**Name of Journal:** *World Journal of Hepatology*

**Manuscript NO:** 71348

**Manuscript Type:** LETTER TO THE EDITOR

**Vitamin D supplementation for autoimmune hepatitis: A need for further investigation**

Sergi CM. Vitamin D and AIH

Consolato M Sergi

**Consolato M Sergi,** Anatomic Pathology Division, Children’s Hospital of Eastern Ontario (CHEO), University of Ottawa, Ottawa K1H 8L1, ON, Canada

**Consolato M Sergi,** Department of Laboratory Medicine and Pathology, University of Alberta, Edmonton T6G 2B7, AB, Canada

**Author contributions:** Sergi CM drafted the manuscript following collection of the literature data.

**Corresponding author: Consolato M Sergi, MD, PhD,** **Chief,** Anatomic Pathology Division, Pediatric Pathologist, Children’s Hospital of Eastern Ontario (CHEO), 401 Smyth Road, Ottawa K1H 8L1, ON, Canada. csergi@cheo.on.ca

**Received:** September 4, 2021

**Revised:** October 25, 2021

**Accepted: December 23, 2021**

**Published online:**

**Abstract**

Autoimmune hepatitis is a chronic liver disease harboring an autoimmune basis and progressive character. Despite still obscurity in etiology and pathogenesis, some evidence supports the importance of sustaining the immune system. Vitamin D is a lipo-soluble vitamin, which has been identified as decreased in our body. It is often due to the daily habit change and decrease of individual sun exposure due to the increase of the ultraviolet-induced potential melanocytic transformation. Here, we emphasize the importance of vitamin D supplementation in patients affected with liver disease.

**Key Words:** Vitamin D; Autoimmune hepatitis; Supplementation; Immunostimulants; Liver

Sergi CM. Vitamin D supplementation for autoimmune hepatitis: A need for further investigation. *World J Hepatol* 2021; In press

**Core Tip:** Autoimmune hepatitis (AIH) is a chronic liver disease with an autoimmune basis. It can progress quite dramatically. The immune system may play a role in determining how this disease progresses. Vitamin D is key in supporting the immune system with or without vitamin deficiency. Here the vitamin D supplementation in patients affected with AIH is emphasized.

**TO THE EDITOR**

We read with interest the article of Fan *et al*[1] on the pathogenesis of autoimmune hepatitis (AIH) in one of the most recent issues of the journal *World Journal of Hepatology*[1]. The authors summarize the evidence on this complex disease with evidence of the last five years. Although several autoimmune conditions may involve the liver, the three most common autoimmune hepatopathies are AIH, primary sclerosing cholangitis, and primary biliary cholangitis. These diseases may occur *seriatim* or as part of “overlap” syndromes. AIH is a chronic progressive liver disease whose, unfortunately, etiopathogenesis is still obscure. AIH has conventional features of autoimmune disorders, including antibodies generated by an organism in response to an element of its own tissues (autoantibodies), association with a complex of genes on chromosome 6 in humans (human leukocyte antigen genes or haplotypes) which encode proteins located on the cell surface and responsible for the regulation of the immune system, and a T-cell mediated necroinflammatory process. Histologically, a prominent inflammatory infiltrate consisting of both lymphocytes and plasma cells is seen. These inflammatory cells form clusters with accentuation at the edges of the portal tracts with striking periportal interface inflammatory activity at places (Figure 1). Genetic susceptibility, immunologic dysregulations, and environmental factors may play a role. In particular, viral infection and drugs may trigger a set of dysfunctions of the immune system. Currently, almost all patients require steroid hormones plus immunosuppressive maintenance therapy independently of age or genetic predisposition. However, long-term medication adverse effects, complications, and relapse after drug withdrawal are pretty variable. It has been suggested that we may need to do more in improving the satisfaction of our patients[2].

