



## Relationship between adipose tissue dysfunction, vitamin D deficiency and the pathogenesis of non-alcoholic fatty liver disease

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### Abstract

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease worldwide. Its pathogenesis is complex and not yet fully understood. Over the years many studies have proposed various pathophysiological hypotheses, among which the currently most widely accepted is the "multiple parallel hits" theory. According to this model, lipid accumulation in the hepatocytes and insulin resistance increase the vulnerability of the liver to many factors that act in a coordinated and cooperative manner to promote hepatic injury, inflammation and fibrosis. Among these factors, adipose tissue dysfunction and subsequent chronic low grade inflammation play a crucial role. Recent studies have shown that vitamin D exerts an immune-regulating action on adipose tissue, and the growing wealth of epidemiological data is demonstrating that hypovitaminosis D is associated with both obesity and NAFLD. Furthermore, given the strong association between these conditions, current findings suggest that vitamin D may be involved in the relationship between adipose tissue dysfunction and NAFLD. The purpose of this review is to provide an overview of recent advances in the pathogenesis of NAFLD in relation to adipose tissue dysfunction, and in the pathophysiology linking vitamin D deficiency with NAFLD and adiposity, together with an overview of the evidence available on the clinical utility of vitamin D supplementation in cases of NAFLD.

**Key words:** Adipose tissue dysfunction; Vitamin D; Non-alcoholic fatty liver disease; Steatosis; Non-alcoholic steatohepatitis; Obesity; Adipokines

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**Core tip:** Obesity-associated chronic low-grade inflammation plays a pivotal role in the development of non-alcoholic fatty liver disease (NAFLD). Vitamin D deficiency is associated with both obesity and NAFLD, and its anti-inflammatory and immune-modulatory properties provided plausible mechanisms by which hypovitaminosis D may link adipose tissue dysfunction and NAFLD. Animal studies showed beneficial effect of vitamin D supplementation on systemic inflammation and NAFLD, but these data are not confirmed by the results of clinical trials so far conducted in humans.

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## INTRODUCTION

### **Definition and epidemiology of non-alcoholic fatty liver disease**

Non-alcoholic fatty liver disease (NAFLD) is a condition characterized by the accumulation of excessive fat in the liver in individuals with no history of alcohol abuse (< 30 g/d in men and < 20 g/d in women) and no competing etiologies for hepatic steatosis. NAFLD represents a spectrum of diseases ranging from simple steatosis to nonalcoholic steatohepatitis (NASH), which may evolve into hepatic fibrosis, cirrhosis, and eventually hepatic carcinoma<sup>[1-5]</sup>.

NAFLD is a global public health problem<sup>[6]</sup>: it is currently the most common chronic liver disease worldwide, affecting approximately 20%-35% of adults in the general population<sup>[7]</sup>. Furthermore, the number of patients affected is growing rapidly, and the disease has now reached epidemic proportions. The reported prevalence of NAFLD is 20%-30% in western countries and approximately 15% in Asian countries. In individuals who are of normal weight and who have no metabolic risk factors, the prevalence of NAFLD is about 16%. Though, it rises dramatically in high-risk individuals such as patients with diabetes (60%), hyperlipidemia (90%) and obese patients (91%)<sup>[8-12]</sup>. In addition to diabetes and obesity, other independent risk factors identified for the disease to progress toward NASH and to develop fibrosis and cirrhosis are

age, female sex, Hispanic ethnicity, smoking<sup>[13,14]</sup>.

Notably, 55% of patients with NAFLD have normal aminotransferase levels<sup>[15]</sup>, suggesting that studies using liver enzymes as a surrogate for NAFLD significantly underestimate the prevalence of this condition. NAFLD diagnosis is usually made by ultrasonography, which enables moderate and severe steatosis to be detected with acceptable sensitivity but only once the level of fat accumulated in the liver exceeds 33%. More sensitive techniques, including nuclear magnetic resonance imaging and spectroscopy, are hindered by the high costs involved and the lack of feasibility in large populations. The American Association for the Study of Liver Diseases sets the limit for the diagnosis of NAFLD at a biopsy-proven hepatic fat content greater than 5%<sup>[7]</sup>. Liver biopsy is therefore still considered to be the gold standard, although its widespread use is restricted by a number of factors, including the cost and lack of feasibility in population-based studies on both ethical and practical grounds.

