Micronutrient Deficiencies Associated with Chronic Hepatitis Infections

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Abstract

Background: Deficiencies in vitamins A, B6, B12, D and folate as well as iron overload have been linked to end-stage liver disease. Deficiencies in vitamins A, and D have been found to decrease the efficacy of anti-viral treatment for hepatitis C. Aims: To determine whether individual micronutrient deficiencies or overload are associated with chronic infection with hepatitis B virus or hepatitis C virus. Methods: Data from NHANES years 2003-2006 were analyzed. Variables selected for analysis were blood levels for vitamins A, B6, B12, D, and E as well as homocysteine and folate. Alcohol intake, age, gender, and HIV infection were also included. Only participants over the age of 20 were considered, and participants were excluded for having incomplete laboratory data. Results: The model for Hepatitis B had an N of 4,659. The model for hepatitis C has an N of 8,113. 635 participants had a hepatitis B infection, 160 had a hepatitis C infection. 66 of those were infected with both hepatitis B and C. In multivariate analysis hepatitis B infection was associated with vitamin B6 deficiency(OR=0.496 0.311-0.791, vitamin D deficiency, and HIV infection with a significant interaction between vitamin D deficiency and HIV infection. For HIV negative patients with a hepatits B infection the association with vitamin D deficiency was (OR=1.9351.358-2.764). Hepatitis C was associated with vitamin A deficiency (OR=4.991 2.961-6.876), vitamin B6 deficiency (OR=1.775 1.149-2.743), and iron overload (OR=3.541 1.444-8.684). Conclusions: Micronutrient abnormalities associated with hepatitis B were different from those associated with hepatitis C. Hepatitis B infection was associated with a lower chance of vitamin B6 deficiency and was only associated with Vitamin D deficiency in the absence of a co-infection with HIV. Hepatitis C was associated with deficiencies in the vitamins A and B6 as well as a condition of iron overload.

Introduction

The most subtle deficiencies in human nutrition are often in the vitamins and minerals referred to as micronutrients. Although the human body needs very small amounts of these substances they are required for the normal function of various bodily systems. [1] Micronutrient deficiencies are most often caused by inadequate dietary intake, however they can also occur if there are difficulties in the digestive system's ability to absorb or metabolize the nutrients properly. [2] Additionally in periods of disease or stress greater than normal amounts of certain vitamins and minerals are required in the body which can lead to deficiencies. [3]

In patients with chronic disease the stresses placed on the body and the immune system can consume greater than normal amounts of vitamins and minerals leading to higher proportions of vitamin deficiencies. [3] These deficiencies can than make it even harder for the body to respond to the disease in addition to any other problems caused by the lack of adequate nutrition. Liver disease is associated with deficiencies in vitamins B6, B12, D, and folate as well as with iron overload .[2] [4] In patients with cirrhosis caused by alcoholic liver disease, the damage to the liver is known to cause deficiencies in B6 due to a limited capacity to metabolize it properly in the liver. [5] A complication for studies analyzing micronutrient deficiencies in patients with alcoholic liver disease however is the fact that alcohol antagonism impedes the uptake of many micronutrients in the gut, meaning that deficiencies might not be entirely linked to liver damage. [5] A study on patients awaiting liver transplantation due to advanced liver disease revealed that deficiencies in vitamins A and D were common among the patients. [4]

Infection with hepatitis B and C viruses can result in chronic disease that causes damage to the liver. For a majority of patients an infection with hepatitis B or C does not progress to cirrhosis. [6] [7] Cirrhosis is a disease acquired over time by the accumulation of fibroids in the liver.Therefore, while it is known that the end stage of liver damage classified as cirrhosis is associated with micronutrient deficiencies, as are long term infections with chronic disease such as HIV, there is very little literature on whether infection with viral hepatitis, either B or C that has not progressed to cirrhosis or end stage liver disease is associated with these deficiencies. [8]

