course of infectious disorders, namely respiratory tract infections (39–41) and tuberculosis (36–38). Lately, there has been evidence linking vitamin D insufficiency to both the severity and advancement of chronic liver illnesses linked to viral hepatitis as well as susceptibility to viral hepatitis[42–44].

Inadequacy of vitamin D in chronic hepatitis B and C

A public health concern that affects over one-third of the world's population is hepatitis infection. Hepatitis infection can remain chronic in certain infected persons, and this can result in consequences such decompensated cirrhosis, hepatocellular cancer, and hepatic fibrosis. Numerous host and environmental factors control the evolution of hepatitis infection to chronic infection and liver breakdown. Nutrition, hormones, and other variables influence the host immune factors. One such chemical that has several effects on fibrosis, inflammation, and immunity is vitamin D [45].

It's unclear if low vitamin D levels contribute to or are the outcome of some illnesses, such as persistent viral liver disorders. A recent systematic review indicated that, rather than being a cause of disease, vitamin D insufficiency may be an outcome and a biological marker of

declining health, driving 25(OH)D to low concentrations. This conclusion was based on 290 prospective and intervention studies [46]. Insufficient amounts of vitamin D can exacerbate inflammation and fibrosis in the liver[10]. According to other research, vitamin D insufficiency is unquestionably linked to poor clinical outcomes and an accelerated course of chronic liver illnesses brought on by alcoholism, viral hepatitis, and nonalcoholic fatty liver disease (NAFLD)[47–51]. Despite the fact that vitamin D is linked to NAFLD, a recent study found no correlation between the two conditions[52]. A thorough analysis of the relationship between vitamin D deficiency and the etiology of non-alcoholic fatty liver disease (NAFLD) found that vitamin D may be taken as a supplement to help treat NAFLD. Clinical trials, however, found that vitamin D supplementation had less of an effect on the pathophysiology of NAFLD, including hepatic steatosis, damage, and fat [54, 55]. Notably, low vitamin D levels may also be a factor in the decreased antiviral responses seen when treating hepatitis B and C with IFN/RBV[56]. There are currently no comparable studies available for more modern treatment plans including IFN-free and direct-acting antiviral medications. Regardless of the cause, a significant prevalence of vitamin D insufficiency is present in the development of nearly all chronic liver diseases[47,57,58]. Serum vitamin D levels < 20 ng/mL range from 16% to 100%, according to investigations on vitamin D insufficiency and deficiency in chronic hepatitis B and C[59,60]. Studies have shown that vitamin D insufficiency/deficiency is highly prevalent in both healthy populations and viral hepatitis patients; however, in hepatitis patients, the rates of deficiency were much greater than in controls [49].

