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Review

A narrative review on effects of vitamin D on main risk factors and severity of Non-Alcoholic Fatty Liver Disease

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ABSTRACT

The global prevalence of Non-alcoholic fatty liver disease (NAFLD) is increasing rapidly. Many studies have been conducted on the treatment of NAFLD; nevertheless, there is still no approved drug treatment for this disease. Although the pathogenesis of NAFLD is not fully understood, but inflammation, insulin resistance, oxidative stress, obesity and dyslipidemia are among the main causes. Epidemiological studies have shown that hypovitaminosis D is associated with these factors causing NAFLD. In addition, rate of Vitamin D deficiency has been shown to be directly related to the severity of NAFLD. Accordingly, it is believed that vitamin D may help to treatment of NAFLD by improving the above-mentioned risk factors. The purpose of this review is to survey the recent advances in the field of Vitamin D efficacy on risk factors and the severity of NAFLD based on existing evidence, especially the clinical efficiency of vitamin D supplementation in patients with NAFLD.

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in the worldwide [1] and it is associated with chronic diseases such as diabetes and cardiovascular diseases [2,3]. Non-alcoholic fatty liver disease is a condition characterized by the accumulation of excessive fat in the liver (more than 5% of the weight of the liver) in individuals with no history of alcohol abuse (<10 g/d) [4]. It is known NAFLD consists of a range of liver damage, from simple steatosis to non-alcoholic steatohepatitis (NASH), and can lead to cirrhosis and liver cancer, if not prevented from developing it [5]. The prevalence of NAFLD in the general population is ~25% in worldwide [6]. Several factors including inflammation, insulin resistance, oxidative stress, obesity and dyslipidemia through various mechanisms (Fig. 1) contribute to the development of NAFLD [4,7–9]. So far there is no effective approved drug for the treatment of this disease and NAFLD therapy still remains a controversial issue [10]. Currently, diet modification, weight loss and physical activity are considered the main line of intervention in NAFLD patients [11,12] (see Table 1).

Studies have shown that the prevalence of vitamin D deficiency in patients with NAFLD is higher than healthy subjects and most patients with chronic liver disease have low vitamin D levels [13–15]. Also the circulating Vitamin D levels are inversely related to the severity of NAFLD [16,17]. As a result, it seems vitamin D deficiency and NAFLD are often found together. Studies have shown that vitamin D status correlated with inflammation, insulin resistance, oxidative stress, obesity and dyslipidemia [18–22]. Therefore it is suggested that receiving vitamin D can be helpful For Treatment of NAFLD and accordingly several randomized controlled trials (RCTs) were planned in this context.

Although the main mechanism that causes this disease is not completely clear, we decided to review the influence of vitamin D in the status of each of the main risk factors for NAFLD in the current study, based on existing studies.

2. Vitamin D, inflammation and NAFLD

Several studies have shown that inflammatory markers such as Tumor Necrosis Factor alpha (TNF-α), Interleukin 6 (IL-6) and C-Reactive Protein (CRP) play an important role in pathogenesis of the NAFLD [23–26]. It has been shown that increased levels of TNF-α is