Liver damage should be associated most with deficiencies in those vitamins who are either stored in the liver or that undergo significant metabolic processing in the liver. Most fat soluble vitamins have some amount of storage in the liver, but vitamins A, D, and K are stored almost exclusively in the liver. Vitamin E does have significant stores in the liver but also has additional stores evenly distributed throughout the body. [2] The water soluble vitamins B12 and folate are also stored primarily in the live, and the vitamins B6 and D undergo crucial processing in the liver to alter the dietary form of the vitamin into the one that

is bio-available in the blood. [5] [9] My hypothesis is that the damage to the liver that causes micronutrient abnormalities may occur at a stage of liver damage before the progression to cirrhosis, especially with the addition of the strain of a chronic viral infection. To determine whether patients suffering from chronic viral hepatitis have a higher incidence of micronutrient abnormalities than that found in the general population participants will be evaluated for vitamin A, B6, B12, D, E, and folate deficiencies as well as abnormalities in Iron levels. Human Immunodeficiency Virus (HIV) status will be considered in the analysis as HIV and hepatitis infections often co-exist and HIV is independently associated with micronutrient abnormalities. [10] [11] As my hypothesis assumes that higher levels of fibrosis will be associated with more nutrient deficiencies I will also perform analysis with risk factors for fibrosis in mind. Men, the elderly, those who drink heavily, and those who have co-infections with HIV are all at higher risk for fibrosis in patients infected with viral hepatitis. [5] [12]

Selection and Description of Participants

Data from the years 2003-2006, which represents two sets of the Continuous National Health and Nutrition Survey (NHANES) data, was used in this analysis. NHANES is a cross-sectional survey representative of the national civilian, non-institutionalized population. For NHANES 2003-2004 12,671 participants were selected and 9,943 had laboratory analysis conducted, that is 75.6% of the total sample. [13] For NHANES 2005-2006 10,348 participants were selected and 9,950 had a medical examination that is 96.15% of the total sample.[14] From the four years total 86.42% of the participants were eligible for analysis based on laboratory data. NHANES uses cluster sampling so sampling weights have been considered in this analysis. New sampling weights were calculated according to the guidelines provided by NHANES in order to accommodate the combining of two 2-year datasets. [15] NHANES consists of an interview, a questionnaire, and a medical examination for the participants. During the medical examination blood was drawn for laboratory work. The data on Hepatitis infection, HIV infection, and blood levels of micronutrients were drawn from the laboratory section of NHANES. Age and gender were taken from the interview portion, and assessment of alcohol intake was drawn from the questionnaire section. Participants were allowed to refuse to have the HIV tests run on their blood samples and the test was only run on those over 18 years of age, therefore out of the 16,933 participants who had laboratory work run only 6,002 (35.45%) were eligible for analysis. Details on the methods used for survey collection and laboratory methods used are available on the NHANES website.[16]

The participants in this analysis are limited to those participants over the age

of 20, as the NHANES questionnaire only gathered data on alcohol intake for participants aged 20 or older.[13] High risk drinking is associated with a quicker progression to cirrhosis in hepatitis patients. [5] High risk drinking is defined by the National Institutes of Health (NIH) as a man who consumes more than 4 drinks in a day or 14 drinks in two weeks, or as a woman who consumes more than 3 drinks a day or 11 drinks in two weeks. [17] For this study, high-risk drinking has been defined as a participant saying that at some period in their life they consumed more than 5 beverages every day, or a participant saying that over the past year they consumed an average of 5 or more drinks per day for men and 4 or more per day for women. Definitions of normal blood ranges for micronutrients vary based on collection and lab analysis techniques; therefore I have used the definitions the Centers for Disease Control and Prevention (CDC) used when analyzing the NHANES data from the years 1988-2006 as described in the Second National Report on Biochemical Indicators of Diet and Nutrition in the U.S. population. [18]

The major goal of this analysis is to determine whether people infected with either hepatitis B or hepatitis C had a higher incidence of micronutrient deficiencies than participants who did not. The analysis was restricted to the four years of NHANES chosen because those were the only years that collected information about all of the relevant micronutrients in a consistent manner. Limiting my analysis to participants over the age of 20 for whom complete information was present for hepatitis infection limited the sample size to 8,976 participants.

Satistical Analyses

All Analyses were conducted in SAS, version 9.2 (SAS institute, Inc., Cary, North Carolina) using survey procedures. Descriptive statistics of the analysis samples demographic characteristics by infection status were carried out. All predictors were entered into multivariable models to test their relationship with one of the two outcome variables adjusted for other variables. The micronutrients folate, vitamin B12, and vitamin E were omitted from the model because they produced cells too small for significance in analysis. The Iron variable was altered to have only two levels; one for those with normal levels and another for those with high levels so the variable could be entered into the model. All variables were assessed for interaction with HIV status, high risk alcohol intake, age, and gender.