Vitamin D can be successful in numerous diseases[3-5], and it is crucial to emphasize the role of vitamin D in AIH. After the turn of the last century, the interest in vitamin D increased enormously. Rickets has accompanied human civilization for centuries in both old and new continents. Still, despite supplementation of this vitamin in our diet, hypovitaminosis and child neglect cases have been diagnosed[6]. Population surveys have indicated that important sectors of childhood and pregnant women will be affected by vitamin D inadequacy in their life. The change of the habits with indoor living, inadequate sunlight exposure, vitamin-deficient diets, and high rates of nutrition allergy are likely playing a significant role in growing the inadequacy of vitamin supplementation for some people worldwide.

Vitamin D is fat-soluble. It plays a leading role in calcium homeostasis[7,8]. Vitamin D is tightly linked to immunity. It plays a remarkable role in inflammatory and cancer pathways[5,9,10]. The immune system's cellular components possess vitamin D receptors (VDRs). These receptors can metabolize the active form of vitamin D or calcitriol, which is also labelled 1,25-dihydroxy vitamin D, and abbreviated as 1,25(OH)2D. The storage form of vitamin D is 25-hydroxyvitamin D or 25(OH)D. It can be transformed by activated T and B lymphocytes to 1,25(OH)2D *in vitro*. In addition, 1,25(OH)2D acts on immunological cells in an obvious autocrine or paracrine fashion. This aspect has been considered crucial for several infections, as suggested in COVID-19 (coronavirus disease-2019), the infection caused by the severe acute respiratory syndrome–related coronavirus 2 (SARS-CoV-2), despite controversial data[11-13].

Peripheral blood mononuclear cells harbor VDR, supporting vitamin D's notable role in regulating the immune system. Other than activity on the cells of the immune system, vitamin D increases the absorption of calcium from the small intestine and participates in cilia movements[14]. Nicolaysen *et al*[15] and Haavaldsen *et al*[16,17] also observed that animals, which were kept for determined set of the experiments on a low calcium diet, exhibited much greater calcium absorption competence than experimental animals kept on a diet with an adequate amount of calcium. Calmodulin, an intermediate calcium-binding messenger protein expressed in all eukaryotic cells, is localized in the hamster's ciliated cells. Indeed, calcium is prominent for cilia's bioenergetic activity and the bile canaliculus[18-21].

Vitamin D is crucial in maintaining innate immunity[22-29]. Various studies have demonstrated that it also behaves as an essential regulator of immnunologic system and host defense. It includes exquisitely respiratory host defense. Transforming growth factor-beta 1 (TGF-β1) decreases the host defense of epithelial cells by altering the vitamin D-reconciled expression of host defense peptides and proteins[30]. When primary CD4+ T cells from healthy donors were obtained and cultured in specific and well detailed Th17-polarizing requirements, vitamin D lowered the expression of Th17 markers. Subsequently, there was also a decrease in the secretion of proinflammatory cytokines. It involved interleukin 17A (IL-17A) and interferon-gamma (IFN-γ) predominantly. It induced an expansion of the CD4+ T cell subset expressing the highest levels of CD25 cells. It also upregulated their expression of CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) and Foxp3 (forkhead box P3) regulatory markers. It seems that vitamin D supplements regulate the microbiome by increasing the abundance of beneficial bacterial strains.

Moreover, vitamin D improves glucocorticoids[31,32], increases the production of glutathione[33], and inhibits hepatic stellate cells[34]. Vitamin D may influence the histological severity of AIH and advanced liver fibrosis, and the need for liver transplantation. A recent systematic review summarized the importance of vitamin D supplementation for AIH[31]. A substantial scientific background supports the use of vitamin D in AIH, showing that circulating concentrations of 25-hydroxyvitamin D are less than 30 ng/mL or 75 nmol/L (1 nmol/L = 0.4 ng/mL 25-hydroxyvitamin D, and 1 ng/mL = 2.5 nmol/L 25-hydroxyvitamin D) in more than four fifths (81%) of Turkish patients with AIH, matched to about two fifths (44%) of healthy individuals[35]. These patients have clearly demonstrated a higher frequency rate of non-response to steroids (glucocorticoid therapy) than patients exhibiting no identifiable vitamin D deficiency (*P* = 0.04). In AIH, severe interface inflammatory activity of the liver or interface hepatitis, higher stages of hepatic fibrosis, and therapy failure have been linked with 25-hydroxyvitamin D3 levels in serum of less than 10 ng/mL. Several international hepatologists have suggested that vitamin D deficiency should be proposed as a prognostic biomarker in AIH[35].