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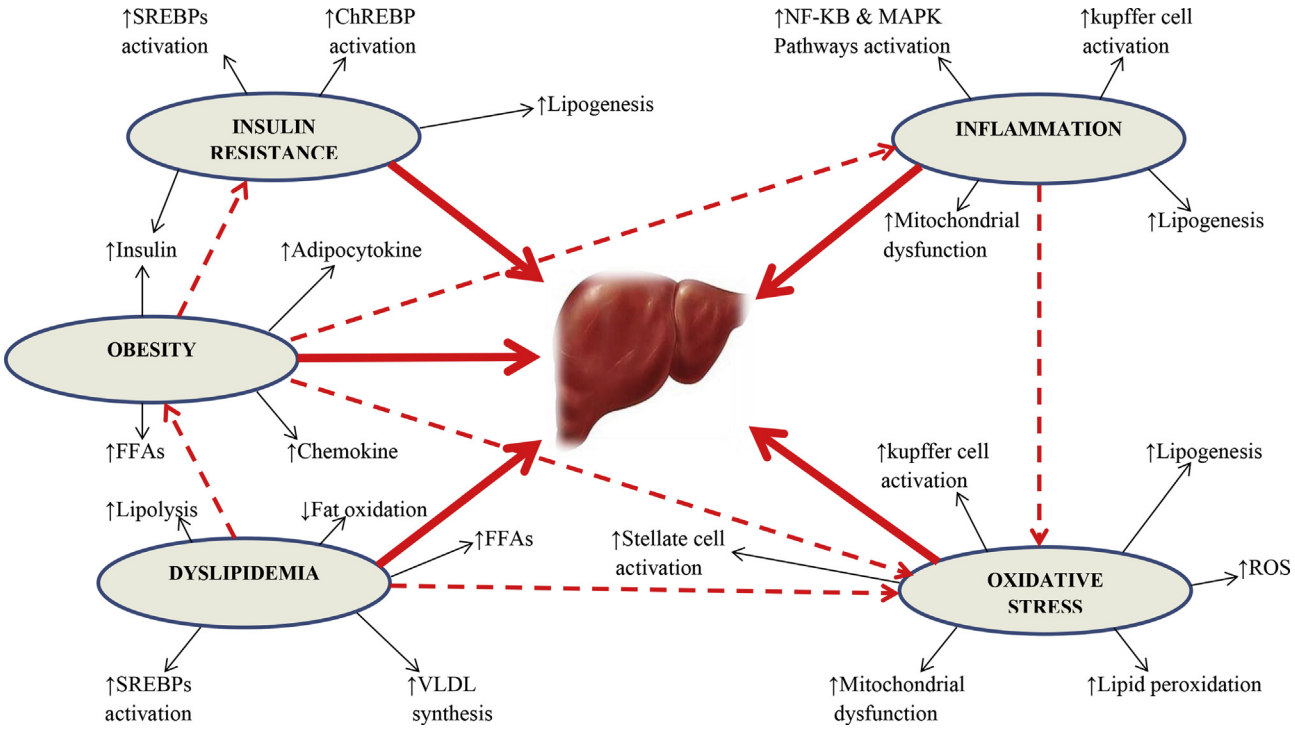

Fig. 1. Overview of the pathophysiological pathways and their mechanisms involved in NAFLD. FFA: Free fatty acid, SREBP: Sterol regulatory element-binding, ChREBP: Carbohydrate-responsive element-binding protein, VLDL: Very low-density lipoprotein, ROS: Reactive oxygen species, NF-κB: Nuclear factor-Kb, MAPK: Mitogen-activated protein kinase.

associated with increased risk of NAFLD in healthy people [23]. Increased levels of inflammatory markers are also directly associated with severity of NAFLD [27,28]. Since vitamin D reduces inflammation in several ways [29–34], it seems reasonable to assume that Vitamin D will probably help to improve NAFLD. Recent animal studies have shown that vitamin D supplementation has reduced levels of inflammatory markers in diet-induced obese mice [18,35]. The effect of vitamin D supplementation on Inflammation among patients with NAFLD in some RCTs has been evaluated.

In the study of Barchetta et al. [36]. after vitamin D supplementation (cholecalciferol (2000 IU/day)) for 24 weeks, no significant change was observed in the levels of CRP. The participants in this study were diabetic patients with NAFLD. In another study that conducted by Foroughi et al. (37). vitamin D supplementation (capsules containing 50,000 IU Vitamin D, weekly) after 10 weeks, had no effect on CRP in the intervention group compared to the placebo group. The short duration of intervention is one of the limitations of this study. Only in the study of Sharifi et al. [38]. after vitamin D supplementation (one oral pearl consisting of 50,000 IU vitamin D3, every 14 days for 4 months), improvement in CRP was near significant; however, there was no significant decrease in TNF-α level. Calcium intake can influence the effects of vitamin D and the strength of this study is to report dietary calcium intake.