Virus	% Population	Total
Hepatitis B	6.37	569
Hepatitis C	1.05	94
Hepatitis B and C	0.74	66
Total	8.16	729

Table 1: Population Prevalence of Hepatitis Infection

Results

The population prevalence of the individual hepatitis viruses is provided in Table 1. Hepatitis B is more common than hepatitis C in the population, and a small portion of the population is infected with both viruses. Characteristics of participants infected with hepatitis B and hepatitis C contrasted with those of the general population are presented in Table 2. The bivariate analysis shows that those with a hepatitis B infection are more likely to be male, HIV positive, and have high-risk alcohol intake than the general population. They also have a mean age approximately five years higher than the general population. Those with hepatitis B are more likely to have a deficiency in the micronutrients vitamin A, vitamin B6, folate, vitamin D, and vitamin E; additionally, they are more likely to have elevated homocysteine levels. The population prevalence of vitamin B12 and iron was equal or lower in those with hepatitis B than in the general population. Those with hepatitis C were also more likely to be male, HIV positive, and have high-risk alcohol intake. However compared to participants with a hepatitis B infection they were less likely to be HIV positive, and more likely to have high-risk alcohol intake. The mean age was within one year of the general population. Participants with hepatitis C had a higher percentage of vitamin A, vitamin B6, and vitamin E deficiency than the general population, as well as a higher percentage of elevated homocysteine and iron levels. These simple statistics are based only on 2x2 tables and do not take into account the weighting of the participants.

The multivariate analysis for hepatitis B shows that age, HIV infection, vitamin B6 blood levels, and vitamin D blood levels are all associated with hepatitis B infection. There was also a significant interaction between HIV infection and Vitamin D levels. The Odds Ratios (OR) generated by this model are presented in Table 3. They show that those with a hepatitis B infection are less likely to have a vitamin B6 deficiency, and that those who were infected with hepatitis B but not with HIV were more likely to have a Vitamin D deficiency. Hepatitis B patients

Characteristic	Hepatitis B		Hepatitis C		Population	
	in %	Mean	in %	Mean	Population %	Mean
Age		55.37		50.53		49.42
Gender						
Female	43.48		42.50		51.77	
Male	56.52		57.50		48.23	
HIV	7.85		3.61		0.66	
Alcohol	21.25		41.26		14.18	
Vitamin A						
Deficiency	5.49		9.55		2.61	
Surplus	5.64		4.46		4.79	
Vitamin B6	19.19		33.75		18.88	
Vitamin B12	2.19		0.63		2.75	
Folate	0.93		0.0		0.39	
Homocysteine	15.86		13.92		9.84	
Vitamin D	30.12		22.5		22.48	
Vitamin E	0.78		2.55		0.53	
Iron						
Deficiency	0.0		0.0		0.02	
Overload	1.72		5.7		2.08	

Table 2: Prevalence of Factors of Interest in the Infected and General Populations

Variable	OR	95% CI
Age	1.048	1.027,1.07
Vitamin B6	0.496	0.311,0.791
Vitamin D		
HIV +	0.34556	0.0705,1.694
HIV-	1.935	1.358,2.764
HIV		
Vitamin D Deficient	16.433	5.239,51.545
Vitamin D Sufficient	92.02866	28.425,297.948

Table 3: Factors Associated with Hepatitis B Infection

with no HIV infection had increased odds of Vitamin D deficiency, with an OR of 1.935; however, co-infected patients had an insignificant OR. These numbers are likely due to the association of Vitamin D deficiency with HIV infection as well as the small number of participants available, there were only 5 participants with Hepatitis B who had an HIV infection and a Vitamin D deficiency. The odds for a participant with low vitamin D levels to have HIV are 3.0589 with a 95% Confidence Interval (CI) of 1.5074 to 6.2071, showing the independent association between vitamin d deficiency and HIV infection. There were 4,659 participants in the analysis for this model.

The model generated for hepatitis C had a sample size of 8,113 and showed that age, high-risk alcohol intake, and blood levels for vitamin A, vitamin B6, and Iron are associated with hepatitis C infection. The odds ratios generated by this model are presented in Table 3. They show that those with hepatitis C are more likely to be deficient in vitamin A and vitamin B6. It also shows that those with hepatitis C are more likely to have iron overload.

