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REVIEW

Lifestyle Interventions Including Nutrition, Exercise, and Supplements for Nonalcoholic Fatty Liver Disease in Children

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Abstract Nonalcoholic fatty liver disease (NAFLD) is the most common cause of liver disease among children. Lifestyle interventions, such as diet and exercise, are frequently recommended. Children with NAFLD have a distinct physiology that is different from obesity alone and has the potential to influence lifestyle treatments. Studies of diet alone in the treatment of pediatric NAFLD have focused on sugar and carbohydrate, but did not indicate any one dietary approach that was superior to another. For children who are obese and have NAFLD, weight loss may have a beneficial effect regardless of the diet used. Exercise is widely believed to improve NAFLD because a sedentary lifestyle, poor aerobic fitness, and low muscle mass are all risk factors for NAFLD. However, there have been no randomized controlled trials of exercise as a treatment for children with NAFLD. Studies of the combination of diet and exercise suggest a potential for improvement in serum alanine aminotransferase activity and/or magnetic resonance imaging liver fat fraction with intervention. There is also enthusiasm for the use of dietary supplements; however, studies in children have shown inconsistent effects of vitamin E, fish oil, and probiotics. This review presents the available data from studies of lifestyle intervention and dietary supplements published to date and highlights challenges that must be addressed in order to advance the evidence base for the treatment of pediatric NAFLD.

Keywords Nonalcoholic steatohepatitis · Obesity · Hypertension · Dyslipidemia · Insulin resistance · Physical activity · Dietary supplements · Probiotics

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in children with an estimated prevalence of 9.6 % in the USA [1]. NAFLD encompasses a broad spectrum of liver disease severity ranging from isolated steatosis to steatohepatitis (NASH) and fibrosis. NAFLD in children can progress rapidly and does reach end-stage liver disease in some adolescents. Moreover, having NAFLD in childhood may be an important risk factor for HCC in adulthood [2–4]. There are no approved pharmacological therapies for NAFLD in children.

Therapeutic lifestyle interventions, typically focused on nutrition and exercise, are commonly recommended for the treatment of NAFLD. The joint practice guideline from the American Association for the Study of Liver Disease (AASLD), the American College of Gastroenterology (ACG), and the American Gastroenterology Association (AGA) advocate lifestyle modifications as treatment for NAFLD [5]. However, specific recommendations are not

provided regarding type, intensity, or duration of diet or exercise.

Our aim was to review the available literature pertaining to lifestyle interventions in the treatment of NAFLD in children. For the purposes of this review, we considered studies of nutrition, exercise, and/or dietary supplements in children with known or suspected NAFLD.

Methods

We performed a structured keyword search in PubMed to identify articles from peer-reviewed journals written in English between January 1, 1990, and August 31, 2015, that evaluated the efficacy of lifestyle interventions. Search parameters included: NAFLD, fatty liver, hepatic steatosis, and NASH. These were then restricted by age using the terms pediatric, child, and adolescent. To be included in this review, articles had to be original clinical studies of children with NAFLD or hepatic steatosis with a measured hepatic outcome, such as serum ALT, hepatic fat fraction, or histology. We excluded review articles and cross-sectional studies. Studies of lifestyle interventions were identified using the terms diet, nutrition, exercise, physical activity, and lifestyle. There were 283 articles obtained, of which 17 met criteria for inclusion in this review (Table 1). Clinical trials of dietary supplements were identified using the terms dietary supplement, vitamins, probiotics, and prebiotics. This search strategy yielded 225 articles, of which 11 met criteria for inclusion (Table 2).

Nutrition

General Recommendations

According to the American Heart Association (AHA), dietary strategies for all children include: "balancing dietary calories with physical activity," eating vegetables and fruits daily, limiting juice intake, reducing intake of sugar-sweetened beverages and foods, using nonfat or low-fat milk and dairy products, eating more fish, and reducing salt intake [6].

The National Heart, Lung, and Blood Institute (NHLBI) recommended similar guidelines for children to have a healthy diet. They include the following: Beverages should be limited to water or fat-free unflavored milk, dietary fat should comprise 25–30 % of daily caloric intake, and diets should include foods high in fiber [7].