Results from these RCTs, as well as findings from other studies in this field [39,40], are not consistent with primary outcomes that suggest positive effects of vitamin D on the improvement of inflammation in NAFLD patients. Further studies with larger sample sizes and well-controlled methods are needed.

3. Vitamin D, insulin resistance and NAFLD

Insulin resistance and excessive fatty acids in the circulation are the “first hit” in the “two Hit” hypothesis of the pathogenesis of NAFLD [9] as it has been shown that 70 to 80% of obese and diabetic patients have NAFLD [41,42]. In addition to muscle levels, insulin sensitivity in the liver and adipose tissue also decreases in the NAFLD patients [43–45]. Through increasing insulin receptors in muscle cells or improving the sensitivity of insulin receptors to insulin and the effect on Peroxisome Proliferator-Activated Receptor delta (PPAR δ), vitamin D elevated insulin sensitivity [46]. Therefore, it seems likely that vitamin D improves insulin resistance in patients with NAFLD. Several RCTs examined the effect of vitamin D supplementation on insulin resistance in NAFLD patients.

In the study that conducted by Sharifi et al. [38]. after 4 months of vitamin D supplementation, no significant change was observed in Homeostatic Model Assessment for Insulin Resistance (HOMA-IR). In this study, used fasting values for glucose and insulin to assess insulin resistance, and if euglycemic clamp technique or intravenous glucose tolerance testing used In order to assess insulin sensitivity, it was more accurate [47]. In another study, vitamin D supplementation was taken for 24 weeks, but no significant difference was found between the intervention and placebo groups in insulin resistance indexes (HOMA-IR, Homeostatic Model Assessment of β-cell function (HOMA-β)%, Quantitative Insulin Sensitivity Check Index (QUICKI), Fasting Blood Insulin (FBI)) after the end of the trial [36]. Also, in a study conducted by Geier et al. [40]. after 48 weeks of vitamin D supplementation, there was no significant difference in glucose metabolism (serum glucose, glycated hemoglobin, insulin) between the intervention and placebo groups. Limitations of this study include the lack of measurement of the HOMA-IR and the small sample size. It should be noted that in one study that showed significant improvement in HOMA-IR after 12 weeks of vitamin D supplementation (25 μg of calcitriol, daily), hypo caloric diet was also prescribed in both groups of study [48]. In this study, dietary calcium intake has been reported. In another study, after supplementing vitamin D supplementation for 12 weeks, HOMA-IR decreased significantly in both treatment groups (calcitriol (25 μg) plus placebo group and calcium (500 calcium

Table 1
Randomized controlled trials that evaluated the effect of vitamin D supplementation on NAFLD patients.

