Editorial

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Shedding new light on vitamin D and fatty liver disease

Andreas Geier*

Department of Gastroenterology and Hepatology, University Hospital Zurich (USZ), CH-8091 Zurich, Switzerland

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Vitamin D in its active form, 1,25-$(OH)_2$ vitamin D, has been shown to play a role in various diseases, such as different types of infectious and autoimmune diseases as well as cancers [1]. It is estimated that one billion people worldwide are vitamin D deficient or insufficient [2]. Sources of vitamin D are diet and dietary supplements as well as endogenously synthesised vitamin D from 7-dehydrocholesterol following exposure to ultraviolet B radiation [1]. To achieve the biologically active form, vitamin D3 undergoes 25-hydroxylation in the liver and subsequent 1-hydroxylation in the kidneys [3]. Meanwhile vitamin D has been reported to control over 200 genes in a direct or indirect way. Among those are genes regulating angiogenesis, apoptosis, cell growth, proliferation and differentiation [4], mainly reducing cell proliferation and inducing terminal differentiation [4,5]. Furthermore, immunomodulatory effects of 1,25-$(OH)_2$ vitamin D are well described, as monocytic cells upregulate vitamin D receptor upon antigen exposure, enhancing innate immune responses. In this view, vitamin D may also favour immune tolerance towards the liver allograft as early vitamin D supplementation in patients post-transplantation was associated with a reduced rate of acute cellular rejection [6].

In the view of bile acid-dependent uptake of vitamin D and its hepatic metabolism, it is reasonable to expect an association between vitamin D status and both cholestatic and non-cholestatic chronic liver disease. Indeed, serum concentrations of 1,25-$(OH)_2$ vitamin D are decreased in patients with cirrhosis versus noncirrhotic patients [7,8] and a gradual decline has been observed in cirrhotic patients according to increasing Child-Pugh class [7] and clinical decompensation [9]. Recently, a significant correlation between lower 25-OH vitamin D levels and an increasing stage of fibrosis and severity of necroinflammatory activity was observed in a population with genotype 1 chronic hepatitis C [10]. Interestingly, reduced 25-OH vitamin D levels can be found in patients with non-alcoholic fatty liver disease (NAFLD) compared to controls with a close association to the histological severity of hepatic steatosis, necroinflammation and fibrosis [11]. Since in this study 25-OH vitamin D was inversely associated with NAFLD features independent of insulin resistance and the metabolic syndrome, it could be hypothesized that inadequate vitamin D status might contribute to the development and progression of NAFLD. These findings were recently confirmed in children with biopsy-proven NAFLD, where low 25-OH vitamin D levels were associated with increased likelihood of fibrosis and necroinflammation [12]. Independent of serum vitamin D levels, alterations in the vitamin D receptor (*VDR*, *NR1I1*) gene have also been described as an important event in a multitude of diseases, among these are hepatic disorders such as primary biliary cirrhosis and autoimmune hepatitis [13,14].

In this issue of the Journal, Nakano and coworkers have investigated the impact of sunlight therapy on the progress of NAFLD in rats [15]. In this study, phototherapy ameliorated insulin resistance and hepatic steatosis caused by a choline-deficient and iron-supplemented L-amino acid-defined (CDAA) diet. In particular, phototherapy improved histology with regard to hepatocyte apoptosis, inflammation and fibrosis, increased serum adiponectin levels and led to a reduced hepatic expression of the profibrotic transforming growth factor (TGF)-β and the hepatic stellate cell activation marker α-smooth muscle actin (SMA). A gradual decrease of apolipoprotein E under CDAA diet was reversed by phototherapy. Comparable to low 25-OH vitamin D levels reported in human NAFLD [11], 25-OH vitamin D and 1,25-$(OH)_2$ vitamin D levels were significantly lower in CDAA diet rats compared to untreated controls. Of mechanistic interest, an elevation of the circulating active form of vitamin D3 has been observed after sunlight therapy and an intervention with vitamin D3 supplementation ameliorated histology, in the same model, as measured by a decreased hepatitis area. However, the effects of phototherapy were less pronounced in leptin receptor-mutant Zucker rats, a more obesity-related model of fatty liver disease. The fact that hepatic steatosis and liver-to-body weight ratio remains unchanged in this second model raises the question, whether sunlight (and/or vitamin D) therapy is rather anti-inflammatory and may have less metabolic or anti-steatotic effects. Recent preliminary data from vitamin D receptor knockout mice point to the fact that the vitamin D status also impacts on hepatic steatosis. In line with the beneficial effect of vitamin D observed in the CDAA model, vitamin D receptor knockout mice spontaneously develop hepatic steatosis [16]. In this study, liver steatosis was observed in 57% of VDR-/- mice under basal conditions, while no steatosis was evidenced in VDR+/+ mice.