Basis for Recommendations in NAFLD

There have not been any clinical trials of diet as a monotherapy for children with biopsy-proven NAFLD. The importance of clinical trials being done in children with biopsy-proven NAFLD cannot be overstated. Many children who are suspected to have NAFLD based upon serum ALT or liver ultrasound may either not have liver disease or have a liver disease other than NAFLD. Of the overweight or obese children referred to a gastroenterology for elevated serum ALT, only 55 % had NAFLD. In addition, elevated serum ALT, defined as two times the upper limit of normal, was shown in overweight and obese children to have a sensitivity of 57 % and specificity of 71 % for NAFLD [8]. Moreover, liver ultrasound evidence of steatosis has been shown to have a positive predictive value of only 47–62 % for NAFLD [9]. The advanced MRI technique of proton density fat fraction has been shown to strongly correlate with hepatic steatosis, but there is not yet standardization for clinically appropriate cutoffs to determine NAFLD [10]. Moreover, approximately one in four children biopsied for suspected NAFLD may have an alternate liver diagnosis [8]. Thus, in order to properly evaluate the results of a specific intervention for NAFLD, it is important to assure that all children participating do in fact have NAFLD.

There were two studies of dietary intervention in children with hepatic steatosis detected by magnetic resonance spectroscopy (MRS) via hepatic fat fraction (HFF). Ramon-Krauel et al. studied 17 obese children with HFF > 9 % at baseline. Participants were randomly assigned to either a low-glycemic diet, emphasizing a selection of carbohydrate-containing foods with a low to moderate glycemic load, or a low-fat diet, which was based on limiting total fat to <30 % of total calories and saturated fat to <10 %, for a 6-month period. Children assigned to low-glycemic diet lost an average of 0.7 kg from baseline while the low-fat group lost an average of 1.5 kg with no significant difference between groups. Both the low-glycemic and low-fat diets had significant decreases in ALT from baseline, -29 U/L for the low-glycemic group and -18 U/L for the low-fat group, though there was no significant difference between the groups. Both diet groups had significant decreases in HFF, from 23.8 % at baseline to 15.4 % for the low-glycemic group and 29.3 to 18.7 % for the low-fat group with no significant difference between the two groups. There was no significant difference in change of HFF or ALT between the two groups [11].

Jin et al. investigated the effect of fructose reduction on overweight and obese children with hepatic fat fraction of >8 % measured by MRS. In this study, 24 overweight adolescents that consumed at least three sugar-sweetened beverages per day were randomly assigned to consume three servings (8 oz each) of either glucose-containing beverages or fructose-containing beverages per day over a 4-week period. There was no significant change in hepatic

Table 1 Studies investigating dietary, exercise, and combined interventions for the treatment of NAFLD in children

Author	Country	Sample size	Mean age (years ± SD)	Population	Study duration	Metric of improvement	Intervention
Nutrition as monotherapy							
Ramon-Krauel 2013 [11]	USA	17	11.8 ± 3.0	Obese children with MRS HFF ≥9 %	6 months	Change in HFF	Low-glycemic diet versus low-fat diet
Jin [12]	USA	24	13.5	Overweight Hispanic children, overweight that consume at least three sweet beverages daily	4 weeks	Change in HFF	Substitute fructose beverages with glucose beverages
Exercise as monotherapy							
van der Heijden [20]	USA	29	15.6 ± 0.4	Sedentary, Hispanic adolescents. Lean group versus obese group	12 weeks	Change in HFF	Aerobic exercise program (30 min, 4 days per week)
van der Heijden [21]	USA	12	15.5 ± 0.5	Obese adolescents	12 weeks	Change in HFF	Resistance exercise program (1 h, 2 days per week)
Lee [19]	USA	45	14.9	Inactive, obese boys	3 months	Change in HFF	Aerobic versus resistance exercise program
Lee [18]	USA	44	14.8	Inactive, obese girls	3 months	Change in HFF	Aerobic versus resistance exercise program
Nutrition and exercise multimodal therapy							
Vajro [22]	Italy	9	8.7 ± 2.1	Chronic ALT >40	12 months	Change in ALT	Individualized regimen of balanced diet and physical exercise
Tazawa [28]	Japan	110	Range: 6–18 yrs	Obese children with persistently elevated LFTs vs those without elevated LFTs	3 months	Change in ALT	20 % reduction in calories + exercise recommendations
Nobili [13]	Italy	84	11.7 ± 3.3	Biopsy-proven NAFLD	1 year	Change in ALT and liver ultrasound appearance	1-h nutritional counseling w/ balanced, low-calorie diet; moderate exercise program (30–45 min/day 3×/week)
Wang [26]	China	76	13.7 ± 1.9	Obese children with abnormal ultrasound and elevated ALT	1 month	Change in ALT and liver ultrasound appearance	Summer camp with 3-hour aerobic exercise (unstructured), dietary management (low calorie) for 1 month
Pozzato [25]	Italy	26	Range: 6–14 yrs	Obese children	1 year	Change in HFF	Recommend balanced diet and active lifestyle
Grønbæk [29]	Denmark	117	12.1 ± 1.3	Obese children with abnormal ultrasound and elevated ALT	10 weeks	Change in liver ultrasound appearance	Summer camp with controlled weight loss diet and moderate to strenuous supervised physical activity
Campos [30]	Brazil	53	17 ± 1.7	Post-pubertal adolescents	1 year	Change in ALT	Weekly dietary lessons and exercise 3x/week (30 min aerobic, 30 min resistance)
Pacifico [31]	Italy	135	11.9	Obese children with abnormal liver ultrasound and elevated ALT	12 months	Change in BMI z-score, ALT, HFF	Diet and exercise education (60 min/day × 5 days/week)