The clinical implications of the alarming prevalence of NAFLD, our limited knowledge of its underlying pathophysiologic mechanisms, and the difficulties in both its diagnosis and treatment explain why NAFLD is currently a field of such intensive research.

### **Pathogenesis of NAFLD**

A histological grading and staging system for non-alcoholic steatohepatitis was proposed by Brunt *et al.*<sup>[16]</sup> in 1999. The amount of fat, fibrosis and necro-inflammation were the parameters included in the Brunt's criteria for grading and staging NASH. The presence of hepatic steatosis and inflammation with hepatocyte injury (ballooning) defined the diagnosis of NASH, according to recently recommended guideline of the American Association for the Study of Liver Disease<sup>[7]</sup>.

In patients with NAFLD, studies have shown that the vast majority of hepatic fat (59%) originates from adipose tissue lipolysis, 26% comes from *de novo* lipogenesis and 15% originates from the diet<sup>[17]</sup>. Hepatic steatosis results when the balance between delivery and synthesis of free fatty acids exceeds the liver capacity to oxidize or export them. Accumulation of lipids can exert toxic effects on the liver by inefficient oxidation or by activation of inflammatory pathways. Further, increased lipid metabolites such as diacylglycerol and ceramides may themselves cause cell injury and insulin resistance (IR) by interfering with the ability of insulin to phosphorylate insulin receptor substrate-2 through activation of protein kinase C-epsilon<sup>[18-21]</sup>.

In 1998, Day *et al.*<sup>[22]</sup> presented the "two hits" hypothesis to describe the pathogenesis of NAFLD. They proposed that the "first hit" was represented by lipid accumulation in the hepatocytes and consequent IR, and that the "second hit" was represented by increased oxidative stress that resulted in hepatic

inflammation, fibrosis and necrosis. This model is now considered obsolete, because it is inadequate to explain the several molecular and metabolic changes which lead to the development of NAFLD.

According to the current "multiple-hits" theory, the "first hit" sensitizes the liver to further insults, which are represented by a variable combination of different hits, such as oxidative stress and subsequent lipid peroxidation, mitochondrial dysfunction, gut microbiota, adipose tissue dysfunction, and adipokine secretion, all of which are ultimately capable of inducing hepatic injury<sup>[23-26]</sup>.

In this context, novel data has unraveled the role of adipose tissue dysfunction as a central player in the ectopic fat distribution associated with obesity and dysmetabolic conditions. In this review, we are therefore focusing on recent findings that provide an insight into the role of adipose tissue dysfunction in the pathogenesis of NAFLD.

## ADIPOSE TISSUE DYSFUNCTION AND NAFLD

Obesity is a major risk factor for the development of NAFLD, but not all patients with obesity go on to develop NAFLD. In the National Health and Nutrition Examination Survey III, 7.4% of lean adults and 27.8% of overweight/obese adults had hepatic steatosis which could be detected by ultrasound<sup>[27]</sup>.

One reason for this incomplete overlap between obesity and NAFLD is related to the use of Body Mass Index (BMI) to define obesity, meaning that, although BMI cut-off points have good specificity for detecting excess adiposity, they lack sensitivity<sup>[28]</sup> and also fail to provide information about the distribution, type and quality of body fat.

Traditionally, adipose tissue was regarded as an inert organ for the storage of energy, but in the last few years this conventional view has been radically altered. Currently, adipose tissue is considered to be the major, and possibly the largest, endocrine organ, having the ability to synthesize and release a variety of hormones, cytokines, both complement and growth factors, extracellular matrix proteins and vasoactive agents, collectively known as adipokines. Therefore, it has been shown that adipose tissue biology is much more complex than previously considered<sup>[29]</sup> and visceral adipose tissue (VAT) dysfunction has been proposed as a major contributor to NAFLD<sup>[30,31]</sup>.

VAT consists of a loose connective tissue that is predominately populated with tightly packed adipocytes that are vascularized by a dense network of capillaries. A second component of VAT is represented by the stromal vascular fraction and includes pre-adipocytes, multi-potent stem cells, fibroblasts, vascular endothelial cells, and immune cells surrounded by the extracellular matrix (ECM). The ECM contains a variety of structural proteins and

collagen networks that anchor adipocytes to maintain the structural and functional integrity of the tissue<sup>[32]</sup>.

