Lower 25-hydroxyvitamin D3 levels and increased risk of liver diseases: is there a causal link?

Giovanni Targher · Christopher D. Byrne

Received: 11 February 2014 / Accepted: 17 February 2014 / Published online: 5 March 2014
© Springer Science+Business Media New York 2014

Vitamin D deficiency is a highly prevalent condition worldwide, reportedly present in approximately 30–60 % of the general adult population [1, 2]. This worldwide pandemic remains generally unrecognized and untreated.

Vitamin D is critical for bone mineralization, and numerous observational studies have assessed outcomes for skeletal health [1, 2].

In the past several years, however, attention has turned to non-skeletal effects of vitamin D deficiency or insufficiency. Indeed, the discovery that many extra-renal tissues also possess the vitamin D receptor(s), and the converting enzyme 1 α -hydroxylase has provided new insights into the important physiologic paracrine/autocrine roles of vitamin D in various tissues and organs that are mainly dependent on the availability of serum 25-hydroxyvitamin D [25(OH)D] from the circulating plasma [1, 2]. Indeed, the presence of nuclear vitamin D receptors in several cell types, including cardiomyocytes, neurons, immune cells, and hepatocytes, has stimulated considerable scientific interest in understanding the putative pleiotropic properties of vitamin D that may regulate hundreds of different genes

and play an important role in regulating cell proliferation, differentiation, and apoptosis in many normal and cancer cells and also have anti-inflammatory and immuno-modulatory effects [1, 2]. Evolving data indicate that vitamin D deficiency/insufficiency may be playing a role in the pathophysiology of cardiovascular disease as well as several other acute and chronic diseases, including common cancers, autoimmune diseases, osteoarthritis, mental disorders, infectious diseases, metabolic syndrome, and diabetes mellitus [1, 2].

To our knowledge, the paper published by Skaaby et al. [3] on this issue of the journal is one of the first prospective studies to demonstrate that lower levels of serum 25(OH)D are significantly associated with a higher incidence of fatal and non-fatal liver diseases (as combined endpoint) in a population-based sample of 2,649 middle-aged Danish individuals, who were followed for a median follow-up period of 16.5 years. Diagnosis of incident liver diseases was based on the Danish National Patient Register. Notably, the association between serum 25(OH)D levels and risk of incident liver diseases remained statistically significant after adjusting for age, sex, season measurement, daily alcohol consumption, body mass index, smoking status, leisure time physical activity, dietary habits, education, and serum alanine aminotransferase level. Notably, the number of patients with chronic viral hepatitis was negligible in this cohort (due to a low prevalence of viral hepatitis in Denmark), and the authors have excluded from analysis subjects with cirrhosis or other established liver diseases at baseline in order to reduce the possibility of reverse causation (i.e., lower serum 25(OH)D levels due to liver failure). Unfortunately, however, the authors did not report measurement of serum 1,25-dihydroxyvitamin D levels as the active moiety of vitamin D, and also did not adjust their results for history of diabetes and renal diseases

G. Targher (✉)
Section of Endocrinology, Diabetes and Metabolism,
Department of Medicine, University and Azienda Ospedaliera
Universitaria Integrata of Verona, Piazzale A. Stefani 1,
37126 Verona, Italy
e-mail: giovanni.targher@univr.it

C. D. Byrne
Nutrition and Metabolism, Faculty of Medicine, University of
Southampton, Southampton, UK

C. D. Byrne
Southampton National Institute for Health Research Biomedical
Research Centre, University Hospital Southampton,
Southampton, UK

or regional fat distribution as potential confounders, possibly influencing the relationship between vitamin D metabolism and liver disease. Additionally, there was a relatively low number of clinical events during the follow-up period; in total there were 62 incident cases of fatal ($n = 6$) and non-fatal ($n = 56$) liver diseases. Most of these incident cases were due to alcohol abuse ($n = 26$) and non-alcoholic fatty liver disease (NAFLD, $n = 11$) and, therefore, separate analyses of the association between serum 25(OH)D levels and incident cases of specific liver diseases were not possible. It cannot be, therefore, excluded that vitamin D deficiency might exert differential adverse effects on different types of liver diseases. Moreover, whether lower baseline 25(OH)D levels simply reflected early pre-existing (undiagnosed) liver disease or instead actively contributed to the pathogenesis of chronic liver disease cannot be determined from the results of this study [3].