Vitamin D and severity of liver fibrosis

The risk of vitamin D insufficiency is elevated in cases of severe liver illness. Additionally, there is proof that low serum levels of vitamin D can exacerbate fibrosis, hasten the onset of cirrhosis, and worsen fibrosis in other body systems. When 1,25 (OH)2 vitamin D is administered to the respiratory system, it causes pro-fibrogenic transforming growth factor (TGF)-1 and other markers of mesenchymal and epithelial cells to be downregulated. As a result, vitamin D may be a physiologically significant inhibitor of lung fibroblasts' and epithelial cells' pro-fibrotic phenotype [61]. causes of vitamin D insufficiency in patients with advanced liver fibrosis. Vitamin D has a strong effect on the extracellular matrix's composition by controlling the migration, differentiation, and proliferation of fibroblasts and vascular smooth muscle cells [62]. Therefore, insufficient vitamin D may alter the balance between specific matrix metalloproteinases (MMPs), such as MMP-2 and -9, and their inhibitors, resulting in increased collagen formation, or it may serve as a signal for fibrogenesis through the secretion of TGF-1. Given their crucial roles in the breakdown of fibronectin and collagen IV in the disseminated tissue, MMP-2 and MMP-9 are especially relevant to the liver [63]. Natural killer cells' antifibrotic effect is enhanced by vitamin D in mice models [64]. Furthermore, because the hepatitis C virus is inactivated by T cells through a vitamin D pathway, it is possible that low serum vitamin D concentrations limit T cell function. In patients with CHC, the ensuing enhanced necroinflammation would exacerbate fibrosis [65]. It has been suggested that vitamin D regulates programmed cell death, or apoptosis. It functions on hepatocytes in the liver as an antiapoptotic factor [66]. Hepatocyte apoptosis has been identified as a key initiator factor for the build-up of extracellular matrix, fibrogenesis, and ultimately cirrhosis. The increased frequency of vitamin D insufficiency among CHC patients and the correlation between the severity of liver fibrosis and vitamin D deficient severity could both be explained by the aforementioned variables. Numerous recent investigations have demonstrated this. However, Stauber et al. [68] found no significant difference in vitamin D levels in 179 genotype 1/4 CHC patients with fibrosis stage F0–2 compared with F3–4 (23.0 ± 13.7 ng/mL vs. 20.2 ± 10.8 ng/mL, P > 0.05). Kastens et al. [67]

found no association between the severity of liver fibrosis and levels of vitamin D in 157 patients with CHC of various genotypes (no additional data were available). As a result, decreased serum vitamin D levels may be a pro-fibrogenic entity and may have a role in the development of histological abnormalities in CHC. As a "general" antifibrotic drug in CHC, vitamin D deficiency correction may therefore have significant therapeutic significance by reducing hepatic apoptosis and hence fibrogenesis [69].

Conclusion:

Vitamin D effectively lowers ALT enzyme levels in individuals with acute hepatitis and reduces the propagation of viruses, as well as albumin and platelet counts. Vitamin D insufficiency has been seen in the majority of hepatitis patients, particularly in advanced liver disorders linked to unfavorable clinical outcomes. On the other hand, vitamin D might have varied effects throughout different stages of an illness. Thus, it is advised to carry out additional research in this field.

References:

1. Wintermeyer E, Ihle C, Ehnert S, Stöckle U, Ochs G, de Zwart P, Flesch I, Bahrs C, Nussler AK. Crucial Role of Vitamin D in the Musculoskeletal System. Nutrients 2016; 8: (6). E319 [PMID: 27258303 DOI: 10.3390/nu8060319]

2. DeLuca HF. Overview of general physiologic features and functions of vitamin D. Am J Clin Nutr 2004; 80: 1689S-1696S [PMID: 15585789]

3. Norman AW. From vitamin D to hormone D: fundamentals of the vitamin D endocrine system essential for good health. Am J Clin Nutr 2008; 88: 491S-499S [PMID: 18689389]

4. Aranow C. Vitamin D and the immune system. J Investig Med 2011; 59: 881-886 [PMID: 21527855 DOI: 10.2310/ JIM.0b013e31821b8755]

5. Baeke F, Takiishi T, Korf H, Gysemans C, Mathieu C. Vitamin D: modulator of the immune system. Curr Opin Pharmacol 2010; 10: 482-496 [PMID: 20427238 DOI: 10.1016/j.coph.2010.04.001]

6.Yang L, Ma J, Zhang X, Fan Y, Wang L. Protective role of the vitamin D receptor. Cell Immunol 2012; 279: 160-166 [PMID: 23246677 DOI: 10.1016/j.cellimm.2012.10.002]

7. Bikle D. Nonclassic actions of vitamin D. J Clin Endocrinol Metab 2009; 94: 26-34 [PMID: 18854395 DOI: 10.1210/jc.2008-1454]

8. Wactawski-Wende J, Kotchen JM, Anderson GL, Assaf AR, Brunner RL, O'Sullivan MJ, *et al*. Calcium plus vitamin D supplementation and the risk of colorectal cancer. N Engl J Med 2006; 354: 684-696 [PMID: 16481636 DOI: 10.1056/ NEJMoa055222]