Table 1 continued

Author	Country	Sample size	Mean age (years ± SD)	Population	Study duration	Metric of improvement	Intervention
DeVore [27]	USA	108	14	Children with ALT >45	1 year	Change in BMI z-score, ALT	Dietary and exercise advice every 3 months
Sanches [32]	Brazil	79	17 ± 2	Obese children with abnormal liver ultrasound	1 year	Change in BMI and ALT	Diet counseling 1×/week, individual nutrition consult; group behavioral counseling; exercise 3×/week combined 30 aerobic, 30 resistance)
Koot [24]	Netherlands	80	14.7 ± 2.4	Obese children with HFF >5 %	6 months	Normalization of HFF and ALT	Four treatment groups: (1) inpatient (2) 2 month inpatient 4×/week, then 4 month 2×/week visits for 2 days each, (3) ambulatory, (4) usual care

fat fraction, body weight, or ALT in either group from baseline [12].

Exercise

General Recommendations

For all children, the NHLBI recommends moderate physical activity for 1 h per day with vigorous exercise 3 days per week along with limiting screen time to no more than 2 h per day. According to the 2008 physical activity guidelines by the US Department of Health and Human Services, children should have 60 min of physical activity every day. In addition, children should have vigorous-intensity physical activity for 3 days of the week, muscle-strengthening physical activity for 3 days of the week, and bone-strengthening physical activity for 3 days of the week [13].

Basis for Recommendations in NAFLD

Exercise is a universally recommended intervention in the treatment of NAFLD in children. There are data in adults that suggest that exercise can by beneficial for NAFLD without dietary change and without weight loss [14–17]. Studies of exercise alone as a therapy alone in NAFLD in children are extremely limited. Furthermore, there have been no studies that have investigated exercise as a treatment for children with biopsy-proven NAFLD. The available studies investigated the effect of exercise on obese children as the target population and all but one measured change in HFF by MRS.

Lee et al. investigated the effect of aerobic and resistance exercise versus control on obese children, with one study in boys and one in girls. Each study had 44 children. The aerobic intervention was comprised of three sessions per week, 60 min per session with treadmill, elliptical, or stationary bike. The resistance intervention was comprised of ten whole-body exercises three times per week for 60 min per session. The investigators reported changes in HFF for the groups overall. However, very few children had sufficient liver fat to have been considered as having NAFLD; there were 12 boys and five girls with HFF > 5.0 %. Furthermore, the mean HFF at baseline was only 3.3 % in boys and 2.3 % in girls. The investigators did report a statistically significant change in HFF in the aerobic group in both boys and girls compared to control, −1.9 vs 0.9 % ($p = 0.05$) and −1.7 vs 0.8 %, respectively. In addition, there was a significant change in HFF in the resistance group for boys, −2.0 vs 0.9 %. However, whether these small changes in group mean HFF are clinically relevant for those children with NAFLD remains unknown [18, 19].