Most people are satisfactorily protected against vitamin D deficiency, but others may show a level of susceptibility. In addition, some individuals may develop such deficiency, which may target several critical functions of the body. Therefore, the National Institutes for Health recommends supplementation of vitamin D for some categories. They include breastfed infants, individuals living in cold climatic conditions, or subjects working night shifts, adults harboring a body mass index of 30 or over, and individuals who underwent gastric bypass surgery, suffer from inflammatory bowel disease, or cover continuously their skin for religious reasons. Infants should receive 400 international units (IU) of vitamin D *per* day until weaning. It equals 10 micrograms (mcg or μg) considering that the mass that gives 1 IU is dependent on the rate or potency of the compound and varies obviously from compound to compound depending on what is being measured. In the case of vitamin D, 1 IU is the biological equivalent of 0.025 mcg ergocalciferol or cholecalciferol. After infancy and up to the 70th year of age, the dosage of vitamin D supplementation should be 600 IU (15 mcg). Individuals older than 70 years should receive 800 IU (20 mcg) of vitamin D. Skin exposure for 5–30 min at least twice *per* week may be sufficient for most individuals. However, underlying conditions may still require an increase in vitamin D supplementation.

In conclusion, vitamin D is not a new miraculous drug but a compound discovered more than half a century ago. It has immunoregulatory, anti-inflammatory, anti-oxidative, and anti-fibrotic effects, affecting remarkably the occurrence and outcome of immune-mediated diseases. Vitamin D may influence the histological severity of AIH, liver fibrosis, and the need for liver transplantation. Thus, the supplementation of this vitamin in these patients is potentially critical in reducing the interface hepatitis. There are still several unexplored fields for vitamin D, and the study of how genetic variants of *VDR* genes can affect the susceptibility of individuals to chronic autoimmune liver diseases should be at the forefront of the developments in hepatology. Still, independently from the *VDR* haplotype, it seems that patients affected with AIH will benefit from vitamin D supplementation, and an advocacy for its use may be critical in internal medicine.

**REFERENCES**

1 **Fan JH**, Liu GF, Lv XD, Zeng RZ, Zhan LL, Lv XP. Pathogenesis of autoimmune hepatitis. *World J Hepatol* 2021; **13**: 879-886 [PMID: 34552694 DOI: 10.4254/wjh.v13.i8.879]

2 **Touré M**, Kouakou CRC, Poder TG. Dimensions Used in Instruments for QALY Calculation: A Systematic Review. *Int J Environ Res Public Health* 2021; **18** [PMID: 33919471 DOI: 10.3390/ijerph18094428]

3 **Abrams** SA. Bone Health in School Age Children: Effects of Nutritional Intake on Outcomes. *Front Nutr* 2021; **8:** 773425 [PMID: 34869539 DOI: 10.3389/fnut.2021.773425]

4 **Ng** JY, Hilal A, Maini I. What traditional, complementary, and integrative medicine recommendations exist across osteoporosis clinical practice guidelines? A systematic review and quality assessment. *Integr Med Res* 2022; **11:** 100803 [PMID: 34840950 DOI: 10.1016/j.imr.2021.100803]

5 **Olabiyi** AA, Passos DF, da Silva JLG, Schetinger MRC, Rosa Leal DB. Role of purinergic system and vitamin D in the anti-cancer immune response. *Life Sci* 2021; **287:** 120110 [PMID: 34743945 DOI: 10.1016/j.lfs.2021.120110]

