Effect of vitamin D deficiency on spontaneous peritonitis in cirrhosis: a meta-analysis

Zhongchen Zhang¹, Lili Wu¹, Guoping Wang¹, Ping Hu¹
¹Department of Gastroenterology, The First People’s Hospital of Wenling, Taizhou, China
²Department of Nursing, Taizhou Cancer Hospital, Taizhou, China

Gastroenterology Rev 2021; 16 (1): 10–14
DOI: https://doi.org/10.5114/pg.2020.101632

Key words: vitamin D, spontaneous peritonitis, cirrhosis.

Introduction: Few studies have reported the relationship between spontaneous peritonitis in cirrhosis and vitamin D, and the result is not very convincing.

Aim: To conduct a meta-analysis to clarify the relationship between vitamin D and spontaneous peritonitis.

Material and methods: Articles published up to 1 October 2019 in the PubMed, Medline, and Embase databases were searched. According to the inclusion and exclusion criteria, relevant statistical data were extracted and analysed by STATA.

Results: Six articles met the inclusion criteria. It was demonstrated that the average 25(OH)D level in spontaneous peritonitis patients was 2.36 less than that in control individuals (SMD = –2.36, 95% CI: –3.92, –0.8, I² = 97.2%, p < 0.01). Moreover, it found that spontaneous peritonitis patients were 4.33 times more likely to be vitamin D deficient than controls (OR = 4.33, 95% CI: 1.57, 11.93, p = 0.111). Sensitivity analysis showed that the meta-analysis results were stable and reliable.

Conclusions: Vitamin D may be an importantly protective factor in spontaneous peritonitis.

Introduction

Cirrhosis results from different mechanisms of liver injury including virus, alcohol, and non-alcoholic liver disease, which lead to necroinflammation and fibrogenesis [1]. Cirrhosis is the 14th most common cause of death in adults worldwide, and it results in 1.03 million deaths per year worldwide [2], which varies from 1% to 57% depending on the occurrence of clinical events [3]. Portal hypertension, ascites, spontaneous peritonitis, and encephalopathy are the most common and serious complications. Spontaneous peritonitis increases mortality in cirrhosis four times and has a poor prognosis [4]. A previous study has reported that vitamin D was closely related to spontaneous peritonitis [5].

Apart from classical effects on bone mineralisation, vitamin D also has distinct immunological functions influencing cell proliferation and differentiation, immunomodulation, and the gut microbiome [6]. In addition, another report indicated that the biologically active form of vitamin D, 1,25(OH)₂D, may reduce inflammation [7].

The anti-inflammatory effect of vitamin D may be beneficial for the prognosis of spontaneous peritonitis. In this study, we aimed to conduct a meta-analysis to confirm whether there is a negative correlation between vitamin D and spontaneous peritonitis.
2) Cirrhosis with spontaneous peritonitis. 3) Complete data for the calculation of vitamin D. Exclusion criteria: 1) Duplicate article. 2) Similar article published by the same author and unit. 3) Published data were not accurate.

**Data abstract**

Risk of bias and quality assessment were assessed through elements of the STROBE checklist for studies included [8]. The work was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [9]. Two investigators independently examined included papers and abstract data in our analyses. If there was a disagreement, a third author would evaluate the disagreement again and form a final result after the trade. First of all, 25(OH)D was the main form of vitamin D considered in the included studies. Data were extracted to Microsoft Excel (2017 edition; Microsoft) for effective organisation. The following information was abstracted for analysis: basic characteristics (author, publication year, research country, and individuals of spontaneous peritonitis), serum 25(OH)D levels as continuous variables, and the cut-off level used to define 25(OH)D deficiency as a dichotomous variable, and so on. In addition, the cut-off level for 25(OH)D deficiency was defined as less than 20 ng/ml [10].

**Statistical analysis**

Odds ratio (OR) and 95% confidence intervals (CIs) were used to describe the ratio of the spontaneous peritonitis occurring in 25(OH)D deficiency individuals vs. controls. Standardised mean difference (SMD) was used for studies that reported mean and standard deviation (SD) values for 25(OH)D levels of spontaneous peritonitis individuals and controls. After the data were archived, pooled estimates were obtained using the random model (M-H heterology) method (I² > 50%, p ≤ 0.1) [11]. Statistical heterogeneity was assessed by Cochran’s Q test and I² statistic. In addition, sensitivity analysis was used to evaluate whether the results were stable and reliable. All analyses were carried out by metan in STATA 15.1.