9. Plum LA, DeLuca HF. Vitamin D, disease and therapeutic opportunities. Nat Rev Drug Discov 2010; 9: 941-955 [PMID: 21119732 DOI: 10.1038/nrd3318]

10. Targher G, Bertolini L, Scala L, Cigolini M, Zenari L, Falezza G, Arcaro G. Associations between serum 25-hydroxyvitamin D3 concentrations and liver histology in patients with non-alcoholic fatty liver disease. Nutr Metab Cardiovasc Dis 2007; 17: 517-524 [PMID: 16928437 DOI: 10.1016/j.numecd.2006.04.002]

11. Heaney RP, Recker RR, Grote J, Horst RL, Armas LA. Vitamin D(3) is more potent than vitamin D(2) in humans. J Clin Endocrinol Metab 2011; 96: E447-E452 [PMID: 21177785 DOI: 10.1210/jc.2010-2230]

12.Bikle DD. Vitamin D metabolism, mechanism of action, and clinical applications. Chem Biol 2014; 21: 319-329 [PMID: 24529992 DOI: 10.1016/j.chembiol.2013.12.016]

13.Lips P, Duong T, Oleksik A, Black D, Cummings S, Cox D, Nickelsen T. A global study of vitamin D status and parathyroid function in postmenopausal women with osteoporosis: baseline data from the multiple outcomes of raloxifene evaluation clinical trial. J Clin Endocrinol Metab 2001; 86: 1212-1221 [PMID: 11238511 DOI: 10.1210/jcem.86.3.7327]

14.Sarkar S, Hewison M, Studzinski GP, Li YC, Kalia V. Role of vitamin D in cytotoxic T lymphocyte immunity to pathogens and cancer. Crit Rev Clin Lab Sci 2016; 53: 132-145 [PMID: 26479950 DOI: 10.3109/10408363.2015.1094443]

15.Hoan NX, Tong HV, Song LH, Meyer CG, Velavan TP. Vitamin D deficiency and hepatitis viruses-associated liver diseases: A literature review. World J Gastroenterol. 2018 Jan 28;24(4):445-460. doi: 10.3748/wjg.v24.i4.445. PMID: 29398866; PMCID: PMC5787780.

16.Holick MF, Siris ES, Binkley N, Beard MK, Khan A, Katzer JT, Petruschke RA, Chen E, de Papp AE. Prevalence of Vitamin D inadequacy among postmenopausal North American women receiving osteoporosis therapy. J Clin Endocrinol Metab 2005; 90: 3215-3224 [PMID: 15797954 DOI: 10.1210/jc.2004-2364]

17. Thomas MK, Lloyd-Jones DM, Thadhani RI, Shaw AC, Deraska DJ, Kitch BT, Vamvakas EC, Dick IM, Prince RL, Finkelstein JS. Hypovitaminosis D in medical inpatients. N Engl J Med 1998; 338: 777-783 [PMID: 9504937 DOI: 10.1056/NEJM199803193381201]

18.Rosen CJ. Clinical practice. Vitamin D insufficiency. N Engl J Med 2011; 364: 248-254 [PMID: 21247315 DOI: 10.1056/ NEJMcp1009570]

19.van den Berg KS, Marijnissen RM, van den Brink RH, Naarding P, Comijs HC, Oude Voshaar RC. Vitamin D deficiency, depression course and mortality: Longitudinal results from the Netherlands Study on Depression in Older persons (NESDO). J Psychosom Res 2016; 83: 50-56 [PMID: 27020077 DOI: 10.1016/j.jpsychores.201 6.03.004]

20. Tangpricha V, Pearce EN, Chen TC, Holick MF. Vitamin D insufficiency among free-living healthy young adults. Am J Med 2002; 112: 659-662 [PMID: 12034416]

