



The Latest Evidence on the Association Between Vitamins and Non-alcoholic Fatty Liver Disease in Childhood

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Abstract

Context: Non-alcoholic fatty liver disease (NAFLD) is the most prevalent chronic liver disease in children, with an increased incidence of overweight and obesity. Currently, no food and drug administration is approved for treating NAFLD in children; however, antioxidants such as vitamins are the safest options for managing this disease. Regarding the unknown aspects of managing NAFLD, this review provides an overview of the latest evidence on the association of vitamins A, B, C, D, and E with NAFLD in children and adolescents.

Evidence Acquisition: In this narrative review, we searched and extracted relevant English publications from the Web of Science, PubMed, Scopus, and Google Scholar using keywords such as non-alcoholic fatty liver disease, NAFLD, children, pediatric, Vitamin A, Vitamin B, Vitamin C, Vitamin D, and Vitamin E.

Results: The level of vitamins A, B, C, D, and E in children with NAFLD has been linked to the disease's prognosis and severity.

Conclusions: Regarding previous studies on this issue, measuring vitamins in children with NAFLD seems logical.

Keywords: Child, Fatty Liver, Vitamins

1. Context

Non-alcoholic fatty liver disease (NAFLD) is the most prevalent chronic liver disease in children, with an increased incidence of overweight and obesity (1). Although the overall prevalence of pediatric NAFLD varies by region, it ranged from 7.5% in the general population to 52.5% in obese people between 2000 and 2017. By 2040, it is predicted to reach about 30.5% (2).

It is defined as when an individual without a substantial history of alcohol consumption has more than 5% of hepatocytes showing macrovascular steatosis (3). Its spectrum ranges from benign hepatic steatosis to non-alcoholic steatohepatitis (NASH). Non-alcoholic steatohepatitis has a potentially progressive course that might result in liver cirrhosis, fibrosis, hepatocellular carcinoma (HCC), and liver transplantation (4).

To avoid the label “non-alcoholic,” which can be used in adults but is inappropriate in children, an international panel of hepatologists advocated the name “metabolic dysfunction associated with fatty liver disease” (MAFLD). This definition was inadequate since it excluded heredi-

tary metabolic diseases, so pediatric fatty liver disease (PeFLD) has been suggested as a more acceptable name, particularly for young children (5). Despite these alterations, we used the term NAFLD for this study since it is still widely used. It has been shown that type 2 diabetes mellitus (T2DM), insulin resistance, metabolic syndrome, hyperlipidemia, and hypertension are all linked to NAFLD. It is also hypothesized that parameters including genetic factors, innate immunity, adipocyte secretion, oxidative stress, insulin resistance, mitochondrial damage, and gut microbiota can damage the liver (6).

No food and drug administration is currently approved for treating NAFLD in children. However, probiotics or antioxidants such as vitamins were the safest options for managing this disease (7). Vitamins have been shown to have anti-inflammatory effects on some infected diseases, such as COVID-19 (8). Moreover, studies have shown that some vitamins may reduce insulin resistance and have anti-inflammatory effects on hepatic cells. These findings suggest that several vitamins, including vitamins A, B, C, D, and E, might be used as treatments for liver injuries in

NAFLD. Since some of these supplements may have adverse effects, they should be prescribed under the supervision of a specialist (9). Regarding the unknown aspects of managing NAFLD, this review provides an overview of the latest evidence on the association of vitamins A, B, C, D, and E with NAFLD in children and adolescents.

2. Evidence Acquisition

In this narrative review, we evaluated the probable relation between vitamins A, B, C, D, and E and NAFLD in children. We searched and extracted relevant English publications from the Web of Science, PubMed, Scopus, and Google Scholar using keywords such as non-alcoholic fatty liver disease, NAFLD, children, pediatric, Vitamin A, Vitamin B, Vitamin C, Vitamin D, and Vitamin E.