In both models the odds for having hepatitis increased with age, the only other variable that was significant in both models is vitamin B6, but the direction of effects in the two models was different.

Discussion

This study expands the literature about the relationship between micronutrient deficiencies and hepatic disease by demonstrating that individual micronutrient deficiencies are associated with hepatitis B and hepatitis C infections. Further this study shows that the micronutrient deficiencies associated with hepatitis B

Variable	OR	95% CI
Age	1.011	1.005,1.018
Alcohol	4.512	2.961,6.876
Vitamin A		
Deficiency	4.991	2.267,10.991
Surplus	0.793	0.273, 2.307
Vitamin B6	1.775	1.149,2.743
Iron Overload	3.541	1.444,8.684

Table 4: Factors Associated with Hepatitis C Infection

are different than those associated with hepatitis C.

The most common cause of iron overload is genetic. Iin patients without a genetic cause iron overload is primarily caused by liver disease. [19] Most of the studies on iron overload start with diagnosed patients and look for etiology, so viral hepatitis has been demonstrated to be the cause of a small minority of iron overload cases. [19] This study demonstrates that patients infected with viral hepatitis C have an increased likelihood of iron overload. The signs and symptoms of iron overload are very general and non-specific and if iron overload is not suspected it is very rarely tested for. [20] The impotence, fatigue, liver damage, joint pain, osteoporosis and diabetes are serious effects of iron overload in any patient [20] but the effects of iron overload that are of real importance to a patient infected with viral hepatitis are those it has on the immune system. Iron overload decreases antibody response and CD4 count while increasing CD8 count which may allow increased growth of cancer cells and infectious organisms. [21] This affects the patient's ability to fight viral infections and may increase the risk for liver cancer in hepatic patients, a population that already has an elevated risk. Given that iron overload is a reversible micronutrient abnormality with symptoms that increase in severity the longer it is untreated it should likely prove beneficial if patients with higher risk for developing iron overload, such as those infected with hepatitis C, received regular blood work to monitor their iron levels.

This study also shows an association between vitamin A deficiency and participants with hepatitis C infection. Previous studies have also shown such an association in a cohort of drug users [22] and in patients with hepatitis C related liver disease. [23] The most recent study on the topic demonstrates not only a strong association between vitamin A deficiency and hepatitis C infection but additionally that vitamin A deficiency is associated with non-response to interferon

therapy. [24] Additional studies have shown that vitamin A plays a role in the immune responses of the liver, and functions as an anti-oxidant to the oxidative damage that viral hepatitis causes to the liver. [23] The results of this study indicate that vitamin A deficiency is strongly associated with hepatitis C infection. Given the strength of the association and the function vitamin A plays in the response of hepatitis C infected patients to interferon therapy the benefits of vitamin A supplementation for patients with hepatitis C should be investigated.

Other studies have shown that low levels of vitamin B6 are associated with both hepatitis B and C. [25] This study found an association between hepatitis C and low levels of vitamin B6, but also found that patients with hepatitis B were less likely to have B6 deficiency than uninfected participants. One explanation for the difference in results is that in this study B6 deficiency was assessed by serum pyridoxal-5'-phosphate (PLP) levels whereas in the other study it was RBC levels that were assessed.[25] It is possible that the difference in methods could account for the difference in results. In a study evaluating the effects of interferon and ribivirin therapy on B vitamin levels in patients infected with hepatitis C it was found that hepatitis C is associated with low vitamin B6 levels and the levels decrease even more during the course of therapy. [26] These results suggest that B vitamin supplementation may be beneficial to patients with hepatitis C infection, especially when they are undergoing anti-viral therapy. Further research should be done on the relationship between hepatitis B and vitamin B6 levels, to determine whether the effect observed in this study is reproducible and if it is to determine why patients infected with hepatitis B would be more likely to have adequate serum B6 than the uninfected population.

Studies on hepatitis C have demonstrated that low vitamin D levels are indicative of more severe liver disease. [9] There is also an increasing number of studies that demonstrate that low vitamin D levels in hepatitis C infected patients decreases the efficacy of interferon therapy. [9] [24] [27] This study found an association between vitamin D deficiency and hepatitis B infection independent of HIV infection although it found no significant association between vitamin D deficiency and hepatitis C infection. Although anti-viral treatments for hepatitis B and C are different they both use interferon therapy. If further studies demonstrate that vitamin D deficiency limits the efficacy of interferon therapy in the treatment of hepatitis B this finding may be of clinical importance.