21.Chailurkit LO, Aekplakorn W, Ongphiphadhanakul B. Regional variation and determinants of vitamin D status in sunshineabundant Thailand. BMC Public Health 2011; 11: 853 [PMID: 22074319 DOI: 10.1186/1471-2458-11-853]

22. Choi HS, Oh HJ, Choi H, Choi WH, Kim JG, Kim KM, Kim KJ, Rhee Y, Lim SK. Vitamin D insufficiency in Korea--a greater threat to younger generation: the Korea National Health and Nutrition Examination Survey (KNHANES) 2008. J Clin Endocrinol Metab 2011; 96: 643-651 [PMID: 21190984 DOI: 10.1210/jc.2010-2133]

23.Lu L, Yu Z, Pan A, Hu FB, Franco OH, Li H, Li X, Yang X, Chen Y, Lin X. Plasma 25-hydroxyvitamin D concentration and metabolic syndrome among middle-aged and elderly Chinese individuals. Diabetes Care 2009; 32: 1278-1283 [PMID: 19366976 DOI: 10.2337/dc09-0209]

24.Fraser DR. Vitamin D-deficiency in Asia. J Steroid Biochem Mol Biol 2004; 89-90: 491-495 [PMID: 15225826 DOI: 10.1016/ j.jsbmb.2004.03.057]

25.Nimitphong H, Holick MF. Vitamin D status and sun exposure in southeast Asia. Dermatoendocrinol 2013; 5: 34-37 [PMID: 24494040 DOI: 10.4161/derm.24054]

26.Nguyen HT, von Schoultz B, Nguyen TV, Dzung DN, DucPT, Thuy VT, Hirschberg AL. Vitamin D deficiency in northern Vietnam: prevalence, risk factors and associations with bone mineral density. Bone 2012; 51: 1029-1034 [PMID: 22878155 DOI:

10.1016/j.bone.2012.07.023]

27.Brock K, Cant R, Clemson L, Mason RS, Fraser DR. Effects of diet and exercise on plasma vitamin D (25(OH)D) levels in Vietnamese immigrant elderly in Sydney, Australia. J Steroid Biochem Mol Biol 2007; 103: 786-792 [PMID: 17215122 DOI: 10.1016/j.jsbmb.2006.12.048]

28Gibney KB, MacGregor L, Leder K, Torresi J, Marshall C, Ebeling PR, Biggs BA. Vitamin D deficiency is associated with tuberculosis and latent tuberculosis infection in immigrants from sub-Saharan Africa. Clin Infect Dis 2008; 46: 443-446 [PMID: 18173355 DOI: 10.1086/525268]

29.Prentice A, Schoenmakers I, Jones KS, Jarjou LM, Goldberg GR. Vitamin D Deficiency and Its Health Consequences in Africa. Clin Rev Bone Miner Metab 2009; 7: 94-106 [PMID: 25110467 DOI: 10.1007/s12018-009-9038-6]

30. Cusick SE, Opoka RO, Lund TC, John CC, Polgreen LE. Vitamin D insufficiency is common in Ugandan children and is associated with severe malaria. PLoS One 2014; 9: e113185 [PMID: 25470777 DOI: 10.1371/journal.pone.0113185]

31.Kibirige D, Mutebi E, Ssekitoleko R, Worodria W, Mayanja-Kizza H. Vitamin D deficiency among adult patients with tuberculosis: a cross sectional study from a national referral hospital in Uganda. BMC Res Notes 2013; 6: 293 [PMID: 23886009 DOI: 10.1186/1756-0500-6-293]

32. Mehta S, Giovannucci E, Mugusi FM, Spiegelman D, Aboud S, Hertzmark E, Msamanga GI, Hunter D, Fawzi WW. Vitamin D status of HIV-infected women and its association with HIV disease progression, anemia, and mortality. PLoS One 2010; 5: e8770 [PMID: 20098738 DOI: 10.1371/journal.pone.0008770]