Van der Heijden and colleagues also performed separate studies on the effect of aerobic and resistance exercise on children. In the study of aerobic exercise, 15 obese and 14 lean children were provided a 30-min intervention twice a week for 12 weeks. For these 29 children, overall there was a decrease in the mean HFF from 9 to 6 % but no significant change in mean ALT, from a baseline of 39 U/L [20]. In the study of resistance training, 12 obese Hispanic adolescents performed a 1-h session twice a week for 12 weeks. Seven out of the 12 adolescents had HFF of >5.6 %; there was no significant change in HFF. No data were provided for ALT at baseline or in response to the intervention [21].

Combination of Nutrition and Exercise

The majority of studies of lifestyle therapy applied a combination of nutrition and exercise. In 1994, Vajro et al. [22] first suggested that ALT can improve in obese children

Table 2 Studies investigating dietary supplements for the treatment of NAFLD in children

Author	Country	Sample size	Mean Age (years ± SD)	Population	Duration	Metric of improvement	Intervention
Vitamin E							
Lavine [34]	USA	11	12.4 ± 1.6	Obese children with elevated ALT and abnormal liver ultrasound	Variable: 4 to 10 months	ALT normalization	Vitamin E 400–1200 IU/day
Vajro [37]	Italy	28	10.3 ± 3.7	Children with ALT ≥ 1.5 ULN	5 months	Change in ALT	Vitamin E 400 mg/day, then 100 mg/day
Nobili [36]	Italy	88	12.1 ± 3.2	Biopsy-proven NAFLD	12 months	Change in ALT	Vitamin E 600 IU/day, Vitamin C 500 mg/day × 12 months
Wang [26]	China	76	13.7 ± 1.9	Obese children with abnormal liver ultrasound and ALT≥1.5 × ULN	1 month	Change in ALT	Vitamin E 100 mg/day
Lavine [35]	USA	173	13.1 ± 2.4	Children 8–17 with biopsy-proven NAFLD and chronic ALT >60 U/L	2 years	Sustained reduction in ALT	Vitamin E 400 IU twice daily
Fatty Acids							
Nobili [38]	Italy	60	12	Biopsy-proven NAFLD	6 months	Change in ultrasound appearance and ALT	DHA 250 mg/day; DHA 500 mg/day
Nobili [39]	Italy	20	10.1 ± 2.0	Continuation study for children with NAFLD in the DHA 250-mg arm of study #38	12 months	Improvement in histology	DHA 250 mg/day
Pacifico [40]	Italy	58	10.9	Biopsy-proven NAFLD	6 months	Change in HFF	DHA 250 mg/day
Janczyk [41]	Poland	76	Median 13.0 (IQR 11.1–15.2)	Children with ALT >1.3 ULN and abnormal liver ultrasound	24 weeks	Decrease in ALT >0.3 times ULN	Omega-3- LC-PUFA (DHA/EPA) 450–1300 mg/day
Probiotics							
Vajro [42]	Italy	20	10.7 ± 2.1	Obese children with ALT >40 and abnormal liver ultrasound	8 weeks	Change in ALT	Lactobacillus rhamnosus (12 billion CFU/day)
Alisi [43]	Italy	48	10.5	Obese children with biopsy-proven NAFLD	4 months	Change in liver ultrasound appearance	VSL #3 1 sachet per day

with elevated liver chemistry in response to a combined program of nutrition and exercise. Only one such trial was performed in children with biopsy-proven NAFLD. Nobili et al. [23] reported an uncontrolled 1-year study of 84 children with NAFLD. All children were instructed to follow a balanced, reduced calorie diet and perform moderate intensity exercise for 30–45 min on 3 days per week. At the conclusion of 1 year, 32 % of children had been lost to follow-up. In the remaining 57 children, there was a significant decrease in the mean weight from 60.9 to 56 kg and a significant decrease in the mean ALT from 62 to 33 U/L.

