

Dietary supplements and pediatric non-alcoholic fatty liver disease: Present and the future

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in children. High prevalence of pediatric obesity and sedentary lifestyle has augmented the incidence of NAFLD in children. Obesity is associated with an increased risk of NAFLD through various mechanisms such as intensification of insulin resistance and increased levels of inflammatory markers. There is no approved medical intervention for treatment of pediatric NAFLD; the only proven strategy in management of pediatric NAFLD is lifestyle modification. Recently, the effects of nutritional supplements have been examined in the management of pediatric NAFLD. The purpose of this review is to summarize the studies evaluating the effects of nutritional supplements on pediatric NAFLD and explain the future direction in this field.

Key words: Pediatric non-alcoholic fatty liver disease; Diet; Nutrition; Dietary supplement; Fatty liver

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Core tip: The purpose of this review is to report the existing evidences and future directions on dietary supplements that can be used for management of pediatric nonalcoholic fatty liver disease. Also we tried to explain the properties of these supplements and needs for future studies.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in children. This disorder includes a wide spectrum from a simple steatosis with the mortality rate lower than one percent to a critical illness such as cirrhosis and hepatic fibrosis that may ultimately lead to hepatocellular carcinoma and death^[1,2]. If NAFLD is not treated at early stages, it can progress to nonalcoholic steatohepatitis (NASH), which is characterized by lobular inflammation and hepatocellular injury which may definitely progress to cirrhosis and liver fibrosis^[3]. Coincident with the rise in prevalence of childhood obesity over the past few decades, NAFLD has become the leading cause of liver disease in children. Insulin resistance and oxidative stress are involved in the pathogenesis of NAFLD^[4].

PREVALENCE

Several conditions such as obesity, sedentary lifestyle and the use of high-calorie foods have caused a sharp increase in the NAFLD prevalence^[5]. The prevalence of NAFLD is different from 5% to 20% in general population and above 40% in obese and type 2 diabetes patients^[6,7]. Also, its prevalence is different between the men and women and increase in the older people. According to the recent studies, NAFLD prevalence in normal children is 3%, rising up to 50%-70% among obese children^[8]. The prevalence in developed countries also increased remarkably from 16.9% to 23.8% for boys and from 16.2% to 22.6% for girls, while in developing countries increased from 8.1% to 12.9% for boys and from 8.4% to 13.4% for girls. In most of the communities, parallel with the rising in prevalence of the obesity, and chronic diseases such as diabetes and dyslipidemia, the prevalence rate of the NAFLD is also increasing^[9].

According to the American Association for the Study of Liver Disease guideline, liver biopsy is a gold standard for diagnoses of NAFLD^[10]; however, because of the invasive nature of this method, it is usually recommended to use the other methods such as magnetic resonance spectroscopy and Fibroscan for screening and staging of this disease^[11].

PATHOPHYSIOLOGY

Pathogenesis of NAFLD is closely associated with obesity and insulin resistance^[12,13]. Obesity especially abdominal obesity can lead to insulin resistance. Insulin plays various roles in metabolism such as oxidative distress and carbohydrate metabolism. In obesity and some chronic diseases such as type 2 diabetes and dyslipidemia, insulin cannot function properly, so lipolysis pathway will be activated leading to an increased influx of

free fatty acids to the liver^[14]. Also, several studies have confirmed that endogenous lipid synthesis is increased in patients with NAFLD^[15]. Hepatic fat derivatives such as malondialdehyde (MDA) can contribute in the progression of NAFLD^[16,17]. In addition, the expression of certain proinflammatory cytokines such as tumor necrosis factor (TNF)- α increases in obese people, which can cause insulin resistance through deterioration of insulin receptors^[15].

Free fatty acids that released from the adipose tissue can inhibit the Cytochrome P450 (an enzymatic system that involved in various pathways specially free fatty acids beta-oxidation), which results in the production of active oxygen radicals and depletion of body antioxidant reserves (such as glutathione and vitamin E)^[18].

Moreover, genetic predisposition plays an important role in NAFLD pathogenesis. The genes involved in the mitochondrial and fatty acids metabolism, affect the disease progression^[19].

MANAGEMENT OF NAFLD

One of the main strategies in the management of pediatric NAFLD is modification of life style and dietary pattern. Several studies have found that gradual weight loss and regular physical activity can help in the treatment of NAFLD through improving the insulin sensitivity, reduction in the body inflammation and resolution of hepatic steatosis^[20-22]. It should be considered that weight loss in obese children (5% to 10% of basal weight) must be quite gradual and the diet must be balanced^[23].