3. Results

3.1. Vitamin A in Non-alcoholic Fatty Liver Disease

Retinoic acid, often known as vitamin A, is a necessary vitamin derived from carotenoids like carotene or retinyl esters. They are taken up and carried by chylomicrons as retinyl esters to the liver, where they are converted to create retinol. Retinol is crucial in vitamin A metabolism and is primarily stored in the hepatic stellate cells in charge of fibrosis. Numerous physiological functions depend on this vitamin, including cell division and proliferation, immunological control, and glucose and lipid metabolism (9).

Vitamin A metabolites play essential roles in the development, function, and maturation of fatty tissue and in regulating lipid metabolism in the liver. Because of insulin resistance, there is a rise in the transit of non-esterified fatty acids from adipose tissue to the liver in obesity-associated NAFLD (10).

In one of the previous research projects, the levels of β -carotene and retinol were examined in 145 cases of morbid obesity. Non-alcoholic fatty liver disease was detected in 70% of their participants, and among them, the serum level of retinol and β -carotene was 10% and 40%, respectively. The results showed that morbidly obese patients with NAFLD had insufficient serum retinol levels (1.05 mol/L) (11). Children who were obese and had NAFLD showed similar results in the cross-sectional study, including 46 schoolchildren assessed by ultrasonography (12). However, low levels of circulating retinol in NAFLD may not indicate vitamin A insufficiency and may be due to abnormal vitamin A metabolism.

The results of one study revealed the relationship between severe liver fibrosis and low levels of serum retinol.

Most patients with NAFLD had significantly lower levels of retinol in their serum. Although they recommended retinol as a crucial indicator of liver disease progression and liver injury was reversible in the early stages (13), prescribing vitamin A to children should be monitored because this supplement may increase their adiposity (14).

3.2. Vitamin B in Non-alcoholic Fatty Liver Disease

There are eight types of vitamin B, including thiamin (B1), riboflavin (B2), niacin (B3), pantothenic acid (B5), pyridoxine (B6), biotin (B7), folate or folic acid (B9), and cyanocobalamin (B12). There is a shortage of evidence regarding the association between all vitamin B compounds and NAFLD, and only the relationship between vitamins B3 and B12 and NAFLD has been reported (14).

B3 reduces hepatic cholesterol levels and prevents liver weight growth. The preventative impact on hepatic steatosis demonstrated the therapeutic efficacy of vitamin B3 in treating NAFLD (15). A previous study on 39 Chinese patients with dyslipidemia treated with B3 for 23 weeks assessed liver fat before and after the study. Their results showed improved liver enzymes and decreased plasma triglyceride levels.

Moreover, liver fat increases remained substantial despite the study's mean body weight reduction of about 1.5% (16). B3 thus appears to affect adipocyte insulin responsiveness via various pathways in NAFLD patients and increase insulin resistance (17). In a study of 45 patients with NAFLD and 30 healthy controls, the levels of folic acid, liver enzymes, and vitamin B12 were compared in both groups. It has been discovered that treatment with vitamin B12 decreases homocysteine levels, improves endothelial dysfunction, and reduces insulin resistance. Therefore, vitamin B12 should also be assessed in the preliminary screening for NAFLD (18).

3.3. Vitamin C in Non-alcoholic Fatty Liver Disease

The influence of inflammation and oxidative stress on the progression of NAFLD, diabetes mellitus, and metabolic syndrome is well proven. Vitamin C, also known as ascorbic acid, is a potent antioxidant that may scavenge free radicals. Therefore, vitamin C might help reduce hepatocellular oxidative stress in NAFLD (19, 20). The metabolism of hepatic lipids is thought to be influenced by vitamin C. In pediatrics diagnosed with NAFLD, a rise in hepatic ballooning was associated with a reduction in blood vitamin C levels (21, 22). According to the previous study, vitamin C shortage hastened the development of dyslipidemia and its hepatic effects. In contrast, a rise in vitamin C intake decreased the severity of the condition and the buildup of lipids in the hepatocellular tissue (23).