The conclusions that can be drawn from this study are limited by the fact that the data set used did not include information on acute liver disease. The laboratory data did include bilirubin, ALT, and AST levels in the blood but none of those markers entered the final models. A more thorough analysis would evaluate the differences between participants with and without cirrhosis, whether the cirrhosis was caused by a viral hepatitis infection or not. Additionally, the information on

high-risk alcohol intake is limited due to both the way it was collected and the way it was coded for analysis. The NHANES questionnaire asked the participants questions about their alcohol use in the past year and recall may have not been accurate.

In conclusion this investigaiton found that infections with viral hepatitis B or C are associated with certain micronutrient abnormalities. Hepatitis B infection is associated with vitamin D deficiency in the absence of HIV infection. Hepatitis B is also associated with a lower risk of vitamin B6 deficiency as measured by serum PLP levels; this is an association that merits further investigation. Hepatitis C infection is associated with deficiency in vitamins A and B6 as well as with the condition of iron overload. These findings suggest that vitamin D supplementation in patients with hepatitis B may have potential benefits, and further research is suggested into determining the effect of vitamin D deficiency on the efficacy of anti-viral treatment for hepatitis B infection. These findings also suggest that vitamin A and B6 supplementation may be advisable for patients with a hepatitis C infection, particularly those undergoing anti-viral treatment.

References

[1] G. T. Keusch, "The history of nutrition:malnutrition, infection, and immunity," *Journal of Nutrition*, vol. 133, pp. 336S–340S, 2003.

[2] M. C. Linder, ed., *Nutritional Biochemistry and Metabolisim:with Clinical Applications*. Elsevier Science Publishing Company, Inc., second ed., 1991.

[3] A. M. Tang, E. Smit, and R. D. Semba, "Nutrition and infection," in *Infectious Disease Epidemiology* (K. E. Nelson and C. M. Williams, eds.), ch. 12, pp. 383–406, Sudbury, MA: Jones and Bartlett Publishers, second ed., 2007.

[4] M. Venu, E. Martin, K. Saeian, and S. Gawrieh, "High prevalence of vitamin a and d deficiency in patients evaluated for liver transplantation.," *Liver Transplantation*, March 2013.

[5] T. Poynard, *Hepatitis C and B: Management and Treatment*. Taylor and Francis, second ed., 2004.

[6] J. H. Hoofnagle, D. A. Shafritz, and H. Popper, "Chronic type B hepatitis and the 'healthy' HBsAg carrier state," *Hepatology*, vol. 7, pp. 758–763, 1987.

[7] M. J. Alter, H. S. Margolis, K. Krawczynski, and et al, "The natural history of community acquired hepatitis C in the united states.," *New England Journal of Medicine*, vol. 327, pp. 1899–1905, 1991.

[8] P. Guenter, N. Muurahainen, G. Simons, and et.al., "Relationships among nutritional status, disease progression, and survival in HIV infection.," *Journal of Aquired Immune Deficiency Syndrome*, vol. 6, pp. 1130–1138, 1993.

[9] S. Petta, C. Cammà, C. Scazzone, C. Tripodo, V. D. Marco, A. Bono, D. Cabibi, G. Licata, R. Porcasi, G. Marchesini, and A. Craxí, "Low vitamin D serum level is related to severe fibrosis and low responsiveness to interferon-based therapy in genotype 1 chronic hepatitis C," *Hepatology*, vol. 51, pp. 1158–67, April 2010.

[10] C. Y. Jones, A. M. Tang, J. E. Forrester, J. Huang, K. M. Hendricks, T. A. Knox, D. Spiegelman, R. D. Semba, and M. N. Woods, "Micronutrient levels and HIV disease status in HIV-infected patients on highly active antiretroviral therapy in the Nutrition for Healthy Living cohort.," *Journal of Acquired Immune Deficiency Syndrome*, vol. 43, pp. 475–82, December 2006.

[11] C. L. Thio, "Hepatitis B in the human immunodeficiency virus infected patient: epidemiology, natural history, and treatment," *Seminars in Liver Disease*, vol. 3, pp. 125–136, 2003.

