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EDITORIAL

Overview of studies of the vitamin D/vitamin D receptor system in the development of non-alcoholic fatty liver disease

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in the world. NAFLD is known to be associated with obesity, type 2 diabetes, metabolic syndrome and increased cardiovascular events: for these reasons, it is becoming a global public health problem and represents an important challenge in terms of prevention and treatment. The mechanisms behind the pathogenesis of NAFLD are multiple and have not yet been completely unraveled; consequently, at moment there are not effective treatments. In the past few years a large body of evidence has been assembled that attributes an important role in hepatic aberrant fat accumulation, inflammation and fibrosis, to the vitamin D/vitamin D receptor (VD/VDR) axis, showing a strong association between hypovitaminosis D and the diagnosis of NAFLD. However, the data currently available, including clinical trials with VD supplementation, still provides a contrasting picture. The purpose of this editorial is to provide an overview of recent advances in the pathogenesis of NAFLD in relation to VD/VDR. Based on recent data from literature, we focused in particular on the hypothesis that VDR itself, independently from its traditional ligand VD, may have a crucial function in promoting hepatic fat accumulation. This might also offer new possibilities for future innovative therapeutic approaches in the management of NAFLD.

Key words: Vitamin D; Vitamin D receptor; Non-alcoholic fatty liver disease; Type 2 diabetes

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Core tip: In the last years, many evidences attribute to the vitamin D/vitamin D Receptor axis an important role in the pathogenesis of non-alcoholic fatty liver disease (NAFLD). The purpose of this editorial is to provide an overview of recent advances in the pathogenesis of NAFLD in relation to vitamin D/vitamin D receptor (VD/VDR). We focused in particular on the hypothesis that VDR itself, independently from its traditional ligand VD, may play a crucial function in promoting hepatic fat accumulation, also offering new possibilities for innovative therapeutic approaches in the management of NAFLD.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is currently considered the most common chronic liver disease worldwide[1]. Recent epidemiologic studies report that the prevalence of NAFLD is increasing, starting from the currently estimated 25% in the general population[2,3], and rising dramatically in obese individuals[4], in subjects with type 2 diabetes (T2D)[5] and those with metabolic syndrome[6]. NAFLD is becoming a global public health problem[7]: In many countries the number of patients affected by the disease is rapidly growing, so that in the last years the disease has reached epidemic proportions. Moreover, several studies have shown increased cardiovascular events in NAFLD patients and demonstrated that NAFLD is an independent risk factor for cardiovascular mortality[8-10].

VITAMIN D AND NAFLD

In spite of the alarming prevalence and the clinical implications of NAFLD, the mechanisms underlying its development and progression are still not fully understood, and currently there are no effective treatments. Over the years many different pathophysiological theories have been put forward, leading to the most widely accepted hypothesis, "multiple parallel hits"[11]. According to this model the steps conducive to hepatic fat accumulation, inflammation and fibrosis are orchestrated by a delicate interplay of factors[11], and in this context the role of the vitamin D/vitamin D receptor (VD/VDR) axis has become an active area of research. Indeed, apart from its central role in bone and mineral homeostasis, VD is a molecule that exerts various effects on a number of biological systems; active VD in particular has been shown to regulate the immune system and to modulate insulin sensitivity in experimental models of metabolic diseases[12-14].

Numerous studies have demonstrated that low VD circulating levels are associated with obesity[15], metabolic syndrome[16-19], and T2D[20-22]. Investigations conducted in several adult populations also showed a strong association between hypovitaminosis D and the diagnosis of NAFLD[23-30]. This association was also confirmed in children, in which low VD levels were found to correlate with the histological severity of NAFLD independently from metabolic characteristics[31,32].

Data from animal studies further support the notion that the impairment of VD balance plays a role in the development of NAFLD. Roth and colleagues showed that in obese rats the lack of VD intake allowed the onset and progression of NAFLD, which was evaluated through liver histology demonstrating a higher NAFLD activity score and increased lobular inflammation[33]. Likewise, under experimental conditions, VD has been shown to have an anti-inflammatory effect, accompanied by a significant inhibition of the hepatic expression of pro-fibrotic mediators, such as platelet-derived growth factor and transforming growth factor. The anti-inflammatory effect was also demonstrated by the suppression of the production of collagen, α-smooth muscle actin and tissue inhibitors of metalloproteinase-1 β[34-37]. In addition, in a study conducted on mice with nonalcoholic steatohepatitis (NASH), phototherapy reduced hepatocyte inflammation and fibrosis and improved insulin resistance by increasing the serum active form of VD[38].

On the basis of these evidences and of both experimental and epidemiological data, VD has attracted the interest for a potential therapeutic option during NAFLD. However, up until now results from randomized clinical trials have failed to demonstrate the efficacy of VD supplementation in improving either fatty liver content, or the histological parameters of inflammation and fibrosis, or transaminases in the course of NAFLD and NASH[39-45].

The clinical significance of VD in NAFLD is thus still controversial. A critical examination of the results from trials conducted so far may provide reasonable grounds for conducting further appropriately designed investigations (for example, personalized supplementation regimes in relation to VD levels at baseline and stage of liver damage, higher VD supplementation doses, longer periods of supplementation) before reaching any final conclusions on this topic. However, at present it is not possible to recognize which real benefits can be obtained from restoring optimal VD values in the case of chronic hepatic damage as a result of NAFLD.

ROLE OF VDR

In addition to the question of vitamin D, the role of VDR *per se* has been investigated in metabolic diseases, focusing in particular on its effect/expression in insulin sensitive tissues and organs, such as adipose tissue and the liver. In 2012, Barchetta *et al*[46] demonstrated for the first time in humans the expression of VDR in different hepatic cell types and reduced VDR expression in the hepatic cells of patients with NASH. Since that time many studies have shown that in the liver VDR regulates necro-inflammation and fibrosis[47-50]. Moreover, Arai *et al*[51] recently demonstrated that, in patients with biopsy-proven NAFLD, polymorphisms of the VDR gene are associated with the severity of liver fibrosis.

Interestingly the data showed that not only VD, but also secondary hydrophobic bile acids, such as lithocholic acid, activate VDR in human hepatocytes[52,53]. Bozic *et al*[50] demonstrated that in animal models, the development of liver steatosis was blunted in the presence of VDR deletion. Notably, data obtained in mice exposed to a high fat diet showed an early induction of hepatic VDR expression in the presence of a fatty liver, followed by a trend towards VDR reduction in the long term, whereupon more severe inflammation and fibrosis occurred[50]. In that same research, an expression analysis of genes related to lipid metabolism in mouse livers indicated that VDR might exert a pro-steatotic activity in the hepatocytes as results of both the activation lipogenic pathways and the inhibition of fat oxidation. Moreover, García-Monzón *et al*[54] very recently demonstrated that hepatic angiopoietin-like protein 8 (ANGPTL8) expression is increased upon VDR activation. It is known that ANGPTL8 is a key regulator of triglycerides metabolism and that higher circulating ANGPTL8 levels are associated with the presence of NAFLD[55-57]. These data suggest that VDR induction is more prominent in simple steatosis than in advanced liver damage, which is likely to indicate that VDR is induced at the early stages of the disease and does not require liver injury or fibrosis to have become established.

The overall data appear to support the hypothesis that, in the course of metabolic diseases, VDR itself, independently from its traditional ligand VD, may have a crucial function in promoting hepatic fat accumulation. Further studies should be oriented in this direction with a view to fully understanding the processes behind hepatic VDR activation and evaluating its role as a new target for innovative therapeutic approaches to the early management of NAFLD.

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