**Results**

**Basic characteristics**

Our study initially identified 58 related references, of which six papers met our inclusion criteria [12–17]. The flowchart describing the process of study selection is shown in Figure 1. Five papers contained data describing mean ± SD of vitamin D in spontaneous peritonitis patients, while four papers described dichotomous data in spontaneous peritonitis patients. In addition, the unit of 25(OH)D using nmol/l was uniformly converted to ng/ml (1 nmol/l = 2.5 ng/ml). 25(OH)D was tested by enzyme-linked immunosorbent assay (ELISA) in five papers, and one paper chose chemiluminescence immunoassay.

**Vitamin D deficiency and spontaneous peritonitis**

Five studies reported the 25(OH)D levels of spontaneous peritonitis patients and control individuals. The main characteristics are listed in Table I. The result showed that the average 25(OH)D level in spontaneous peritonitis patients was 2.36 less than that in control individuals (SMD = –2.36, 95% CI: –3.92, –0.8, I² = 97.2%, p < 0.01; Figure 2). It showed significant heterogeneity.

![Figure 1. Article selection flow chart](image)

**Table I. Basic characteristics of vitamin D in spontaneous peritonitis patients and controls**

| Author    | Year | Country | Spontaneous peritonitis | Control |
|-----------|------|---------|-------------------------|---------|
|           |      |         | N | Mean [ng/ml] | SD | N | Mean [ng/ml] | SD |
| Monkez    | 2019 | Egypt   | 45 | 7.2          | 2.1 | 45 | 16.3          | 6.6 |
| Rodolphe  | 2014 | France  | 38 | 6.6          | 5.3 | 50 | 11.2          | 8.2 |
| Haidi     | 2019 | Egypt   | 42 | 17.3         | 2.5 | 45 | 41.1          | 3.1 |
| Zhang     | 2012 | China   | 19 | 13.7         | 1.0 | 28 | 13.7          | 1.1 |
| Abdelkader| 2015 | Egypt   | 30 | 8.0          | 3.4 | 30 | 15.0          | 5.4 |
By sensitivity analysis, data from Haidi’s study made the result fluctuant. However, it was still stable and reliable (Figure 3). In addition, we aimed to determine whether individuals with vitamin D deficiency were more susceptible to spontaneous peritonitis. We integrated data from four articles (Table II), and the result showed that spontaneous peritonitis patients were 4.33 times more likely to be vitamin D deficient than controls (OR = 4.33, 95% CI: 1.57, 11.93, I² = 50.1%, p = 0.111; Figure 4).

**Discussion**

There are few clinical studies on the relationship between vitamin D and spontaneous peritonitis. In this study, we collected relevant articles and data to derive the results, which demonstrated that cirrhosis patients with spontaneous peritonitis had lower vitamin D levels. And vitamin D deficiency had higher incidence rate of spontaneous peritonitis. It can be seen that vitamin D may be an important protective factor in cirrhosis patients with spontaneous peritonitis.

Vitamin D is involved in a variety of biological processes. Vitamin D exerts its biological activity via combination with VDR, which expresses in almost all target

**Figure 2.** The average 25(OH)D level in spontaneous peritonitis patients was 2.36 less than that in control individuals (SMD = −2.36, 95% CI: −3.92, −0.8, I² = 97.2%, p < 0.01)

**Figure 3.** Sensitivity analysis showed that the result was stable and reliable

| ID      | SMD (95% CI)         | Weight % |
|---------|----------------------|----------|
| Monkez  | −1.86 (−2.36, −1.37) | 20.51    |
| Rodolphe| −0.65 (−1.09, −0.22) | 20.61    |
| Haidi   | −8.42 (−9.75, −7.09) | 18.17    |
| Zhang   | 0.01 (−0.57, 0.59)   | 20.35    |
| Abdelkader | −1.55 (−2.13, −0.97) | 20.36 |
| Overall (I² = 97.2%, p < 0.001) | −2.36 (−3.92, −0.80) | 100.00 |