In obese subjects, excessive nutrient intake and the consequent accumulation of triglycerides result in an expansion of VAT that causes adipocytes hypertrophy and alters the stromal vascular compartment<sup>[33,34]</sup>. Progressive adipocytes hypertrophy is associated with increased adipokine and pro-inflammatory cytokine production<sup>[35]</sup> and leads to hypoxia and adipocyte cell death<sup>[36,37]</sup>. Dysfunctional VAT also undergoes excessive fibrosis by enhancing the expression of different ECM components such as collagen VI<sup>[32,38,39]</sup>; progressive fibrosis may also limit the amount of fat stored in the adipocytes, thus promoting the deposition of ectopic fat in liver and muscle<sup>[40]</sup>.

One hallmark of adipose tissue dysfunction is the accumulation of inflammatory cells in the context of VAT; in particular, active macrophages infiltrate VAT<sup>[41,42]</sup> and surround dead adipocytes in typical "crown-like structures"<sup>[43]</sup> (Figure 1).

Two major subtypes of macrophage are found in adipose tissue: "alternatively activated" M2 macrophages and "classically activated" M1 macrophages, and the proportions of these cell populations in VAT are dependent on the tissue microenvironment. M2 macrophages maintain VAT homeostasis in lean individuals through the secretion of anti-inflammatory cytokines, such as IL-10, whereas in obese individuals, pro-M1 polarized macrophages secrete pro-inflammatory cytokines, including TNF $\alpha$ , IL-1 $\beta$  and IL-6, which can promote the proliferation of other inflammatory immune cells, chronic local and systemic inflammation, and can directly alter insulin receptor signaling in adipocytes, leading to IR<sup>[44,45]</sup>. The mechanisms leading to increased infiltration of macrophages into VAT are not entirely clear; however, it is known that in obese individuals adipocytes increase their expression of monocyte chemoattractant protein 1 (MCP-1) in order to recruit macrophages<sup>[46]</sup>.

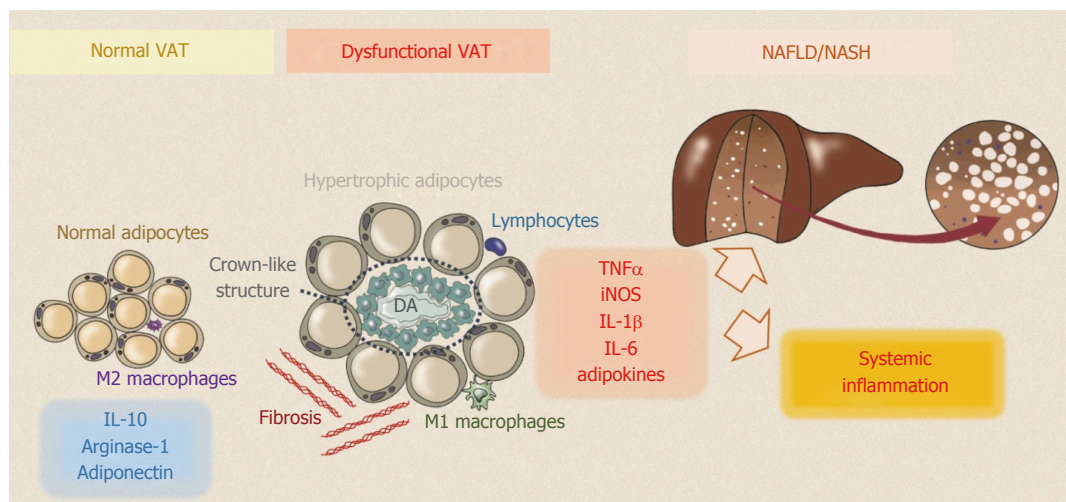
Moreover, adipose tissue secretes a large number of adipokines. These are delivered directly to the liver *via* its portal vein, and then exert local and peripheral effects. It is increasingly recognized that an impaired pattern of adipokines secretion could play a pivotal role in the development of NAFLD<sup>[47]</sup>.

### Adipokines and NAFLD

Several investigators have attempted to demonstrate a role for adipokines in the pathogenesis of NAFLD and in the progression to NASH, although the data on many of the adipokines apparently involved are sometimes controversial. Adipokines are characterized by complex interactions and the role they may exert in the pathogenesis of NAFLD is often difficult to interpret<sup>[48]</sup>. Those adipokines whose effects on the liver are defined and supported by solid data are adiponectin, leptin, TNF- $\alpha$  and IL-6.