33. Gutiérrez OM, Farwell WR, Kermah D, Taylor EN. Racial differences in the relationship between vitamin D, bone mineral density, and parathyroid hormone in the National Health and Nutrition Examination Survey. Osteoporos Int 2011; 22: 1745-1753 [PMID: 20848081 DOI: 10.1007/s00198-010-1383-2]

34. Emilion E, Emilion R. Estimation of the 25(OH) vitamin D threshold below which secondary hyperparathyroidism may occur among African migrant women in Paris. Int J Vitam Nutr Res 2011; 81: 218-224 [PMID: 22237770 DOI: 10.1024/0300-9831/a000073]

35. Kruger MC, Kruger IM, Wentzel-Viljoen E, Kruger A. Urbanization of black South African women may increase risk of low bone mass due to low vitamin D status, low calcium intake, and high bone turnover. Nutr Res 2011; 31: 748-758 [PMID: 22074799 DOI: 10.1016/j.nutres.2011.09.012]

36. Chocano-Bedoya P, Ronnenberg AG. Vitamin D and tuberculosis. Nutr Rev 2009; 67: 289-293 [PMID: 19386033 DOI: 10.1111/ j.1753-4887.2009.00195.x]

37. Daley P, Jagannathan V, John KR, Sarojini J, Latha A, Vieth R, Suzana S, Jeyaseelan L, Christopher DJ, Smieja M, Mathai D. Adjunctive vitamin D for treatment of active tuberculosis in India: a randomised, double-blind, placebo-controlled trial. Lancet Infect Dis 2015; 15: 528-534 [PMID: 25863562 DOI: 10.1016/ S1473-3099(15)70053-8]

38. Talat N, Perry S, Parsonnet J, Dawood G, Hussain R. Vitamin d deficiency and tuberculosis progression. Emerg Infect Dis 2010; 16: 853-855 [PMID: 20409383 DOI: 10.3201/eid1605.091693]

39. Cannell JJ, Vieth R, Umhau JC, Holick MF, Grant WB, Madronich S, Garland CF,

Giovannucci E. Epidemic influenza and vitamin D. Epidemiol Infect 2006; 134: 1129-1140 [PMID: 16959053 DOI: 10.1017/S0950268806007175]

40. Fleming DM, Elliot AJ. Epidemic influenza and vitamin D. Epidemiol Infect 2007; 135: 1091-1092; author reply 1092-1095 [PMID: 17352841 DOI: 10.1017/S0950268807008291]

41. Schwalfenberg G. Vitamin D for influenza. Can Fam Physician 2015; 61: 507 [PMID: 26071153]

42 Fisher L, Fisher A. Vitamin D and parathyroid hormone in outpatients with noncholestatic chronic liver disease. Clin Gastroenterol Hepatol 2007; 5: 513-520 [PMID: 17222588 DOI: 10.1016/j.cgh.2006.10.015]

43.Fedirko V, Duarte-Salles T, Bamia C, Trichopoulou A, Aleksandrova K, Trichopoulos D, *et al*. Prediagnostic circulating vitamin D levels and risk of hepatocellular carcinoma in European populations: a nested case-control study. Hepatology 2014; 60: 1222-1230 [PMID: 24644045 DOI: 10.1002/hep.27079]

44.Ding N, Yu RT, Subramaniam N, Sherman MH, Wilson C, Rao R, Leblanc M, *et al*. A vitamin D receptor/SMAD genomic circuit gates hepatic fibrotic response. Cell 2013; 153: 601-613 [PMID: 23622244 DOI: 10.1016/ j.cell.2013.03.028]