**Table II.** Basic characteristics of vitamin D status in spontaneous peritonitis patients and controls

| Author | Year | Country | SP/VD Deficiency (n) | SP/VD Sufficiency (n) | Control/VD Deficiency (n) | Control/VD Sufficiency (n) |
|--------|------|---------|----------------------|-----------------------|--------------------------|--------------------------|
| Monkez | 2019 | Egypt   | 45                   | 0                     | 35                       | 10                       |
| Rodolphe | 2014 | France  | 27                   | 11                    | 23                       | 27                       |
| Haidi  | 2019 | Egypt   | 13                   | 32                    | 0                        | 42                       |
| Trépo  | 2013 | Belgium | 22                   | 8                     | 120                      | 104                      |

*VD – vitamin D, SP – spontaneous peritonitis.*
The mechanisms of increased risk of infection in cirrhotic patients with a low 25(OH)D level are still unclear. The most likely mechanism is the anti-inflammatory effect of vitamin D. As is well-known, vitamin D is mediated by antigen-presenting cells such as macrophages and dendritic cells. The active form of the 1,25-OH vitamin D binding to vitamin D receptor, which is able to increase the production of proteins with antibacterial effects such as LL-37 cathelicidin, a vitamin D-dependent endogenous antibacterial peptide [18, 19]. LL-37 is closely related to infection. Liu et al. showed that lower LL-37 and vitamin D-mediated innate immunity may contribute to susceptibility to microbial infection [20]. Other studies also reported the role of LL-37 in Streptococcus suis and Staphylococcus aureus [21, 22]. Xie et al. found that Streptococcus suis blunts the innate host defences via ApdS protease-mediated LL-37 cleavage [22]. Also, Kang et al. revealed that LL-37 has potential clinical application in the eradication of biofilms and treatment of prosthetic joint infection [21]. In addition, in patients undergoing haemodialysis, lower LL-37 led to a higher risk of death from infection [23]. In a follow-up study conducted by Zhang et al. it was reported that vitamin D supplementation could up-regulate peritoneal macrophage VDR and LL-37 expressions, which resulted in an enhanced immunological defence against spontaneous peritonitis in patients with cirrhosis and ascites [24]. The mechanism may be that in the ascitic fluid in spontaneous peritonitis patients, decreased secretion of Th2-type cytokines such as IL-4, IL-10, and IL-13 induce Bcl-3, which may result in the change in LL-37 regulation [15].

Another potential mechanism might be linked to the gut microbiota, which recently emerged as an important actor implicated in chronic hepatic disorders through the gut–liver axis [25]. Gut bacterial overgrowth and increased gut permeability could lead to an increased risk of bacterial translocation in the enterococci. On the one hand, vitamin D itself inhibits cirrhosis progression. Roth et al. reported that rats fed a vitamin-deficient diet had significantly worsened steatosis and more lobular inflammation than controls [26]. On the other hand, Liu et al. proved that vitamin D can protect the gut mucosal epithelial barrier and strengthen the tight junction, which could inhibit bacterial translocation [27].

Although we have achieved encouraging results, there were still some shortcomings. The most important issue was the heterogeneity of included articles. Although the sensitivity analysis showed that the results was still stable, some factors still may lead to the existence of heterogeneity. First, differences in vitamin D detection methods, types and causes of cirrhosis, and the number of patients enrolled may be sources of heterogeneity. The emergence of heterogeneity might reduce the credibility of the conclusion, while it could still provide sufficient evidence. Second, there were too few articles to provide data of analysis. We believe that a greater number of articles can provide more data and research evidence. In addition, this meta-analysis lacked prospective randomised controlled studies. Therefore, we could not directly confirm the causal relationship between vitamin D and spontaneous peritonitis. Infection can lead to decreased absorption of the gastrointestinal tract, which may affect vitamin D
absorption. These are points that follow-up research can improve.

Conclusions
This meta-analysis demonstrated that vitamin D levels in cirrhosis patients with spontaneous peritonitis were lower than controls, suggesting that vitamin D may be a protective factor in spontaneous peritonitis. In the future, more prospective studies are needed to validate the results of this study.

Acknowledgments
Zhongchen Zhang and Lili Wu contributed equally to the article.

This work was supported by the Wenling Science and Technology Plan Project (grant number 2018C312003).

Conflict of interest
The authors declare no conflict of interest.