Reference	Population	Study design	Duration (Weeks)	Outcomes related to our study	findings
Sharifi et al., 2014 [38]	53	Intervention group: 50000 IU/ week vitamin D (n = 27) Control group: Placebo (n = 26)	16 week	Hs-CRP TNF-α, HOMA-IR, MDA, TAC, Grade of NAFLD	Hs-CRP ↓ MDA ↓ No significant changes in values of other outcomes
Barchetta et al., 2016 [36]	55	Intervention group: 2000 IU/ day cholecalciferol (n = 29) Control group: Placebo (n = 26)	24 week	CRP, HOMA-IR, HOMA-β%, QUICKI, FBI, SAT, VAT, VAT/SAT area, HFF	No significant changes in any of the outcomes' measures
Lorvand amiri et al., 2016 [48]	73	Intervention group: 25 μg/day calcitriol + hypocaloric diet (n = 36) Control group: Placebo + hypocaloric diet (n = 37)	12 week	HOMA-IR, BMI, WC, TC, TG, LDL, HDL, Grade of NAFLD	Grade of NAFLD ↓ TG ↓ HDL ↑ HOMA-IR ↓ No significant difference between groups in values of other outcomes
Lorvand amiri et al., 2016 [49]	110	Intervention group 1: 1000 IU/ day calcitriol + weight loss program (n = 37) Intervention group 2: 1000 IU/ day calcitriol + 500 mg calcium + weight loss program (n = 37) Control group: Placebo + weight loss program (n = 36)	12 week	HOMA-IR, WEIGHT, BMI, TC, TG, LDL, HDL, Grade of NAFLD	Intervention group 1, 2: Grade of NAFLD ↓ HOMA-IR ↓ HDL ↑ TG ↓ No significant difference between groups in values of other outcomes
Dabbaghmanesh et al., 2018 [50]	91	Intervention group 1: 50000 IU/ week cholecalciferol (n = 31) Intervention group 2: 0.25 mg/ day calcitriol (n = 28) Control group: Placebo (n = 32)	12 week	Fasting Blood Sugar (FBS), TC, TG, LDL, HDL	Intervention group 2: HDL ↓ Intervention group 1: No significant change in value of HDL No significant difference between groups in values of other outcomes
Foroughi et al. 2014 [37]	60	Intervention group: 50000 IU/ week vitamin D (n = 30) Control group: Placebo (n = 30)	10 week	Hs-CRP	No significant change in value of Hs-CRP
Geier et al., 2018 [40]	18	Intervention group: 2100 IU/ day cholecalciferol (n = 8) Control group: Placebo (n = 10)	48 week	Hs-CRP, serum glucose, HbA1c, TG, LDL, HDL, Hepatic steatosis	No significant changes in any of the outcomes' measures
Della Corte et al., 2016 [61]	41	Intervention group:800 IU/day vitamin D + 500 mg DHA (n = 18) Control group: Placebo (n = 23)	12 month	BMI NAS	BMI ↓ NAS ↓

NAFLD: Non-Alcoholic Fatty Liver Disease, TNF-α: Tumor Necrosis Factor alpha, Hs- CRP: High-sensitivity C-Reactive Protein, HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, HOMA-β: Homeostatic Model Assessment of β-cell function, QUICKI: Quantitative Insulin Sensitivity Check Index, FBI: Fasting Blood Insulin, HbA1c: Glycated Hemoglobin, FPG: Fasting Plasma Glucose, LDL: Low-Density Lipoprotein, HDL: High-Density Lipoprotein, TG: Triglyceride, TC: Total Cholesterol, NAS: NAFLD Activity Score, HFF: Hepatic Fat Fraction.

carbonate) plus calcitriol (25 μg) group) [49].

Also, The effects of vitamin D intake on glucose metabolism in other studies [39,50] contradicts The primary findings.

In order to better conclusion in this context, it is required to conduct studies with stronger methodologies that evaluates the effects of vitamin D supplementation alone.

4. Vitamin D, oxidative stress and NAFLD

Based on “two Hit” hypothesis, oxidative stress is considered as the “second hit”, which, along with the “first hit” (insulin resistance and excessive fatty acids in the circulation), causes NAFLD [9]. In oxidative stress, an increase in reactive oxygen species (ROS) and consequently an augment in lipid peroxidation occur and ultimately lead to intracellular damage [51]. The concentration of lipid peroxidation biomarkers has been shown to correlate with the severity of liver disease [52]. Studies have shown that the concentration of oxidative stress biomarkers in people with low levels of vitamin D is high and vitamin D intake also reduces oxidative stress response [53,54].

Two animal studies showed a decrease in levels of more oxidative stress indices after vitamin D intake [18,55], but in one of these studies, no significant improvement in total antioxidant capacity (TAC) was observed [55].

So far, Only Sharifi et al. [38]. examined the effect of vitamin D supplementation on oxidative stress indices in patients with NAFLD. In this study, malondialdehyde (MDA) levels were significantly reduced, but there was no significant decrease in TAC levels.