TNF- $\alpha$  is the most commonly investigated and





**Figure 1** Normal visceral adipose tissue consists of a loose connective tissue that is populated with tightly packed adipocytes. In lean individuals VAT homeostasis is maintained by adiponectin released by adipocytes and by M2 macrophages through the secretion of anti-inflammatory cytokines, such as interleukin (IL)-10 and arginase-1. During obesity, dysfunctional visceral adipose tissue (VAT) undergoes excessive fibrosis and accumulation of inflammatory cells. Active macrophages surround dying adipocytes (DA) in typical “crown-like structures”. Pro-M1 polarized macrophages secrete pro-inflammatory cytokines including TNF $\alpha$ , IL-1 $\beta$  and IL-6, which can promote chronic local and systemic inflammation. VAT secretes a large number of adipokines which could play a pivotal role in development of NAFLD. NAFLD: Non-alcoholic fatty liver disease.

characterized. It is secreted by AT-associated macrophages as a response to chronic inflammatory activity. Human and experimental studies have suggested that TNF- $\alpha$  plays a role in all of the phases of fatty liver disease, from simple steatosis to steatohepatitis and cirrhosis; TNF- $\alpha$  also enhances IR<sup>[49-51]</sup> and promotes the development of IR complications *in vitro*<sup>[52,53]</sup>. Human studies have revealed that a high TNF- $\alpha$  level increases the risk of developing NAFLD in healthy individuals<sup>[49]</sup> and predicts the progression and severity of NASH<sup>[49,54-60]</sup>.

In the pathogenesis and progression of IR and NAFLD, IL-6 exerts a role extensively investigated in both experimental models of steatosis and liver injury, and in humans. *In vitro* studies have shown that IL-6 promotes IR *via* several mechanisms<sup>[61-63]</sup>, and in animal models this effect was evident in the liver<sup>[64-66]</sup>. Serum IL-6 levels were increased in subjects with biopsy-proven NAFLD compared to controls<sup>[67]</sup>, and these levels correlated with the degree of inflammation, the stage of the fibrosis and with IR<sup>[68]</sup>.

Leptin plays a role in both the development and progression of NAFLD, contributing to IR, steatosis and, through a pro-inflammatory role in the regulation of hepatic stellate cells, to hepatic fibrosis<sup>[69]</sup>. In NASH patients leptin levels were found to be increased and to be related to the grade of hepatic steatosis<sup>[70-72]</sup>.

Adiponectin is produced specifically by differentiated adipocytes<sup>[73]</sup> and is an anti-inflammatory and insulin-sensitizing hormone<sup>[74]</sup>. It has been largely demonstrated that adiponectin prevents hepatocytes lipid accumulation by enhancing  $\beta$ -oxydation and by reducing synthesis of free fat acids<sup>[75-77]</sup>, that it mediates anti-inflammatory activity by lowering NF $\kappa$ B action<sup>[78]</sup>, and antagonizes leptin-induced STAT3

phosphorylation in activated hepatic stellate cells<sup>[79]</sup>.

Certain *in vivo* studies have shown that low serum levels of adiponectin are associated with NAFLD<sup>[75,76,80-85]</sup> and that low adiponectin was an independent risk factor for NAFLD<sup>[86]</sup>; furthermore, that adiponectin is a good predictor of necro-inflammation and fibrosis in animal and *in vitro* models of NAFLD<sup>[78,87-89]</sup>. Moreover, studies in humans have shown reduction of adiponectin in the serum, as well as reduction of the expression of its receptor in the liver of patients with NASH when compared to BMI-matched patients with steatosis<sup>[54,83,90]</sup>, providing robust evidence that decreased adipocyte production of adiponectin plays an important role in the progression of NAFLD.

The identification of serum adipokines associated with liver histology and, more specifically, with the severity of steatosis, fibrosis and inflammation might provide useful information about NAFLD pathogenesis and form the basis for new diagnostic and therapeutic approaches.

## VITAMIN D, ADIPOSITY AND NAFLD

There is growing evidence to indicate that in addition to maintaining calcium and phosphorus homeostasis and bone health<sup>[91]</sup>, vitamin D also displays pleiotropic actions on several tissues, organs and metabolic processes<sup>[92-96]</sup>. Vitamin D deficiency is currently a global health issue and may contribute to the pathogenesis of many disorders, such as obesity, metabolic syndrome and type 2 diabetes<sup>[97-99]</sup>.