Collectively, the results of the Skaaby's study confirm and extend the recent work of Wang et al. [4] showing an inverse, independent, association between serum 25(OH)D levels and risk of chronic liver disease mortality over 22 years of follow-up among participants of the Linxian Nutrition Intervention Trials. In addition, the results of the Skaaby's study also extend some recent observations from case–control studies suggesting that lower 25(OH)D levels are associated with the presence and severity of NAFLD, independently of several potential confounders, including obesity and other features of the metabolic syndrome [5–8]. For example, we studied circulating 25(OH)D levels in patients with histologically confirmed NAFLD, and healthy non-steatotic controls of comparable age, sex, body mass index and season measurement, and found decreased serum 25(OH)D levels in those with NAFLD (20.4 ± 9 vs. 29.8 ± 6 ng/ml, $p < 0.001$). Furthermore, among patients with NAFLD, decreased 25(OH)D levels were independently associated with the histological severity of hepatic steatosis, necro-inflammation, and fibrosis [8].

To date, the putative underlying mechanisms that link vitamin D deficiency to NAFLD and other liver diseases remain incompletely understood. However, a variety of biologically plausible mechanisms may mediate a hepatoprotective role for the active metabolite of vitamin D. Experimentally, it has been demonstrated that vitamin D modulates the hepatic insulin signaling pathway/insulin resistance, suppresses fibroblast proliferation and collagen production, exerts anti-coagulant and pro-fibrinolytic effects, modulates macrophage activity and inflammatory cytokine generation, and decreases the hepatic production of bile acids (for a more detailed review see [9]).

However, it is important to underline that despite the recent focus in the media on the potential beneficial role of

vitamin D in reducing the risk of various chronic diseases, data are currently lacking from large randomized, controlled trials designed to determine whether vitamin D supplementation reduces the risk of major chronic diseases, including liver diseases. There is, therefore, an urgent need to advance our understanding of the biological pathways through which vitamin D may affect the liver and to conduct additional large-scale intervention clinical trials to firmly establish the relevance of vitamin D status to liver health. In the meantime, it is important to reiterate that although vitamin D deficiency is widespread, it can be safely corrected with a variety of supplement types and regimens, and it should be identified and treated in clinical practice.

Conflict of interest None of the authors have any conflicts of interest.

References

1. J.S. Adams, M. Hewison, Update in vitamin D. *J. Clin. Endocrinol. Metab.* **95**, 471–478 (2010)
2. G. Targher, I. Pichiri, G. Lippi, Vitamin D, thrombosis, and hemostasis: more than skin deep. *Semin. Thromb. Hemost.* **38**, 114–124 (2012)
3. Skaaby T, Husemoen LL, Borglykke A, Jørgensen T, Thuesen BH, Pisinger C, Schmidt LE, Linneberg A (2013) Vitamin D status, liver enzymes, and incident liver disease and mortality: a general population study. *Endocrine*. 2013 Nov 23 [Epub ahead of print]. DOI: [10.1007/s12020-013-0107-8](https://doi.org/10.1007/s12020-013-0107-8)
4. J.B. Wang, C.C. Abnet, W. Chen, S.M. Dawsey, J.H. Fan, L.Y. Yin et al., Association between serum 25(OH) vitamin D, incident liver cancer and chronic liver disease mortality in the Linxian nutrition intervention trials: a nested case-control study. *Br. J. Cancer* **109**, 1997–2004 (2013)
5. I. Barchetta, F. Angelico, M. Del Ben, M.G. Baroni, P. Pozzilli, S. Morini et al., Strong association between non alcoholic fatty liver disease (NAFLD) and low 25(OH) vitamin D levels in an adult population with normal serum liver enzymes. *BMC Med.* **9**, 85 (2011)
6. K.L. Jablonski, A. Jovanovich, J. Holmen, G. Targher, K. McFann, J. Kendrick et al., Low 25-hydroxyvitamin D level is independently associated with non-alcoholic fatty liver disease. *Nutr. Metab. Cardiovasc. Dis.* **23**, 792–798 (2013)
7. E.J. Rhee, M.K. Kim, S.E. Park, C.Y. Park, K.H. Baek, W.Y. Lee et al., High serum vitamin D levels reduce the risk for nonalcoholic fatty liver disease in healthy men independent of metabolic syndrome. *Endocr. J.* **60**, 743–752 (2013)
8. G. Targher, L. Bertolini, L. Scala, M. Cigolini, L. Zenari, G. Falezza et al., Associations between serum 25-hydroxyvitamin D3 concentrations and liver histology in patients with non-alcoholic fatty liver disease. *Nutr. Metab. Cardiovasc. Dis.* **17**, 517–524 (2007)
9. G. Targher, E. Scorletti, A. Mantovani, C.D. Byrne, Nonalcoholic fatty liver disease and reduced serum vitamin D3 levels. *Metab. Syndr. Relat. Disord.* **11**, 217–228 (2013)