Koot et al. performed a randomized, controlled trial in 51 severely obese children aged 8–18 years with hepatic steatosis defined as a HFF of >5 % by MRS. The intervention of interest was an inpatient lifestyle intervention. Participants were randomly assigned to one of the four treatments: (1) long inpatient intervention (6 months of inpatient treatment on working days), (2) short inpatient intervention (2 months of inpatient treatment followed by 4 months of biweekly return visits), (3) ambulatory intervention (16 days of ambulatory visits at increasing time intervals over a 6-month period), or (4) usual care group. The primary treatment goal was normalization of liver fat, which was achieved in only a minority of participants in any group. There was significantly greater rate of achieving the outcome in relation to the intensity of the intervention (inpatient 43 %, ambulatory 33 %, usual care 22 %). A similar trend was seen for normalization of ALT (inpatient 41 %, ambulatory 33 %, usual care 6 %) [24].

Pozzato et al. [25] performed an uncontrolled trial in 26 obese children, nine of whom had hepatic steatosis determined by MRS (HFF $\geq$ 9 %). The intervention was 1 h of nutritional counseling with written guidelines and moderate exercise of 30–45 min per day for 1 year. Among the nine children with HFF $\geq$ 9 % at baseline, seven had a decrease in HFF to below 9 %, decreasing from a mean of 18.7–1.3 %. There was not a significant decrease in ALT; however, the mean ALT at baseline was relatively low, 31 U/L.

Many studies were performed in children with suspected NAFLD based upon measurement of ALT and/or abdominal ultrasound. Wang et al. performed a randomized controlled trial (RCT) in China of 76 obese children age 10–17 years with elevated ALT and evidence of hepatic steatosis by ultrasound. These children were randomly assigned to one of the three groups: (1) residential summer camp; (2) usual care; or (3) usual care plus 100 IU/day of vitamin E. The intervention was for a duration of 1 month. At the camp, children were provided a reduced calorie diet and daily unstructured aerobic exercise. The group at camp had a significant decrease in BMI from 29.1 to 27.2 kg/m^2 ($p < 0.05$) and a significant decrease in mean ALT from 152 to 64 ($p < 0.05$). There was no significant improvement in the usual care groups relative to the lifestyle intervention [26].

In Cincinnati, Ohio, DeVore and colleagues reported on 83 children seen in a dedicated fatty liver clinic with chronic elevation of ALT > 45 U/L. All children were recommended to meet with a pediatric gastroenterologist and a registered dietitian once every 3 months for counseling on nutrition and exercise. Liver biopsy was performed to establish a diagnosis in 24 children. Notably, children that had a liver biopsy were nearly twice as likely to continue with gastroenterology care for 1 year (71 %) than those children who did not have a liver biopsy for diagnosis (37 %). For those children who continued to be followed for 1 year, there was a decrease in serum ALT and stabilization of BMI z-score [27].

In Japan, an uncontrolled trial of lifestyle intervention was performed in 73 obese children aged 6–14 years with elevated ALT (ALT $\geq$ 30). Children were instructed to exercise and to decrease their portion sizes by 20 % for a duration of 3 months. Weight loss was observed in 36 out of 73 children, and in ten children the weight loss was >5 % of body weight. Normalization of ALT was observed in 20/73 (27 %) of participants [28].

In Denmark, Grønbæk et al. [29] performed an uncontrolled trial of weight loss in obese children via a 10-week weight loss camp. During the camp, children were provided with healthy low-fat (<24 % of caloric intake from fat) food and had 1 h of moderate intensity exercise daily. The study included 117 obese children, most of whom did not have NAFLD or suspected NAFLD at entry. For the group overall, there was an approximately 10 % weight loss. Based upon liver ultrasound, there was hepatic steatosis in 43 % at baseline and 31 % following the weight loss intervention. In addition, it was reported that 50 % of the children had ALT > 25 U/L at baseline, and all were noted to have some unspecified decrease in ALT after the 10-week intervention.

In Brazil, Campos et al. performed an uncontrolled trial in 53 post-pubertal obese adolescents. The intervention included nutritional counseling once a week and three sessions per week of a combination exercise program that included 30 min of aerobic and 30 min of resistance training. Psychological counseling was also provided as needed. The treatment duration was 1 year. Of the 53 adolescents who began the intervention, 13 of them dropped out. Out of the remaining 40 adolescents, based upon liver ultrasound, NAFLD was suspected in 45 % of children at baseline. After 1 year, mean ALT decreased from 29 to 24 U/L [30].