The result of pharmacological interventions in treatment of pediatric NAFLD is contradictory. The main family of medications that evaluated for treatment of pediatric NAFLD are insulin sensitizers specially metformin^[24]. These medications play a positive role in the treatment of NAFLD by improving insulin sensitivity; however, these beneficial effects have not been shown in long term treatment^[25]. Recently, the beneficial effects of some supplements specially vitamin E^[9], probiotics^[26] and omega-3 fatty acids^[27] in NAFLD management have been shown.

The purpose of this review is to report the effectiveness of some dietary supplements in the management of the pediatric NAFLD and future directions in this field.

LITERATURE STUDY

A MEDLINE, PubMed and Cochrane Review database search used a combination of keywords, including NAFLD, pediatric, treatments, lifestyle changes, NASH, supplements, nutrition, vitamins, minerals, vitamin E, vitamin D, polyunsaturated fatty acids, probiotic, symbiotic, polyphenols, curcumin, resveratrol, quercetin, anthocyanin, herbal medicine, green tea polyphenols, cinnamon, ginger and their related MeSH terms. The articles were selected based on their relevance to the review.

POLYUNSATURATED FATTY ACIDS

Several studies have evaluated the beneficial effects of Omega-3 long-chain polyunsaturated fatty acids on the treatment of NAFLD^[27]. Janczyk *et al.*^[28] have shown that supplementation with long chain omega-3 for 6 mo resulted in a significant decrease in aspartate aminotransferase and gamma-glutamyl transpeptidase levels compared with the control group; however, it did not significantly reduce the levels of alanine aminotransferase (ALT) and liver steatosis. Nobili *et al.*^[29] have reported that Docosahexaenoic acid (DHA) supplementation for 24 mo resulted in a significant reduction in triglyceride and ALT levels and improved liver steatosis compared with the control group. As noted, one of the major risk factors that involved in NAFLD pathogenesis is insulin resistance^[13]. Nobili *et al.*^[30] have shown that DHA increased insulin sensitivity and decreased triglyceride levels in children with NAFLD. Di Minno *et al.*^[27] have also proposed that omega-3 supplementation has a therapeutic effect on pediatric NAFLD. Also in another study, St-Jules *et al.*^[31] have shown that lack of fish and long-chain omega-3 fatty acid intake in children was associated with greater portal and lobular inflammation in children with NAFLD. It seems that omega-3 fatty acids supplementation has beneficial effects on pediatric NAFLD through its anti-inflammatory and insulin sensitizer effects; however, no study has examined its long term effects.

Vitamin E

Several previous studies have evaluated the beneficial effects of vitamin E, as a potent antioxidant, in the management of pediatric NAFLD. Nobili *et al.*^[32] prescribed vitamin E in children with NAFLD and observed a similar decrease in the levels of ALT and HOMA-IR in the intervention and control groups after 12 mo. A large, well designed, clinical trial^[25] has shown that vitamin E is not superior to placebo in attaining the sustained reduction in ALT level in patients with pediatric NAFLD after 96 wk; however vitamin E could significantly reduce the ALT levels at weeks 24, and 48. Moreover, it could significantly improve the histopathological features of the disease at week 96. Finally, Sarkhy *et al.*^[33] in a systematic review and meta-analysis have shown that vitamin E supplementation decreases level of ALT. It seems that vitamin E can improve the characteristics of pediatric NAFLD and specially NASH patients in short time, but not in the long term supplementation.

Prebiotics and probiotics

Probiotics are among the major supplements which have attracted the attention of many investigators regarding their application for the treatment of NAFLD and NASH^[34]. Probiotics can modify some NAFLD risk factors such as insulin resistance, liver fat and oxidative stress^[26,35-37]. Prebiotics are chemicals that induce the growth or activity of microorganisms. In some animal studies, researchers have shown that mice fed with prebiotic products exhibited a lower plasma of

