European **Rev**iew for **Med**ical and **Pharmacol**ogical **Sci**ences 2022; 26: 2220-2221

Letter to the Editor

Comment on: Effect of Vitamin D supplementation in patients with liver cirrhosis having spontaneous bacterial peritonitis: a randomized controlled study

Dear Editor,

we read with great interest the paper by Mohamed et al[1] regarding vitamin D (vit D) supplementation in cirrhotic patients affected by Spontaneous Bacterial Peritonitis (SBP). In this randomized study the author found that the vit D deficient was a predictor factor of SBP and death, while its supplementation improved the response to treatment.

Liver disease mortality reports accounts for about 2 million deaths per year worldwide, of which 1 million due to cirrhosis complications, and has also been associated with increased in-hospital mortality due to COVID-19 infection[2-4]. Cirrhosis aetiology vary from Western and industrialised countries, where alcohol and non-alcoholic fatty liver disease have overtaken viral hepatitis, to China and other Asian countries where hepatitis B still represent the leading cause[5]. This differentiation is mostly due to diet habits and to the introduction of novel therapy against viral hepatitis C, which improved patients' outcome[6-8]. It is well-know the role of nutrition as risk factors in the chronic liver diseases that could be a determinant progression factor toward cirrhosis, hepatocellular carcinoma (HCC) and its complication[9,10]. In this perspective, the daily use of antioxidant nutrients, such as vit E, sylimarin, is included in several national healthy programs[11]. SBP develops in patients with liver cirrhosis due to bacterial increased translocations by changes in the intestinal bacteria and mucosal barriers, associated with inappropriate host immune response which is unable to remove both bacteria and/or their products. Gram-negative bacteria are the main actors of SBP, e.g., *Escherichia coli* and *Klebsiella species*, with increasing infections by Gram-positive bacteria. Bacterial products translocation into the hepato-splanchnic is in turn responsible of the increased proinflammatory response and bacterial colonization of the ascites[12]. A healthy intestinal epithelium and intact *mucus* layer are fundamental in preventing bacterial translocation, and it has been proved that vitamin D helps to sustain this function. In fact, it has been suggested that vitamin D plays a key role in maintaining tight junctions stem. Moreover, vitamin D supplementation strengthens the epithelial barrier by reducing paracellular permeability of polarized epithelial cells, and by upregulating antimicrobial peptide mRNA and protein expression. Antimicrobial peptides are mostly secreted by Paneth cells in the gut and are important modifiers of microbiome composition[13,14]. In contrast, data supporting bacterial influence upon vitamin D metabolism are increasing. In fact, some bacteria are capable of processing and activating vitamin D by expressing enzymes involved in hydroxylation of steroids[13]. This evidence provides even more prominence to what reported by Mohamed et al[1] in their paper, though, additional studies are needed to understand the mutual relationship between vitamin D and gut microbiota.

Globally, the altered levels of vit D are associated with several pathological conditions, such as osteoporosis, cancer, immunological and infectious diseases. Despite being present in different types of food, the best way to achieve physiological levels of Vit D remains the exposure to UVB radiation[15]. Recently, some scholars[16] aimed at studying the potential role of vitamin D in development and progression of multiple cancers. Inci et al[17] compared the median serum vit D level between a large cohort of cancer patients (1027) and healthy subjects (3887). The results showed a significantly lower levels of vit D in cancer group, with an increase of cancer risk, particularly if it was less than 15.2 ng/ml.

The suspected involvement in the cancer field includes important regulatory roles of controlling proliferation, differentiation and growth. Indeed, the administration of vitamin D ana-

Corresponding Author: Alfredo Caturano MD; e-mail: alfredo.caturano@unicampania.it

logues or the active metabolite of vitamin D activates apoptotic pathways, has antiproliferative effects and inhibits angiogenesis, particularly with interaction with its receptor (VDR)[18]. These considerations could offer food for thought to evaluate a possible role about HCC.

Conflict of interest

The Authors declare that they have no conflict of interests.