Two studies included in this review of combined lifestyle intervention did not have their primary aims focus on hepatic changes, but rather vascular changes. However, they both included hepatic outcomes as part of their studies. In the first study, Pacifico et al. [31] reported an uncontrolled study of the effect of lifestyle intervention on vascular flow parameters. The nutrition intervention included a dietary prescription for a hypocaloric diet (25–30 calories/kg/day) with 50–60 % carbohydrates, 23–30 % fats, and 15–20 % protein. The exercise intervention was moderate intensity activity 60 min per day for $\geq$5 days per week. They enrolled 135 children with suspected hepatic steatosis based upon liver ultrasound. The program was completed by 89 % of children (120/135) who had a mean weight loss of −2.0 kg and a decrease in mean ALT from 54 to 37 U/L. In addition, in 38 % of children (52/135) liver MRS was performed to assess HFF which decreased from a mean of 15.2 % at baseline to 6.4 % at 1 year.

In the second study, Sanches et al. [32] also investigated the effect of a 1-year lifestyle intervention on vascular flow parameters. The therapeutic regimen included 1 h per week of nutritional counseling, 1 h per week of psychological counseling, and 1 h per week of physical therapy, along with a 1 h combined aerobic and resistance exercise program three times per week. The study included 131 adolescents aged 15–19 years of whom 25 % had suspected hepatic steatosis based upon liver ultrasound. There were 79 participants who completed the study and had a decrease in mean BMI from 39.5 to 34.6 kg/m^2. They also reported that mean ALT decreased from 27 to 21 U/L.

Dietary Supplements

The US Food and Drug Administration (FDA) notes that "a dietary supplement is a product intended for ingestion that contains a 'dietary ingredient' intended to add further nutritional value to (supplement) the diet" [33]. Potential medical therapies in the form of supplements that have tested in children for NAFLD include vitamin E, omega-3 fatty acids, and probiotics.

Vitamin E

Potential etiologic mechanisms for NAFLD include mitochondrial dysfunction and damage from reactive oxygen species; thus, antioxidants, such as vitamin E, have been tested as treatments for NAFLD. The use of vitamin E for the treatment of NAFLD was first proposed by Lavine, who performed a pilot study in 11 children with elevated serum ALT and ultrasound evidence of hepatic steatosis [34]. Subsequently, there have been four studies that investigated Vitamin E, two of which had children with biopsy-proven NAFLD. Vitamin E can be dosed in international units (IU) or milligram, and in order to convert between these two, one must know the form of vitamin E that was used. Because most studies did not report the form of vitamin E used, the dosing is reported in IU or milligram as stated in the respective study. The Treatment of NAFLD in Children (TONIC) trial was designed with a primary outcome of sustained reduction in ALT for 96 weeks of treatment. In this study, 58 children were randomized to take 400 IU of vitamin E twice a day for 2 years, and 58 children were randomized to placebo. There was no significant effect of vitamin E on serum ALT; 26 % of the children taking vitamin E had sustained reduction in ALT compared to 17 % of children in the control group. Liver biopsy was repeated after 2 years of therapy in 87 % of the children. There was a significant improvement in hepatocyte ballooning; 38 % of the vitamin E group had improvement versus 17 % of the control group. There was no significant improvement in steatosis, lobular inflammation, portal inflammation, or fibrosis for children taking vitamin E compared to placebo [35].

Nobili and colleagues studied the effect of vitamin E and vitamin C on serum ALT in 88 children with biopsy-proven NAFLD. Children were randomized to receive a combination of vitamin E 600 IU/day and vitamin C 500 mg/day or placebo for 12 months. Children in both groups were also counseled to follow a balanced, hypocaloric diet. After 12 months of intervention, there was no significant difference in normalization of ALT for children receiving combination of vitamins E and C versus placebo (38 % treatment group vs. 31 % placebo group) [36].

Vajro et al. [37] investigated the effect of vitamin E on decreasing serum ALT in 28 children with suspected NAFLD based upon the combination of serum ALT $>$ 60 U/L and obesity. Children were randomized to receive either vitamin E (400 mg/day for 2 months, then vitamin E 100 mg/day for 3 months) or placebo. After 5 months, there was no significant difference in change in ALT between the vitamin E group and placebo.