6 **Sergi C**, Linderkamp O. Pathological case of the month: classic rickets in a setting of significant psychosocial deprivation. *Arch Pediatr Adolesc Med* 2001; **155**: 967-968 [PMID: 11483129 DOI: 10.1001/archpedi.155.8.967]

7 **Hernigou P**, Sitbon J, Dubory A, Auregan JC. Vitamin D history part III: the "modern times"-new questions for orthopaedic practice: deficiency, cell therapy, osteomalacia, fractures, supplementation, infections. *Int Orthop* 2019; **43**: 1755-1771 [PMID: 31037319 DOI: 10.1007/s00264-019-04334-w]

8 **Davis RL**, Aksornsri A, Papachrisanthou MM. Vitamin D Screening Variations in Children and Adolescents: Who should be Screened? *J Pediatr Nurs* 2019; **45**: 57-61 [PMID: 30753957 DOI: 10.1016/j.pedn.2019.02.002]

9 **Floreani A**, Restrepo-Jiménez P, Secchi MF, De Martin S, Leung PSC, Krawitt E, Bowlus CL, Gershwin ME, Anaya JM. Etiopathogenesis of autoimmune hepatitis. *J Autoimmun* 2018; **95**: 133-143 [PMID: 30385083 DOI: 10.1016/j.jaut.2018.10.020]

10 **Shapiro H**, Thaiss CA, Levy M, Elinav E. The cross talk between microbiota and the immune system: metabolites take center stage. *Curr Opin Immunol* 2014; **30**: 54-62 [PMID: 25064714 DOI: 10.1016/j.coi.2014.07.003]

11 **Pinzon RT**, Angela, Pradana AW. Vitamin D deficiency among patients with COVID-19: case series and recent literature review. *Trop Med Health* 2020; **48**: 102 [PMID: 33342439 DOI: 10.1186/s41182-020-00277-w]

12 **Wise J**. Covid-19: Evidence is lacking to support vitamin D's role in treatment and prevention. *BMJ* 2020; **371**: m4912 [PMID: 33334783 DOI: 10.1136/bmj.m4912]

13 **Mariani J**, Giménez VMM, Bergam I, Tajer C, Antonietti L, Inserra F, Ferder L, Manucha W. Association Between Vitamin D Deficiency and COVID-19 Incidence, Complications, and Mortality in 46 Countries: An Ecological Study. *Health Secur* 2021; **19**: 302-308 [PMID: 33325788 DOI: 10.1089/hs.2020.0137]

14 **Sergi CM.** Vitamin D and Primary Ciliary Dyskinesia: A Topic to Be Further Explored. *App Sci* 2021; **11:** 3818

15 **Nicolaysen R**. The influence of vitamin D on the absorption of calcium from the intestine of rats; experiments with isolated loops. *Acta Physiol Scand* 1951; **22**: 260-266 [PMID: 14933150 DOI: 10.1111/j.1748-1716.1951.tb00776.x]

16 **Haavaldsen R**, Egnund KM, Nicolayser R. Studies in calcium metabolism in rats. II. The interaction of vitamin D and the endogenous factor. *Acta Physiol Scand* 1956; **36**: 108-113 [PMID: 13313210 DOI: 10.1111/j.1748-1716.1956.tb01309.x]

17 **Haavaldsen R,** Nicolaysen R. Studies in calcium metabolism in rats. I. A long term study in rats given an optimal diet with and without vitamin D. *Acta Physiol Scand* 1956; **36:** 102-107 [DOI: 10.1111/j.1748-1716.1956.tb01308.x]

18 **Lasagni** A, Cadamuro M, Morana G, Fabris L, Strazzabosco M. Fibrocystic liver disease: novel concepts and translational perspectives. *Transl Gastroenterol Hepatol* 2021; **6:** 26 [PMID: 33824930 DOI: 10.21037/tgh-2020-04]