Despite several epidemiological studies showing the existence of a close relationship between obesity and hypovitaminosis D<sup>[100-105]</sup>, the mechanisms underlying

this association are largely unknown. Interestingly, many studies have suggested that adipose tissue could be a direct target of vitamin D, and that this molecule might have a role in modulating adipose tissue pathophysiology<sup>[106-116]</sup>.

Notwithstanding the inverse association between BMI and fat mass<sup>[114]</sup>, higher plasma 25OHD has been associated with lower amounts of VAT and with reduced omental adipocyte size<sup>[115-119]</sup>, suggesting a link between vitamin D status and fat distribution. This is further substantiated by reports of the regulatory effects of vitamin D on adipose tissue and lipid storage and by the fact that vitamin D receptor (VDR) is expressed in adipocytes both in animals models and in humans. In particular, the expression of VDR gene has been reported in cultured adipocytes<sup>[110]</sup>, in human pre-adipocytes<sup>[111]</sup> and human subcutaneous and visceral adipose tissue<sup>[112,113]</sup>.

Interestingly, it has been suggested that vitamin D may provide a protective effect in obese individuals who have healthy metabolic profiles as characterized by the absence of IR-related conditions and low systemic inflammation despite an increased body fat mass<sup>[120-122]</sup>.

Thus, these data suggest an involvement of vitamin D in the regulation of adipose tissue inflammation. The transduction of inflammatory pathways in adipose tissue involves the activation of nuclear factor  $\kappa$ - $\beta$  (NF- $\kappa$ B) that regulates the transcription of a wide range of inflammatory mediators. Several *in vitro* studies showed that vitamin D exerts an anti-inflammatory action on both mouse and human adipocytes by decreasing chemokines and cytokines expression *via* the involvement of p38 MAP kinase and the NF- $\kappa$ B classical inflammatory pathway<sup>[123-125]</sup>. Very recently, Karkeni *et al.*<sup>[126]</sup> demonstrated that vitamin D modulates the expression of miRNAs in adipocytes *in vitro* and in adipose tissue *in vivo* through the NF- $\kappa$ B signaling pathway, representing, thus, a new mechanism of regulation of adipose tissue inflammation by vitamin D.

In line with these data, vitamin D supplementation has been recently demonstrate to decrease circulating pro-inflammatory adipokines, in particular IL-6 and TNF- $\alpha$ , in diet-induced obese mice<sup>[127,128]</sup>. Moreover, in a large cohort of human patients, serum 25OHD concentration correlated with low leptin<sup>[129]</sup> and high adiponectin levels, irrespective of their BMI<sup>[130]</sup>.

The role of vitamin D in the pathogenesis of NAFLD is an active area of research<sup>[131]</sup>. The existence of an independent association between hypovitaminosis D and NAFLD has been largely demonstrated in studies conducted using liver imaging<sup>[132-136]</sup> and biopsy<sup>[137,138]</sup>. In particular, low vitamin D levels were associated with the histological severity of NAFLD/NASH<sup>[137-143]</sup> and with the prevalence of NAFLD among individuals with normal liver enzymes<sup>[131]</sup>. Overall, in the only meta-analysis available in the literature, a 26% additional risk of vitamin D deficiency has been reported in

subjects with NAFLD compared to controls subjects<sup>[139]</sup>.

Experimental studies have shown that vitamin D also directly exerts anti-inflammatory, anti-proliferative and anti-fibrotic activities in the liver<sup>[144,145]</sup> by linking VDR, widely expressed throughout the liver, in hepatocytes, cholangiocytes, and lymphocytes<sup>[146-148]</sup>. There is extensive evidence to show that the VDR function in the liver regulates not only the hepatic lipid metabolism but also hepatic necro-inflammation and fibrosis; notably, in chronic hepatic diseases VDR expression negatively correlates with the inflammatory damage<sup>[149]</sup>.

*In vitro* and *in vivo* preclinical studies have found that vitamin D decreased hepatic stellate cell activation, suggesting it may have a potential role to protect against hepatic fibrosis<sup>[150,151]</sup>.