Whereas a variety of data suggest the potentially beneficial role of vitamin D in treatment of NAFLD, the underlying

* Laboratory for Molecular Hepatology, Department of Gastroenterology and Hepatology, University Hospital Zurich, Rämistrasse 100, CH-8091 Zurich, Switzerland. Tel.: +41 44 255 2259; fax: +41 44 255 4503.
E-mail address: andreas.geier@usz.ch

mechanisms are less well established. Hepatocytes express only low levels of *VDR* mRNA [17,18], so vitamin D effects on the liver are most likely not conferred by direct signalling in parenchymal liver cells. In contrast, non-parenchymal hepatic cells such as sinusoidal endothelial cells, Kupffer cells and hepatic stellate cells (HSC) do express *VDR* mRNA and functionally active VDR protein [19]. More recent cell culture studies showed marked anti-inflammatory and antifibrotic effects of VDR-signalling in HSC. During inflammatory liver injury after endotoxin injection the activation of VDR signalling by vitamin D resulted in attenuation of liver damage *in vivo* [20]. Besides these effects on non-parenchymal hepatic cells, vitamin D also activates intestinal fibroblast growth factor (Fgf) 15 (human ortholog FGF19) in mice, an intestine-derived hormone that acts on liver to inhibit the hepatic cholesterol 7α-hydroxylase (Cyp7a1) [21,22]. This Fgf-dependent regulation of bile acid metabolism is conserved between rodents and humans and the FGF19-mediated phosphorylation of the hepatic FGF receptor (FGFR) 4 with subsequent activation of the Erk1/2 pathway inhibits human CYP7A1 [23]. The central role of CYP7A1 inhibition in hepatic dyslipidemia becomes evident from studies in mice with transgenic expression of Cyp7a1 in the liver which prevents high fat diet-induced obesity and insulin resistance [24].

Interestingly, insulin and FGF15/19 both target the PI 3-kinase pathway and inhibit forkhead transcription factor 1 (FOXO1) the latter represents a central mediator in the convergence of FGF and insulin signalling pathways which functions as an integrator of glucose and bile acid metabolism [24]. Increasing evidence exists for the beneficial effects of vitamin D on glucose metabolism and insulin resistance in man. Low serum 25-OH vitamin D is predictive of future glycemia and insulin resistance in non-diabetic subjects [25] and inversely associated with metabolic syndrome in the 1958 British Birth Cohort [26]. Furthermore, low vitamin D levels have been associated in non-diabetic adults with several markers of insulin resistance such as plasma glucose, insulin, HOMA-IR and adiponectin [27,28]. A close correlation between body mass index and 25-OH vitamin D level has been described in which each BMI increase of 1 kg/m^2 was associated with a 1.3 nmol/L decrease in vitamin D [29]. The hepatic response to FGF19 is impaired in NAFLD patients with insulin