19 **Sergi C**, Kahl P, Otto HF. Contribution of apoptosis and apoptosis-related proteins to the malformation of the primitive intrahepatic biliary system in Meckel syndrome. *Am J Pathol* 2000; **156**: 1589-1598 [PMID: 10793071 DOI: 10.1016/S0002-9440(10)65031-6]

20 **Johnson CA**, Gissen P, Sergi C. Molecular pathology and genetics of congenital hepatorenal fibrocystic syndromes. *J Med Genet* 2003; **40**: 311-319 [PMID: 12746391 DOI: 10.1136/jmg.40.5.311]

21 **Sato Y**, Harada K, Sudo Y, Watanabe K, Nakahama T, Morimoto H, Nakanuma Y. Autoimmune hepatitis associated with bile duct injury resembling chronic non-suppurative destructive cholangitis. *Pathol Int* 2002; **52**: 478-482 [PMID: 12167107 DOI: 10.1046/j.1440-1827.2002.01377.x]

22 **Pacheco-Gonzalez RM**, Garcia-Marcos PW, Garcia-Marcos L. Vitamin D and Atopic Dermatitis. *Mini Rev Med Chem* 2015; **15**: 927-934 [PMID: 25985948 DOI: 10.2174/1389557515666150519110209]

23 **Jiao J**, Castro M. Vitamin D and asthma: current perspectives. *Curr Opin Allergy Clin Immunol* 2015; **15**: 375-382 [PMID: 26106827 DOI: 10.1097/ACI.0000000000000187]

24 **Toniato E**, Spinas E, Saggini A, Kritas SK, Caraffa A, Antinolfi P, Saggini R, Pandolfi F, Conti P. Immunomodulatory effects of vitamin D on skin inflammation. *J Biol Regul Homeost Agents* 2015; **29**: 563-567 [PMID: 26403394]

25 **Liu WC**, Zheng CM, Lu CL, Lin YF, Shyu JF, Wu CC, Lu KC. Vitamin D and immune function in chronic kidney disease. *Clin Chim Acta* 2015; **450**: 135-144 [PMID: 26291576 DOI: 10.1016/j.cca.2015.08.011]

26 **Suaini NH**, Zhang Y, Vuillermin PJ, Allen KJ, Harrison LC. Immune Modulation by Vitamin D and Its Relevance to Food Allergy. *Nutrients* 2015; **7:** 6088-6108 [PMID: 26225992 DOI: 10.3390/nu7085271]

27 **Kroner Jde C**, Sommer A, Fabri M. Vitamin D every day to keep the infection away? *Nutrients* 2015; **7:** 4170-4188 [PMID: 26035244 DOI: 10.3390/nu7064170]

28 **Ardesia M**, Ferlazzo G, Fries W. Vitamin D and inflammatory bowel disease. *Biomed Res Int* 2015; **2015**: 470805 [PMID: 26000293 DOI: 10.1155/2015/470805]

29 **Trochoutsou AI**, Kloukina V, Samitas K, Xanthou G. Vitamin-D in the Immune System: Genomic and Non-Genomic Actions. *Mini Rev Med Chem* 2015; **15**: 953-963 [PMID: 25985946 DOI: 10.2174/1389557515666150519110830]

30 **Schrumpf JA**, Ninaber DK, van der Does AM, Hiemstra PS. TGF-β1 Impairs Vitamin D-Induced and Constitutive Airway Epithelial Host Defense Mechanisms. *J Innate Immun* 2020; **12**: 74-89 [PMID: 30970352 DOI: 10.1159/000497415]

31 **Czaja AJ**, Montano-Loza AJ. Evolving Role of Vitamin D in Immune-Mediated Disease and Its Implications in Autoimmune Hepatitis. *Dig Dis Sci* 2019; **64**: 324-344 [PMID: 30370494 DOI: 10.1007/s10620-018-5351-6]

32 **Dimeloe S**, Nanzer A, Ryanna K, Hawrylowicz C. Regulatory T cells, inflammation and the allergic response-The role of glucocorticoids and Vitamin D. *J Steroid Biochem Mol Biol* 2010; **120**: 86-95 [PMID: 20227496 DOI: 10.1016/j.jsbmb.2010.02.029]