45.Banerjee, A.; Athalye, S.; Khargekar, N.; Shingade, P.; Madkaikar, M. Chronic Hepatitis B and Related Liver Diseases Are Associated with Reduced 25- Hydroxy-Vitamin D Levels: A Systematic Review and MetaAnalysis. Biomedicines 2023, 11, 135. Analysis. https://doi.org/10.3390/ biomedicines11010135

46. Autier P, Boniol M, Pizot C, Mullie P. Vitamin D status and ill health: a systematic review. Lancet Diabetes Endocrinol 2014; 2: 76-89 [PMID: 24622671 DOI: 10.1016/S2213-8587(13)70165-7]

47. Wong GL, Chan HL, Chan HY, Tse CH, Chim AM, Lo AO, Wong VW. Adverse effects of vitamin D deficiency on outcomes of patients with chronic hepatitis B. Clin Gastroenterol Hepatol 2015; 13: 783-790.e1 [PMID: 25445773 DOI: 10.1016/ j.cgh.2014.09.050]

48. Trépo E, Ouziel R, Pradat P, Momozawa Y, Quertinmont E, Gervy C, Gustot T, Degré D, Vercruysse V, Deltenre P, Verset L, Gulbis B, Franchimont D, Devière J, Lemmers A, Moreno C. Marked 25-hydroxyvitamin D deficiency is associated with poor prognosis in patients with alcoholic liver disease. J Hepatol 2013; 59: 344-350 [PMID: 23557869 DOI: 10.1016/j.jhep.2013.03.024]

49. Lange CM, Bojunga J, Ramos-Lopez E, von Wagner M, Hassler A, Vermehren J, Herrmann E, Badenhoop K, Zeuzem S, Sarrazin C. Vitamin D deficiency and a CYP27B1-1260 promoter polymorphism are associated with chronic hepatitis C and poor response to interferon-alfa based therapy. J Hepatol 2011; 54: 887-893 [PMID: 21145801 DOI: 10.1016/j.jhep.2010.08.036]

50.Eliades M, Spyrou E. Vitamin D: a new player in non-alcoholic fatty liver disease? World J Gastroenterol 2015; 21: 1718-1727 [PMID: 25684936 DOI: 10.3748/wjg.v21.i6.1718]

51. Kwok RM, Torres DM, Harrison SA. Vitamin D and nonalcoholic fatty liver disease (NAFLD): is it more than just an association? Hepatology 2013; 58: 1166-1174 [PMID: 23504808 DOI: 10.1002/ hep.26390]

52.Ha Y, Hwang SG, Rim KS. The Association between Vitamin D Insufficiency and Nonalcoholic Fatty Liver Disease: A PopulationBased Study. Nutrients 2017; 9: pii: E806 [PMID: 28749418 DOI: 10.3390/nu9080806]

53.Barchetta I, Cimini FA, Cavallo MG. Vitamin D Supplementation and Non-Alcoholic Fatty Liver Disease: Present and Future. Nutrients 2017; 9: 10-15 [PMID: 28906453 DOI: 10.3390/ nu9091015]

54. Barchetta I, Del Ben M, Angelico F, Di Martino M, Fraioli A, La Torre G, Saulle R, Perri L, Morini S, Tiberti C, Bertoccini L, Cimini FA, Panimolle F, Catalano C, Baroni MG, Cavallo MG. No effects of oral vitamin D supplementation on non-alcoholic fatty liver disease in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled trial. BMC Med 2016; 14: 92 [PMID: 27353492 DOI: 10.1186/s12916-016-0638-y]

55. Sharifi N, Amani R, Hajiani E, Cheraghian B. Does vitamin D improve liver enzymes, oxidative stress, and inflammatory biomarkers in adults with non-alcoholic fatty liver disease? A randomized clinical trial. Endocrine 2014; 47: 70-80 [PMID: 24968737 DOI: 10.1007/s12020-014-0336-5]