According to these studies, maybe the anti-lipid peroxidation effects of vitamin D to be more than its antioxidant effects. In this context, there are not enough studies to conclusion, and the need for further studies is strongly felt.

5. Vitamin D, obesity and NAFLD

There is a close correlation between obesity and NAFLD, so that the prevalence of this disease in obese people is about 80% [56]. Insulin resistance and inflammation, which are among the main causes of NAFLD, are caused by obesity [8]. As mentioned, there is no approved drug treatment for NAFLD [10], and now weight loss is

part of the main line of treatment for this disease [11,12,57]. There is a link between components of body composition and vitamin D status [58], so that the prevalence of vitamin D deficiency is high in obese people [59,60]. So, the primary finding is that vitamin D supplementation may help to treat NAFLD by improving obesity. The effect of vitamin D supplementation on body composition indicators among patients with NAFLD was evaluated in several RCTs.

In the study of Barchetta et al. [36]. there was no significant improvement in body composition indicators such as body mass index (BMI), waist circumference (WC) and also indicators of body fat distribution including Subcutaneous Adipose Tissue (SAT), Visceral Adipose Tissue (VAT) and VAT/SAT area) after supplementation with vitamin D for 24 weeks. In another study, after supplementing vitamin D for 12 weeks, although weight and BMI decreased significantly in all groups, there was no significant difference in the intervention groups compared to the placebo group [49]. It should be noted that all participants in this study followed the weight loss program. Only in one RCT, vitamin D supplementation plus Docosahexaenoic Acid (DHA) in obese children with biopsy-proven NAFLD and vitamin D deficiency, significantly reduced BMI [61]. In this study, the group that received only vitamin D did not exist, and the effect of vitamin D supplementation alone is unclear.

Also In the study of Papapostoli et al. [62]. patients received vitamin D for 6 months, but no significant changes were observed in any of the body composition indicators such as BMI, Fat-free mass, Fat-mass and Visceral fat index. In this study, only patients with insufficient vitamin D levels (serum 25-hydroxyvitamin D < 20 ng/ml) received vitamin D supplement. The limitation of this study was the lack of control group.

As with the results mentioned above, also, the results of some other studies (39,48) are in contradiction with The primary findings that expressed vitamin D supplementation is likely to affect obesity.

6. Vitamin D, dyslipidemia and NAFLD

In the “two hit” theory of NAFLD pathogenesis, the accumulation of fat due to abnormal lipid metabolism (such as increased lipolysis, Liver free fatty acid (FFA) uptake and very-low density lipoprotein (VLDL) synthesis also reduced FFA oxidation and Triglyceride (TG export)) is known as part of the “first hit” [9,63,64]. Abnormal lipid metabolism through increased liver fat accumulation increases inflammation, oxidative stress and production of adipokines and therefore, plays an important role in the pathogenesis of NAFLD [65–68]. Sterol regulatory element-binding proteins (SREBPs) are transcription factors that control lipid homeostasis and vitamin D plays a role in regulating lipid metabolism through inhibiting the SREBPs activation [69]. The relationship between vitamin D status and lipid profile levels (indicating the status of lipid metabolism) has been observed [70]. Given the evidence, vitamin D was thought to be able to improve dyslipidemia in patients with NAFLD. Several RCTs investigated the effect of vitamin D supplementation on lipid profiles in NAFLD patients.

In the study of Dabbaghmanesh et al. [50]. after 3 months of vitamin D supplementation, no significant change was observed in the lipid profile in the intervention (calcitriol and vitamin D3 groups) and placebo groups. Only in the calcitriol group, high-density lipoprotein cholesterol (HDL-c) levels improved significantly after the end of treatment. In this study, dietary vitamin D intake was not recorded. In another study, after 48 weeks of vitamin D supplementation, no significant changes were observed in the lipid profiles of the intervention group [40]. In the study of Lorvand Amiri et al. [48]. there was a significant improvement in HDL and TG levels after 12 weeks of vitamin D supplementation with hypo caloric diet. In this study, the effect of vitamin D supplementation was not evaluated without hypo caloric diet. With regard to the results mentioned, as well as the outcomes of other studies [36,49], So far, few promising results have been achieved in this context.