References
1. Tsochatzis EA, Bosch J, Burroughs AK. Liver cirrhosis. Lancet 2014; 383: 1749-61.
2. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012; 380: 2095-128.
3. L’Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol 2006; 44: 217-31.
4. Arvaniti V, L’Amico G, Fede G, et al. Infections in patients with cirrhosis increase mortality four-fold and should be used in determining prognosis. Gastroenterology 2010; 139: 1246-56, S6.e1-5.
5. Buonomo AR, Arcipinto M, Scotto R, et al. The serum-ascites vitamin D gradient (SADG): a novel index in spontaneous bacterial peritonitis. Clin Res Hepatol Gastroenterol 2019; 43: e57-60.
6. Nielsen OH, Hansen TI, Gubatan JM, et al. Managing vitamin D deficiency in inflammatory bowel disease. Frontline Gastroenterol 2019; 10: 394-400.
7. van Etten E, Mathieu C. Immunoregulation by 1,25-dihydroxyvitamin D3: basic concepts. J Steroid Biochem Mol Biol 2005; 97: 93-101.
8. Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. PLoS Med 2007; 4: e297.
9. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med 2009; 6: e1000100.
10. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2011; 96: 1911-30.
11. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002; 21: 1539-58.
12. Yusuf MM, Sadek A, Farrag HA, et al. Associated vitamin D deficiency is a risk factor for the complication of HCV-related liver cirrhosis including hepatic encephalopathy and spontaneous bacterial peritonitis. Intern Emerg Med 2019; 14: 753-61.
13. Anty R, Tonhououan M, Ferrari-Panaï P, et al. Low levels of 25-hydroxy vitamin D are independently associated with the risk of bacterial infection in cirrhotic patients. Clin Transl Gastroenterol 2014; 5: e56.
14. Ramadan HK, Makhlouf NA, Mahmoud AA, et al. Role of vitamin D deficiency as a risk factor for infections in cirrhotic patients. Clin Res Hepatol Gastroenterol 2019; 43: 51-7.
15. Zhang C, Zhao L, Ma L, et al. Vitamin D status and expression of vitamin D receptor and LL-37 in patients with spontaneous bacterial peritonitis. Dig Dis Sci 2012; 57: 182-8.
16. Abdelkader NA, Sabry D, Al-Ghussein MAS, et al. Correlation between vitamin D receptor and monocyte chemotactic protein-1 polymorphisms and spontaneous bacterial peritonitis in decompensated liver disease. J Gastroenterol Hepatol Res 2015; 4: 1815-20.
17. Trepo E, Ouziel R, Pradat P, et al. Marked 25-hydroxyvitamin D deficiency is associated with poor prognosis in patients with alcoholic liver disease. J Hepatol 2013; 59: 344-50.
18. Combart AF. The vitamin D-antimicrobial peptide pathway and its role in protection against infection. Future Microbiol 2009; 4: 1151-65.
19. White JH. Vitamin D signaling, infectious diseases, and regulation of innate immunity. Infect Immun 2008; 76: 3837-43.
20. Liu PT, Stenger S, Li H, et al. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. Science 2006; 311: 1770-3.
21. Kang J, Dietz MJ, Li B. Antimicrobial peptide LL-37 is bactericidal against Staphylococcus aureus biofilms. PLoS One 2019; 14: e0216676.
22. Xie F, Zan Y, Zhang Y, et al. The cysteine protease Apd5 from Streptococcus suis promotes evasion of innate immune defenses by cleaving the antimicrobial peptide cathelicidin LL-37. J Biol Chem 2019; 294: 17962-77.
23. Combart AF, Bhan I, Borregaard N, et al. Low plasma level of cathelicidin antimicrobial peptide (hCAP18) predicts increased infectious disease mortality in patients undergoing hemodialysis. Clin Infect Dis 2009; 48: 418-24.
24. Zhang C, Zhao L, Ding Y, et al. Enhanced LL-37 expression following vitamin D supplementation in patients with cirrhosis and spontaneous bacterial peritonitis. Liver Int 2016; 36: 68-75.
25. Goel A, Gupta M, Aggarwal R. Gut microbiota and liver disease. J Gastroenterol Hepatol 2014; 29: 1139-48.
26. Roth CL, Elfers CT, Figlewicz DP, et al. Vitamin D deficiency in obese rats exacerbates nonalcoholic fatty liver disease and increases hepatic resistin and Toll-like receptor activation. Hepatology 2012; 55: 1103-11.
27. Liu W, Chen Y, Golan MA, et al. Intestinal epithelial vitamin D receptor signaling inhibits experimental colitis. J Clin Invest 2013; 123: 3983-96.

Received: 11.03.2020
Accepted: 5.05.2020

Gastroenterology Review 2021; 16 (1)