56. García-Álvarez M, Pineda-Tenor D, Jiménez-Sousa MA, Fernández-Rodríguez A, Guzmán-Fulgencio M, Resino S. Relationship of vitamin D status with advanced liver fibrosis and response to hepatitis C virus therapy: a meta-analysis. Hepatology 2014; 60: 1541-1550 [PMID: 24975775 DOI: 10.1002/hep.27281]

57.Stokes CS, Volmer DA, Grünhage F, Lammert F. Vitamin D in chronic liver disease. Liver Int 2013; 33: 338-352 [PMID: 23402606 DOI: 10.1111/liv.12106]

58.Chan HL, Elkhashab M, Trinh H, Tak WY, Ma X, Chuang WL, Kim YJ, Martins EB, Lin L, Dinh P, Charuworn P, Foster GR, Marcellin P. Association of baseline vitamin D levels with clinical parameters and treatment outcomes in chronic hepatitis B. J Hepatol 2015; 63: 1086-1092 [PMID: 26143444 DOI: 10.1016/ j.jhep.2015.06.025]

59.Zhao XY, Li J, Wang JH, Habib S, Wei W, Sun SJ, Strobel HW, Jia JD. Vitamin D serum level is associated with Child-Pugh score and metabolic enzyme imbalances, but not viral load in chronic hepatitis B patients. Medicine (Baltimore) 2016; 95: e3926 [PMID: 27399065 DOI: 10.1097/MD.0000000000003926]

60.Esmat G, El Raziky M, Elsharkawy A, Sabry D, Hassany M, Ahmed A, Assem N, El Kassas M, Doss W. Impact of vitamin D supplementation on sustained virological response in chronic hepatitis C genotype 4 patients treated by pegylated interferon/ ribavirin. J Interferon Cytokine Res 2015; 35: 49-54 [PMID: 25061714 DOI: 10.1089/jir.2014.0060]

61. Ramirez AM, Wongtrakool C, Welch T, Steinmeyer A, Zugel U, Roman J. Vitamin D inhibition of pro-fibrotic effects of transforming growth factor beta1 in lung fibroblasts and epithelial cells. J Steroid Biochem Mol Biol 2010; 118: 142–50.

62. Timms PM, Mannan N, Hitman GA, et al. Circulating MMP9, vitamin D and variation in the TIMP-1 response with VDR genotype: mechanisms for inflammatory damage in chronic disorders? QJM 2002; 95: 787–96.

63. Han YP. Matrix metalloproteinases, the pros and cons, in liver fibrosis. J Gastroenterol Hepatol 2006; 21(Suppl. 3): S88–S91.

64. Doron S, Amer J, Abu-Tair L, Mahamid M, Abu-Mouch S, Safadi R. Anti-fibrotic immune modulation effects of 25-OH vitamin D in HCV and mice fibrosis model. J Hepatol 2011; 54: S68.

65. Shen L. Vitamin D controls T cell activation: implication for causal association between vitamin D deficiency and fibrosis in chronic hepatitis C. Hepatology 2010; 52: 1864.

66. Nakano T, Cheng YF, Lai CY, et al. Impact of artificial sunlight therapy on the progress

of non-alcoholic fatty liver disease in rats. J Hepatol 2011; 55: 415– 25

67. Kastens S, Grüngreiff K, Terkamp C, et al. Serum zinc but not serum vitamin D levels are associated with disease severity and treatment response in chronic hepatitis C virus infection. J Hepatol 2011; 54: S458.

68.Stauber R, Scherzer T, Putz-Bankuti C, et al. Baseline vitamin D levels do not influence SVR in patients with chronic HCV genotype 1 or 4 infection undergoing peginterferon/ribavirin treatment. J Hepatol 2011; 54: S468

69. Suneetha PV, Sarin SK, Goyal A, Kumar GT, Shukla DK, Hissar S. Association between vitamin D receptor, CCR5, TNF-alpha and TNFbeta gene polymorphisms and HBV infection and severity of liver disease. J Hepatol 2006; 44: 856–63.