7. Vitamin D and severity of NAFLD

Roth et al. showed rats with obesity that did not receive vitamin D had higher NAFLD activity score as evaluated by liver histology [71]. Other animal study has shown that increased serum levels of vitamin D are associated with reduced NAFLD severity [29]. Also, human studies have shown a direct relationship between hypovitaminosis D and severity of NAFLD [17,72]. These observations, along with the theoretical mechanisms that vitamin D can affect NAFLD risk factors; suggest that supplementation of vitamin D may lead to a reduction in grade of NAFLD. The effect of vitamin D supplementation on the improvement of NAFLD severity was investigated in several RCTs.

After 4 months of vitamin D supplementation, there was no significant improvement in the degree of NAFLD in the study Sharifi et al. [38]. In the study of Geier et al. [40]. after 48 weeks of vitamin D supplementation, there was a decreasing trend in hepatic steatosis, which was not significant. Small sample size (n = 18) can be a reason why the hepatic steatosis is not statistically significant. The strength of this study is the use of liver biopsy to detect NAFLD. Liver biopsy is the gold standard method of NAFLD diagnosis [73]. In the study that conducted by Barchetta et al. [36]. there was no significant difference between the intervention group and the placebo group in the hepatic fat fraction (HFF) (measured by Magnetic resonance imaging) after 24 weeks of vitamin D supplementation in diabetic patients with NAFLD. Contrary to the studies mentioned, in the study of Lorvand Amiri et al. [48]. In the intervention group, decreased NAFLD grade was significantly higher than the control group. In this study, both groups followed the hypo-caloric diet. Lorvand Amiri et al. [49]. showed, After 12 weeks of vitamin D supplementation with a caloric restriction diet, Improve in the stage of NAFLD in the treatment groups (calcitriol (25 μg) plus placebo group and calcium (500 mg calcium carbonate) plus calcitriol (25 μg) group) was significantly higher than the control group, but there was no significant difference between the two treatment groups. All groups in this study followed a weight loss diet. Also, in the study of corte et al. [61]. The supplementation of a mixture of vitamin D and DHA significantly reduced NAFLD activity score (NAS) in obese children with biopsy-proven NAFLD. In the study conducted by Papapostoli et al. [62]. hepatic steatosis significantly decreased in NAFLD patients with vitamin D deficiency. In this study, transient elastography was used to assess hepatic steatosis and the control group was not used.

In this context, the results are not integrated at the present. More studies are needed to make a better conclusion.

8. Conclusion

Primary studies have reported a reverse relationship of vitamin D status and NAFLD risk factors such as inflammation, insulin resistance, oxidative stress, obesity and dyslipidemia. Animal studies also found that taking vitamin D could reduce NAFLD severity. Accordingly, it was expected that supplementation of vitamin D could improve NAFLD. But our review did not show promising results in improving the most risk factors of NAFLD. Also, due to the small number of studies that have examined the effect of vitamin D supplementation on oxidative stress, we cannot conclude accurately in this regard. In the treatment group of RCTs that showed improved NAFLD grade, vitamin D has mostly receive with other factors such as energy-restricted diet, calcium or DHA

supplementation, and in RCTs that investigated the effect of vitamin D supplementation alone, there was no significant improvement in the severity of NAFLD. Consequently, it cannot be concluded with certainty in this regard.

Of course, due to the limitations of RCT studies such as the lack of use of liver biopsy as the gold standard for diagnosis of NAFLD, small sample size, and lack of evaluation of oxidative stress indices in most of these studies, we could not conclude decisively.

To design future RCTs, we propose factors such as season, sex, vitamin D and calcium dietary intake, supplementation of vitamin D in a separate group and use of oxidative stress indices, higher accuracy diagnostic methods and larger sample size considered.

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