References

1) Mohamed AA, Al-Karmalawy AA, El-Kholy AA, El-Damas DA, Abostate HM, Mostafa SM, Hamada M, Khalik Elkady MA, Hassan Y, Al-Hussain E, Khalil MG, Badawy I, Elebeedy D, Alsfouk BA, Shaheenl MM. Effect of Vitamin D supplementation in patients with liver cirrhosis having spontaneous bacterial peritonitis: a randomized controlled study. Eur Rev Med Pharmacol Sci 2021; 25: 6908-6919.
2) Asrani SK, Devarbhavi H, Eaton J, Kamath PS. Burden of liver diseases in the world. J Hepatol 2019; 70: 151-171.
3) Galiero R, Pafundi PC, Simeon V, Rinaldi L, Perrella A, Vetrano E, Caturano A, Alfano M, Beccia D, Nevola R, Marfella R, Sardu C, Coppola C, Scarano F, Maggi P, De Lucia Sposito P, Vocciante L, Rescigno C, Sbreglia C, Fraganza F, Parrella R, Romano A, Calabria G, Polverino B, Pagano A, Bologna C, Amitrano M, Esposito V, Coppola N, Maturo N, Adinolfi LE, Chiodini P, Sasso FC; COVOCA Study Group. Impact of chronic liver disease upon admission on COVID-19 in-hospital mortality: Findings from COVOCA study. PLoS One 2020; 15: e0243700.
4) Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, 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: 2095-2128
5) Galiero R, Pafundi PC, Nevola R, Rinaldi L, Acierno C, Caturano A, Salvatore T, Adinolfi LE, Costagliola C, Sasso FC. The Importance of Telemedicine during COVID-19 Pandemic: A Focus on Diabetic Retinopathy. J Diabetes Res 2020; 2020: 9036847.
6) Rinaldi L, Pafundi PC, Galiero R, Caturano A, Morone MV, Silvestri C, Giordano M, Salvatore T, Sasso FC. Mechanisms of Non-Alcoholic Fatty Liver Disease in the Metabolic Syndrome. A Narrative Review. Antioxidants (Basel). 2021; 10: 270.
7) Galiero R, Caturano A, Vetrano E, Cesaro A, Rinaldi L, Salvatore T, Marfella R, Sardu C, Moscarella E, Gragnano F, Calabrò P, Sasso FC. Pathophysiological mechanisms and clinical evidence of relationship between non-alcoholic fatty liver disease (NAFLD) and cardiovascular disease. Rev Cardiovasc Med 2021; 22: 755-768.
8) Sasso FC, Pafundi PC, Caturano A, Galiero R, Vetrano E, Nevola R, Petta S, Fracanzani AL, Coppola C, Di Marco V, Solano A, Lombardi R, Giordano M, Craxi A, Perrella A, Sardu C, Marfella R, Salvatore T, Adinolfi LE, Rinaldi L. Impact of direct acting antivirals (DAAs) on cardiovascular events in HCV cohort with pre-diabetes. Nutr Metab Cardiovasc Dis 2021; 31: 2345-2353.
9) Di Francia R, Rinaldi L, Troisi A, Di Benedetto F, Berretta M. Effect of anti-oxidant agents in patients with hepatocellular diseases. Eur Rev Med Pharmacol Sci 2015; 19: 3993-3995.
10) Valente G, Rinaldi L, Sgambato M, Piai G. Conversion from twice-daily to once- daily tacrolimus in stable liver transplant patients: effectiveness in a real-world setting. Transplant Proc 2013; 45: 1273-1275.
11) Di Francia R, Rinaldi L, Cillo M, Varriale E, Facchini G, D'Aniello C, Marotta G, Berretta M. Antioxidant diet and genotyping as tools for the prevention of liver disease. Eur Rev Med Pharmacol Sci 2016; 20: 5155-5163.
12) Wiest R, Lawson M, Geuking M. Pathological bacterial translocation in liver cirrhosis. J Hepatol 2014; 60: 197-209.
13) Yamamoto EA, Jørgensen TN. Relationships Between Vitamin D, Gut Microbiome, and Systemic Autoimmunity. Front Immunol 2020; 10: 3141.
14) Caturano A, Acierno C, Nevola R, Pafundi PC, Galiero R, Rinaldi L, Salvatore T, Adinolfi LE, Sasso FC. Non-Alcoholic Fatty Liver Disease: From Pathogenesis to Clinical Impact. Processes 2021; 9: 135.
15) Di Rosa M, Malaguarnera L, Nicolosi A, Sanfilippo C, Mazzarino C, Pavone P, Berretta M, Cosentino S, Cacopardo B, Pinzone MR, Nunnari G.Vitamin D3: an ever green molecule. Front Biosci (Schol Ed) 2013; 5: 247-260.
16) Imran Ali Shah S. Beneficial role of vitamin D in common cancers: is the evidence compelling enough? WCRJ 2020; 7: e1574.
17) İnci F, İnci H, Karataş F, Adahan D. Is low serum Vitamin D level associated with cancer? WCRJ 2020; 7: e1683.
18) El-Sharkawy A, Malki A. Vitamin D Signaling in Inflammation and Cancer: Molecular Mechanisms and Therapeutic Implications. Molecules 2020; 25: 3219.

A. Caturano, V. Brunelli, R. Galiero, S. Spiezia, R. Ferrara, F.C. Sasso

Department of Advanced Medical and Surgical Sciences, University of Campania "Luigi Vanvitelli", Naples, Italy