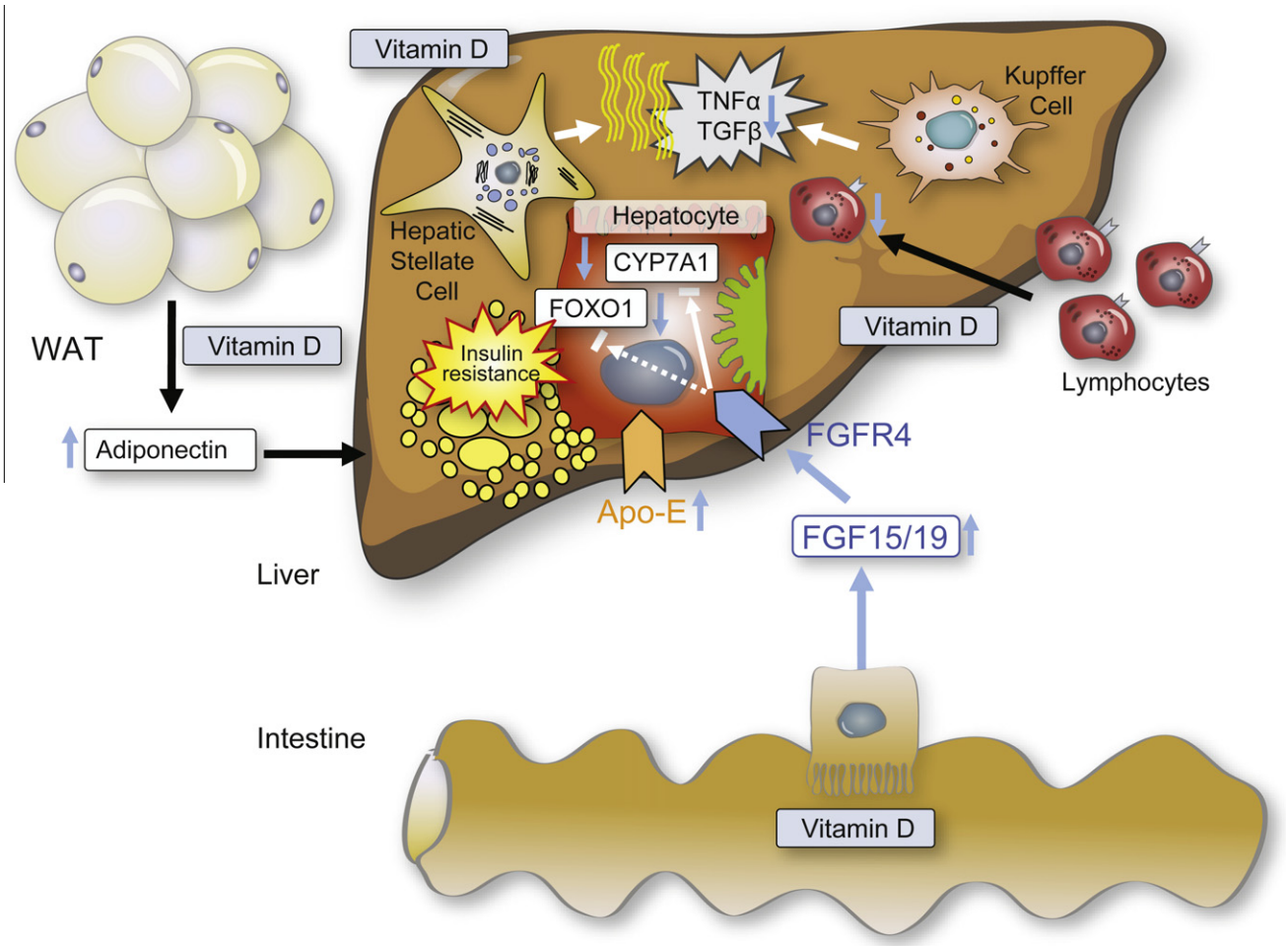

Fig. 1. Vitamin D-mediated effects on fatty liver disease. Anti-inflammatory, anti-fibrotic, and metabolic effects of vitamin D on parenchymal (hepatocytes) and non-parenchymal hepatic cells (hepatic stellate cells, Kupffer cells, and lymphocytes) are induced in fatty livers. Metabolic effects of vitamin D on the cholesterol 7α-hydroxylase (CYP7A1) and on forkhead transcription factor 1 (FOXO1), a central mediator in the insulin signalling pathway, are mediated via intestinal activation of fibroblast growth factor 15/19 and hepatic FGF receptor 4 (FGFR4) signalling. Furthermore, apolipoprotein (APOE) expression is induced. In white adipose tissue (WAT), adiponectin expression is activated by vitamin D treatment.

resistance (HOMA score $\geqslant$2.5) [30]. Both decreased vitamin D levels and this impaired hepatic response to FGF19 may contribute to the dysregulation of lipid homeostasis in NAFLD. Most interestingly, therapeutic intervention with vitamin D substitution leads to the amelioration of insulin resistance without affecting insulin secretion [31,32]. All of these findings clearly support a central role of vitamin D signalling in glucose homeostasis and the metabolic syndrome and warrant further study of mechanistic detail. A synopsis of vitamin D-mediated effects on the liver and particularly fatty liver disease is given in Fig. 1.

Understanding the complex interplay between vitamin D signals and lipid/glucose metabolism and differentiating specific metabolic effects from nonspecific anti-inflammatory properties in fatty liver disease may open new therapeutic interventions for the future in this constantly increasing threat to public health. The first confirmation of therapeutic potency of sunlight therapy and vitamin D in an animal model of fatty liver disease clearly builds the basis for subsequent human therapeutic trials in NAFLD. Vitamin D substitution represents a simple, cheap and almost side effect-free candidate approach to reduce the burden of end-stage liver failure and liver cancer in this frequent disease entity for which medical interventions with proven longterm efficacy are still lacking.

Conflict of interest

The author declared that he does not have anything to disclose regarding conflict of interest with respect to this manuscript.

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