inflammatory markers such as TNF- α and interleukin-1 α in comparison to controls^[38]. Some of the prebiotics such as lactulose and galacto-oligosaccharides can promote the growth of certain intestinal bacteria such as *Lactobacillus* and down-regulate levels of inflammatory factors. In a clinical trial, researchers showed that supplementation with oligofructose decreased levels of liver enzymes specially ALT^[39]. Alisi *et al.*^[40] performed a clinical trial and prescribed VSL#3 [a mixture of eight probiotic strains including: *Streptococcus thermophilus*, *Bifidobacteria* (*B. breve*, *B. infantis*, *B. longum*), *Lactobacillus acidophilus*, *L. plantarum*, *L. paracasei*, and *L. delbrueckii* subsp. *Bulgaricus*] in children with NAFLD for four months and evaluated changes in fatty liver severity after 4 mo as detected by ultrasonography. The results of this study showed that probiotic supplementation reduced the severity of NAFLD but it did not cause significant differences in levels of triglyceride, ALT and HOMA-IR in comparison to the placebo group. The authors discussed that this beneficial effect is due to the increased levels of glucagon-like peptide 1. Vajro *et al.*^[41] proposed that supplementation with *Lactobacillus rhamnosus* strain GG decreases the level of ALT in children with persistently elevated aminotransferases and echogenic livers. Further clinical trials are needed to find the best combination of probiotics for achieving the best results from supplementation.

Vitamin D

Vitamin D is a crucial nutrient for children's health and development^[42]. Several studies have reported the vitamin D deficiency in obese children^[43]; on the other hand, NAFLD is more prevalent in obese children than normal weight children^[8]. These data urged the investigators to evaluate the association of plasma vitamin D levels with NAFLD pathogenesis. Misra *et al.*^[43] evaluated the vitamin D level in children with biopsy-proven NAFLD. They reported a high prevalence of vitamin D deficiency in children with NAFLD; however, they did not find any association between vitamin D deficiencies and the severity of NAFLD. Black *et al.*^[44] analyzed the association of vitamin D and NAFLD severity in adolescents with NAFLD; they have reported a high vitamin D deficiency in these patients. In addition, they showed an inverse association between serum vitamin D levels and severity of NAFLD. In a similar study, Nobili *et al.*^[45] have demonstrated a reverse association between vitamin D level in serum and severity of NAFLD and fibrosis in 73 children with elevated serum aminotransferase levels and hyperechogenic liver on ultrasonography.

Little is known about the effect of vitamin D supplementation on NAFLD in children; however, a clinical trial in adults resulted in a reduction in MDA and hs-CRP levels without any significant change in ALT levels^[46]. Conducting clinical trials in children are needed.

Polyphenols

Polyphenols are plant-derived compounds which have been used for treatment of NAFLD due to their anti-

inflammatory and antioxidant properties^[47]. One of the main members of polyphenols family is resveratrol; supplementation with resveratrol has been shown to be useful in reduction of the severity of the disease. It has been shown that resveratrol reduces the level of liver enzymes and inflammatory cytokines^[48,49] and attenuates hepatic steatosis^[50]. Other members of the polyphenols family such as curcumin^[47], quercetin^[51], anthocyanin^[47] and green tea polyphenols^[52] have been also indicated to have promising outcomes in the treatment of adults NAFLD. The beneficial roles of polyphenols in adults NAFLD propose its effectiveness in pediatric NAFLD. Thus, clinical trials in children are needed to confirm it.

INSULIN SENSITIZERS AND LIPID LOWERING AGENTS

Herbal medicine has been used in traditional medicine of many countries for treatment of different disorders^[53]. Since these medications can improve the insulin sensitivity and lipid profile, they are proposed for treatment of NAFLD^[54]. Several studies have shown satisfactory results from these insulin sensitizers and lipid reducing agents such as cinnamon, curcumin^[55] and ginger^[56] in the management of NAFLD; however, studies have not conducted to examine the effects of these supplements on pediatric NAFLD. More extensive investigations are needed to fully determine the therapeutic potential of these components for treating NAFLD.

CONCLUSION

Due to the sharp rise in obesity prevalence in children and a dramatically increase in pediatric NAFLD prevalence, therapeutic strategies are urgently needed. Dietary supplements play a pivotal role in pediatric management through insulin sensitizer, anti-oxidant and anti-inflammatory properties. In recent years, the beneficial effects of some of these supplements have been shown; however, several of them have not yet been evaluated. Further clinical trials are needed to support the use of supplements, either as preventive or therapeutic agents in pediatric NAFLD.

More studies related to the pediatric NAFLD performed to assess changes in children lifestyle^[57]. Recently, the beneficial effects of nutritional supplements have been shown in both pediatric and adult NAFLD^[9]; however, several of these supplements' effects are assessed only in adults. Thus, evaluating the effects of these potentially beneficial supplements in pediatric NAFLD is highly recommended.

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