Data from animal studies further support the notion that vitamin D plays an immunomodulatory role in NAFLD. Roth *et al.*<sup>[152]</sup> showed that a lack of vitamin D intake in obese rats led to the progression of NAFLD with increased lobular inflammation and a higher NAFLD activity score as evaluated by liver histology; at the same time, mRNA levels of resistin, IL-6 and TNF- $\alpha$ , were increased in the liver. All the above markers are involved in oxidative stress and hepatic inflammation. Therefore, in another study on NASH rat, phototherapy, by increasing the serum active form of vitamin D, reduced hepatocyte inflammation and fibrosis, improved insulin resistance, and increased serum adiponectin, while at the same time reducing the hepatic expression of inflammatory genes TNF- $\alpha$  and TGF- $\beta$ <sup>[153]</sup>.

It has also been demonstrated that a vitamin D-deficient high-fat diet hampers the enterohepatic circulation of bile acids, leading to NASH<sup>[154]</sup>. Furthermore, a recent study evidenced that long-term dietary vitamin D depletion could generate spontaneous liver fibrosis in a mice model<sup>[155]</sup>. Han *et al.*<sup>[156]</sup> demonstrated that vitamin D supplementation in mice with NASH reduced the hepatic levels of cytokeratin 18 apoptotic fragment M30, a widely validated marker of hepatic damage<sup>[157]</sup>.

These observations regarding the link between vitamin D serum levels and the development and progression of NAFLD suggest that vitamin D supplementation might represent a new therapeutic option in the management of NAFLD. Nevertheless, controversies exist due to the limited number of studies and the conflicting results of prospective randomized clinical trials in humans designed to examine the role of vitamin D supplementation in NAFLD.

Our group has recently published the results of a randomized, double-blind, placebo-controlled trial involving 55 patients with type 2 diabetes and MRI-diagnosed NAFLD. In our study, the participants underwent a 24-wk course of high-dose oral vitamin D supplementation and no effect was shown on either the hepatic fat content or on markers of hepatic injury,

*i.e.*, serum transaminases, CK-18 and PIIINP<sup>[158]</sup>.

Lorvand Amiri *et al.*<sup>[159]</sup> conducted a randomized placebo-controlled double-blind clinical trial to evaluate the potential beneficial effects of oral calcium plus calcitriol supplementation versus calcitriol alone on liver enzymes and ultrasound-measured fat liver content in 120 patients with NAFLD, showing decreased improved serum ALT in the calcium plus calcitriol treated group.

Previously, a prospective small pilot study evaluated the impact of a 24-wk course of high-dose oral vitamin D supplementation on the liver histology of 12 non-cirrhotic NASH patients. The study found no beneficial effects of this treatment on hepatic damage or insulin sensitivity<sup>[160]</sup>.

Sharifi *et al.*<sup>[161]</sup> also investigated the effect of oral vitamin D supplementation in patients with NAFLD in a placebo-controlled trial and their results showed no effect on serum levels of hepatic enzymes, HOMA-IR, or on the degree of hepatic steatosis. However, their study did demonstrate the beneficial effects of vitamin D on serum malondialdehyde, a marker of lipid peroxidation, and on CRP levels.

Studies with a longer intervention period are warranted in order to explore the effects of long term exposure to vitamin D on NAFLD and on the associated systemic inflammation it causes, as well as on the prevention of NAFLD.

## CONCLUSION

There is a well-established inverse relationship between vitamin D status and obesity, and hypovitaminosis D is associated with an unfavorable metabolic and inflammatory profile. Obesity-related systemic low grade inflammation characterized by alterations in levels of circulating adipokines is suggested to be involved in the pathogenesis of NAFLD and in its progression to NASH. Vitamin D deficiency is also associated with NAFLD and has even been correlated with the severity of the disease. Recent data has suggested that vitamin D's anti-inflammatory and immune-modulatory properties provide plausible mechanisms by which hypovitaminosis D may link adipose tissue dysfunction to the various steps in the progression of NAFLD. Several animal studies have added further weight to this hypothesis by showing the beneficial effect of vitamin D supplementation on systemic inflammation and on NAFLD in a murine model, although these data are not yet confirmed by the results of the clinical trials conducted to date in humans. Further specifically-designed long-term randomized placebo-controlled trials are needed to clarify the therapeutic impact of vitamin D supplementation in NAFLD.

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