Nobili et al. studied 90 children with biopsy-proven NAFLD in a double-blind study (24). One group took a diet-added placebo, and another group added vitamins E and C to the diet. After one year, there was no noticeable difference between the group taking a variety of vitamins C and E and the group receiving a placebo (24). In a study of 1000 individuals, approximately 10% of patients had NAFLD at the beginning of the study. It was reported that atorvastatin 20 mg combined with vitamins C and E reduced the probability of developing NAFLD after four years of treatment (25). Williams et al. assessed the effect of using vitamins C and E as an antioxidant supplement in rats (26). Even though beneficial effects such as decreased hepatic glucose and improved insulin sensitivity have been reported, they could not determine whether these effects are driven by one or a combination of these vitamins (26).

3.4. Vitamin D in Non-alcoholic Fatty Liver Disease

Vitamin D's positive effects have broadened, including immunological regulation, cell division, and proliferation. Existing data suggest a connection between fatty liver disease and vitamin D, which is consistent with the variety of features of vitamin D. At the same time as vitamin D insufficiency is a global problem, NAFLD is a rapidly spreading form of metabolic syndrome. Low levels of vitamin D and NAFLD have been described in some epidemiological research, which shows that these diseases have a variety of common risk factors. Notably, necro-inflammatory injury correlates with insufficient serum vitamin D levels (27, 28).

As part of one interventional study, 200 overweight and obese children (108 of whom had liver ultrasonography-proven fatty liver) were given vitamin D (50000 U) weekly for three months. The study revealed that vitamin D supplementation might improve the grade of fatty liver reported by liver ultrasonography. Furthermore, the levels of ALT decreased, and it might be the result of less inflammation (29). Li et al. demonstrated that vitamin D might prevent hepatic steatosis brought on by a high-fat diet or free fatty acids (30). They proposed that vitamin D might be a beneficial clinical option for treating hepatic steatosis (30). Moreover, according to one study, vitamin D might control hepatic steatosis. They demonstrated how vitamin D affects liver inflammation, fibrogenesis, and insulin sensitivity (31). A cohort study on 103 children with biopsy-proven NAFLD reported low vitamin D status, especially in winter. Furthermore, only 20% of pediatric patients had sufficient vitamin D levels (32). Due to the apparent relationship between Vitamin D and NAFLD, screening those at risk for NAFLD for vitamin D deficiency is recommended (33).

3.5. Vitamin E in Non-alcoholic Fatty Liver Disease

The most convincing evidence of vitamin E's therapeutic potential in liver diseases comes from its role as a fat-soluble and strong chain-breaking antioxidant in the body (34). Vitamin E supplements are frequently administered to NAFLD patients by specialists despite the lack of a standardized guideline for the treatment of NAFLD (35). According to research by Foster et al. on 1000 individuals (nearly 10% of them diagnosed with NAFLD), vitamins E and C, coupled with the cholesterol-lowering drug atorvastatin (20 mg), significantly decreased hepatic steatosis by approximately 70% in people with NAFLD (25).

A previous study used vitamin E in children with increased aminotransferase levels and no other signs of liver injury. They noted that both aminotransferase levels returned to normal during the medication, but liver brightness remained unchanged (36). Although vitamin E treatment in adults improved liver histology or normalization of biochemical blood markers, children showed no significant improvement. Based on the results of one systematic review, a short study period might be a limitation to concluding the efficiency and safety of suggested therapies in children (35).

4. Conclusions

As it was shown that the level of vitamins in children with NAFLD had been linked with the disease's prognosis and severity, measuring them seems logical.

Footnotes

Authors' Contribution: Conceptualization: A. H. R., S. S., S. M., and A. F. Y.; methodology: A. H. R., S. S., S. M., and A. F. Y.; validation: A. H. R., S. S., S. M., and A. F. Y.; investigation: A. H. R., S. S., S. M., and A. F. Y.; resources: A. H. R., S. S., S. M., and A. F. Y.; data curation: A. H. R., S. S., S. M., and A. F. Y.; writing, original draft preparation: A. H. R., S. S., S. M., and A. F. Y.; writing, review and editing: A. H. R., S. S., S. M., and A. F. Y.; supervision: A. H. R., S. S., S. M., and A. F. Y.; project administration: A. H. R., S. S., and A. F. Y.

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