33 **Ansari MGA**, Sabico S, Clerici M, Khattak MNK, Wani K, Al-Musharaf S, Amer OE, Alokail MS, Al-Daghri NM. Vitamin D Supplementation Is Associated with Increased Glutathione Peroxidase-1 Levels in Arab Adults with Prediabetes. *Antioxidants (Basel)* 2020; **9** [PMID: 32013162 DOI: 10.3390/antiox9020118]

34 **Abramovitch S**, Dahan-Bachar L, Sharvit E, Weisman Y, Ben Tov A, Brazowski E, Reif S. Vitamin D inhibits proliferation and profibrotic marker expression in hepatic stellate cells and decreases thioacetamide-induced liver fibrosis in rats. *Gut* 2011; **60**: 1728-1737 [PMID: 21816960 DOI: 10.1136/gut.2010.234666]

35 **Efe C**, Kav T, Aydin C, Cengiz M, Imga NN, Purnak T, Smyk DS, Torgutalp M, Turhan T, Ozenirler S, Ozaslan E, Bogdanos DP. Low serum vitamin D levels are associated with severe histological features and poor response to therapy in patients with autoimmune hepatitis. *Dig Dis Sci* 2014; **59**: 3035-3042 [PMID: 25002309 DOI: 10.1007/s10620-014-3267-3]

**Footnotes**

**Conflict-of-interest statement:** No conflicts of interest with regard to this manuscript exist.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review started:** September 4, 2021

**First decision:** October 18, 2021

**Article in press:**

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** Canada

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

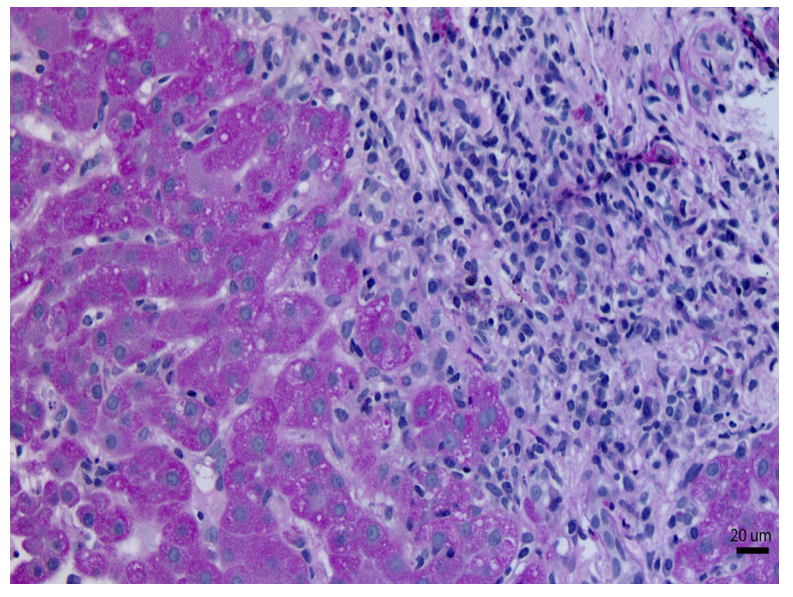
Grade C (Good): C, C

Grade D (Fair): 0

Grade E (Poor): E

**P-Reviewer:** Bocsan I, Lee WS, Qiu F, Sahoo J **S-Editor:** Fan JR **L-Editor:** Wang TQ **P-Editor:** Fan JR

**Figure Legends**



**Figure 1 Autoimmune hepatitis.** The portal tract shows a prominent inflammatory infiltrate consisting of numerous lymphocytes and plasma cells with interface inflammatory activity (upper right corner). The hepatocytes are highlighted using periodic acid Shiff (PAS) stain due to the accumulation of glycogen (lower left corner) (PAS stain, × 200 original magnification, bar = 20 micrometers).