

Editorial

Vitamin D, An Old but New Biomarker for Hepatocellular Carcinoma?

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Hepatocellular Carcinoma (HCC) is a major health concern worldwide, and more than 70,000 cases are diagnosed yearly, with an age-adjusted worldwide incidence of 16 cases per 100,000 people [1,2]. Many patients with HCC present with an intermediate to advanced stage of the disease at diagnosis. Despite advances in treatment, the prognosis of patients with HCC remains poor. The identification of better prognostic biomarkers for HCC is therefore urgently required to optimize the selection of treatments.

Vitamin D is recognized as a key player in calcium and bone homeostasis. During the last decade, growing evidence has indicated that vitamin D also regulates cell proliferation and differentiation, and has immunomodulatory, anti-inflammatory and anti-fibrotic properties [3]. Vitamin D deficiency is associated with an increased risk of diabetes mellitus, cardiovascular disease and cancer [4]. With respect to cancer, vitamin D deficiency has been reported to have a negative prognostic role in breast cancer, colon cancer, prostate cancer and melanoma [5].

Recently, in vol. Finkelmeier et al. 39 of *Alimentary Pharmacology and Therapeutics*, Finkelmeier reported their investigation of serum vitamin D as a prognostic parameter in 200 patients with HCC [6]. The authors investigated the association between the serum levels of 25-hydroxyvitamin D3 (25(OH) D3) and the patient baseline characteristics and Overall Survival (OS). The mean serum 25(OH) D3 concentration was 17±13ng/ml, and ranged from 1-72 ng/ml. Lower serum 25(OH) D3 concentrations were associated with a decreased liver functional reserve, as indicated by a higher Child-Pugh grade and MELD score. Lower serum 25 (OH) D3 concentrations were also associated with a higher BCLC stage and CLIP score. The overall survival rates in patients with lower serum 25 (OH) D3 concentrations (≤10ng/ml) were significantly lower than those in patients with higher serum 25 (OH) D3 concentrations (>10ng/ml). In a multivariate analysis, the serum 25 (OH) D3 levels were found to be independently associated with the overall survival. Consequently, the authors concluded that 25 (OH) D3 deficiencies were associated with tumor progression and a poor prognosis in patients with HCC [6].

The genomic actions of vitamin D are mediated through its binding to the Vitamin D Receptor (VDR), which allows it to modulate the expression of genes in a cell-and tissue-specific manner [7]. The VDR directly or indirectly regulates the expression of more than 200 genes that influence cell proliferation, differentiation and apoptosis, as well as immunomodulation and angiogenesis [3].

Abe et al. first reported the pro-differentiation effect of vitamin D on cancer cells in 1981. They demonstrated that 1, 25 (OH) D3 induced the differentiation of myeloid leukemia cells into macrophages [8]. Since then, investigators have shown that 1α, 25 (OH) D3 exhibited growth inhibitory effects on prostate, breast, lung, colon and pancreatic cancer cells [7,9-12].

With regard to HCC, Pourgholami et al. Demonstrated that 1α, 25 (OH) D3 had a significant inhibitory effect on HCC cell lines, especially Hep-3B and Hep-G2 cells [13]. Moreover, they showed that the inhibitory effects of 1α, 25 (OH) D3 on the growth of the Hep-G2 HCC cell line were attributable to arrest in the G0/G1 phase of the cell cycle, leading to a decrease in the number of cells in the S phase [14]. These experimental studies support the tumor inhibitory effects of vitamin D on HCC cells, suggesting that vitamin D deficiency may play an important role in the development and progression of HCC.

In the clinical setting, Hammad indicated that vitamin D, as well as IL-6 and IL-17, was a potential biomarker for the development of HCC in patients with hepatitis C [15]. Lange also demonstrated that vitamin D deficiency was associated with the development of HCC in patients with hepatitis C [16].

Clinicians should therefore recognize that this old biomarker may also be a new biomarker for the development and prognosis of HCC. Moreover, further studies are needed to determine the potential therapeutic value of vitamin D in patients with HCC.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

References

1. Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. *Lancet*. 2012; 379: 1245-1255.
2. Bruix J, Gores GJ, Mazzaferro V. Hepatocellular carcinoma: clinical frontiers and perspectives. *Gut*. 2014; 63: 844-855.
3. Kitson MT, Roberts SK. D-livering the message: the importance of vitamin D status in chronic liver disease. *J Hepatol*. 2012; 57: 897-909.
4. Rosen CJ. Clinical practice. Vitamin D insufficiency. *N Engl J Med*. 2011; 364: 248-254.
5. Buttigliero C, Monagheddu C, Petroni P, Saini A, Dogliotti L, Ciccone G, et al. Prognostic role of vitamin d status and efficacy of vitamin D supplementation in cancer patients: a systematic review. *Oncologist*. 2011; 16: 1215-1227.

6. Finkelmeier F, Kronenberger B, Köberle V, Bojunga J, Zeuzem S, Trojan J, et al. Severe 25-hydroxyvitamin D deficiency identifies a poor prognosis in patients with hepatocellular carcinoma - a prospective cohort study. *Aliment Pharmacol Ther.* 2014; 39: 1204-1212.
7. Chiang KC, Yeh CN, Chen MF, Chen TC. Hepatocellular carcinoma and vitamin D: a review. *J Gastroenterol Hepatol.* 2011; 26: 1597-1603.
8. Abe E, Miyaoura C, Sakagami H, Takeda M, Konno K, Yamazaki T, et al. Differentiation of mouse myeloid leukemia cells induced by 1 alpha, 25-dihydroxyvitamin D3. *Proc Natl Acad Sci U S A.* 1981; 78: 4990-4994.
9. Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. *Am J Clin Nutr.* 2004; 80: 1678S-88S.
10. Flanagan JN, Zheng S, Chiang KC, Kittaka A, Sakaki T, Nakabayashi S, et al. Evaluation of 19-nor-2alpha-(3-hydroxypropyl)-1alpha,25-dihydroxyvitamin D3 as a therapeutic agent for androgen-dependent prostate cancer. *Anticancer Res.* 2009; 29: 3547-3553.
11. Chiang KC, Chen TC. Vitamin D for the prevention and treatment of pancreatic cancer. *World J Gastroenterol.* 2009; 15: 3349-3354.
12. Akhter J, Goerdel M, Morris DL. Vitamin D3 analogue (EB 1089) inhibits in vitro cellular proliferation of human colon cancer cells. *Br J Surg.* 1996; 83: 229-230.
13. Pourgholami MH, Akhter J, Lu Y, Morris DL. In vitro and in vivo inhibition of liver cancer cells by ,25-dihydroxyvitamin D3. *Cancer Lett.* 2000; 151: 97-102.
14. Caputo A, Pourgholami MH, Akhter J, Morris DL. 25-Dihydroxyvitamin D(3) induced cell cycle arrest in the human primary liver cancer cell line HepG2. *Hepatol Res.* 2003; 26: 34-39.
15. Hammad LN, Abdelraouf SM, Hassanein FS, Mohamed WA, Schaalaa MF. Circulating IL-6, IL-17 and vitamin D in hepatocellular carcinoma: potential biomarkers for a more favorable prognosis? *J Immunotoxicol.* 2013; 10: 380-386.
16. Lange CM, Miki D, Ochi H, Nischalke HD, Bojunga J, Bibert S, et al. Genetic analyses reveal a role for vitamin D insufficiency in HCV-associated hepatocellular carcinoma development. *PLoS One.* 2013; 8: e64053.