[12] Z. Younossi, L. Zheng, M. Stepanova, C. Venkatesan, and H. M. Mir, "Moderate, excessive or heavy alcohol consumption: each is significantly associated with increased mortality in patients with chronic hepatitis C.," *Alimentary Pharmacology and Therapeutics*, vol. 37, pp. 703–9, April 2013.

[13] CDC/National Center for Health Statistics, "2003-2004 data documentation, codebook, and frequencies." `http://www.cdc.gov/nchs/nhanes/nhanes2003-2004/DEMO_C.htm`, 2009. accessed 03/21/2013.

[14] CDC/National Center for Health Statistics, "2005-2006 data documentation, codebook, and frequencies." `http://www.cdc.gov/nchs/nhanes/nhanes2005-2006/DEMO_D.htm`, 2009. accessed 03/21/2013.

[15] National Center for Health Statistics, "NHANES analytic and reporting guidelines," tech. rep., Centers for Disease Control and Prevention, 2006.

[16] CDC/National Center for Health Statistics, "Questionnaires, datasets, and related documentation." `http://www.cdc.gov/nchs/nhanes/nhanes_questionnaires.htm`, 2012. accessed 03/21/2013.

[17] National Institute on Alcohol Abuse and Alcoholism, "Moderate and binge drinking." `http://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/moderate-binge-drinking`, 2013. accessed 03/21/2013.

[18] National Center for Environmental Health, "Second national report on biochemical indicators of diet and nutrition in the u.s. population," tech. rep., Centers for Disease Control and Prevention, 2012.

[19] K. Wong and P. C. Adams, "The diversity of liver disease among outpatient referrals for elevated serum ferritin," *Canadien Journal of Gastroenterology*, vol. 20, pp. 467–470, July 2006.

[20] R. E. Fleming and P. Ponka, "Iron overload in human disease," *New England Journal of Medicine*, vol. 366, pp. 348–359, January 2012.

[21] E. M. Walker Jr. and S. M. Walker, "Effects of iron overload on the immune system," *Annals of clinical and laboratory science*, vol. 30, pp. 354–65, October 2000.

[22] J. E. Forrester, X. D. Wang, T. A. Knox, C. G. Borek, A. M. Tang, and E. J. Johnson, "Factors associated with serum retinol, alpha-tocopherol, carotenoids, and selenium in hispanics with problems of HIV, chronic hepatitis C, and drug use," *Journal of Public Health Policy*, vol. 30, pp. 285–299, 2009.

[23] W. A. Peres, G. V. Chaves, J. C. Gonclaves, A. Ramalho, and H. S. Coelho., "Vitamin a deficiency in patients with hepatitis c virus-related chronic liver disease.," *Brazilian Journal of Nutrition*, vol. 106, pp. 1724–31, December 2011.

[24] D. Bitetto, N. Bortolotti, E. Falleti, S. Vescovo, C. Fabris, G. Fattovich, A. Cussigh, S. Cmet, E. Fornasiere, E. Ceriani, M. Pirisi, and P. Toniutto, "Vitamin a deficiency is associated with hepatitis c virus chronic infection and with unresponsiveness to interferon-based antiviral therapy," *Hepatology*, vol. 57, pp. 925–33, March 2013.

[25] C. Lin, W. Liu, Z. Wang, and M. Yin, "Vitamins b status and antioxidative defense in patients with chronic hepatitis b or hepatitis c virus infection," *European Journal of Nutrition*, vol. 50, pp. 499–506, 2011.

[26] C. Lin and M. Yin, "Vitamins b depletion, lower iron status and decreased antioxidative defense in patients with chronic hepatitis c treated by pegylated interferon alfa and ribavirin," *Clinical Nutrition*, vol. 28, pp. 34–38, 2009.

[27] D. Bitetto, G. Fattovich, C. Fabris, E. Ceriani, E. Falleti, E. Fornasiere, M. Pasino, D. Ieluzzi, A. Cussigh, S. Cmet, M. Pirisi, and P. Tonutto, "Complementary role of vitamin D deficiency and the interleukin-28b rs12979860

C/T polymorphism in predicting antiviral response in chronic hepatitis C," *Hepatology*, vol. 53, no. 4, pp. 1118–1126, 2011.