In the vitamin E arm of the study by Wang et al. [26], children received 100 mg/day of vitamin E in addition to usual care at home. These children were compared to those receiving usual care only. In children receiving vitamin E, ALT improved significantly more than children receiving usual care, but this was less than the improvement seen for children who participated in the summer camp lifestyle program.

Omega-3 Fatty Acids

Omega-3 fatty acids are polyunsaturated fatty acids that are thought to regulate transcription factors related to hepatic lipid metabolism, leading to increased fatty acid oxidation and down-regulation of pro-inflammatory genes. These include linolenic acid, which is found in plant oils, along with docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), both found in fish oils. Supplementation with omega-3 fatty acids has been investigated as a treatment of NAFLD in children in three studies; two studies used DHA alone, and one used a combination of DHA and EPA.

Nobili et al. [38] investigated the effect of 6 months of DHA supplementation on children with biopsy-proven NAFLD. In this study, 60 children were randomized to take either 250 mg of DHA or 500 mg of DHA or placebo orally once a day. There was no significant change in weight or ALT in any of the groups. The authors reported an improvement in the appearance of the liver by ultrasound for those receiving DHA compared to placebo.

In a second report, Nobili et al. [39] followed the 20 children in the DHA 250 mg/day arm for an additional 12 months. For these children, after a total of 18 months, there was an increase in the mean weight from 57.1 to 59.8 kg and a significant decrease in mean ALT from 65 to 39 U/L. Liver biopsies were performed and improvements in steatosis, lobular inflammation, and ballooning were noted.

Pacifico et al. [40] investigated the effect of 6 months of DHA on liver fat in 58 children with biopsy-proven NAFLD. Participants were randomly assigned to receive either 250 mg/day of DHA or placebo. The primary outcome was change in HFF measured by MRS, which decreased significantly more in the group receiving DHA versus placebo (14.0–6.5 vs 15.5–12.0 %). Serum ALT

also decreased significantly in the DHA group, but this was not different when compared to placebo.

Janczyk et al. [41] investigated the effect of 24 weeks of omega-3 fatty acids on serum ALT in a mixed population of 76 children with either biopsy-proven NAFLD or suspected hepatic steatosis based upon ultrasound. Children were randomized to receive either fish oil containing omega-3 long-chain polyunsaturated fatty acids (LC-PUFA) [DHA and EPA (EPA in a 3:2 proportion 450–1300 mg/day)] or placebo (sunflower oil, containing omega-6 LC-PUFA). The dose of omega-3 fatty acids was determined by baseline weight (<40 kg—450 mg/day, 40–60 kg—900 mg/day, >60 kg—1300 mg/day). In addition, children met with an experienced dietitian in order to promote weight loss of 0.5 kg per week using an individualized diet plan and increased physical activity. Only the omega-3 group had a significant decrease in BMI. There was no significant improvement in ALT with omega-3 fatty acid supplementation.

Probiotics

Disturbance of the gut–liver axis is also believed to play a role in the development of NAFLD through changes such as small intestinal bacterial overgrowth, increased intestinal permeability, and intestinal dysbiosis. The potential for probiotics to correct these abnormalities has led to enthusiasm that probiotics may be beneficial for NAFLD. In children, there have been two such studies, one with Lactobacillus, a single-strain preparation, and the other with VSL#3, a proprietary multi-strain blend.

Vajro et al. [42] studied the effect of 8 weeks of Lactobacillus rhamnosus on 20 obese children with elevated ALT and suspected hepatic steatosis evaluated by ultrasound. The children were randomized to receive 12 billion colony-forming units (CFU) per day of lactobacillus or placebo. Children taking lactobacillus had a significant improvement in serum ALT compared to those who received placebo (70–40 vs 64–61 U/L).

In a study by Alisi et al. [43], 48 obese children with biopsy-proven NAFLD were given 1 sachet per day of VSL#3 or placebo for 4 months. The authors proposed a new ultrasound probability score and report that the score improved in the VSL#3 group compared to the control group. The authors also noted that ALT did not improve with VSL#3 treatment.

Discussion

We performed a review of lifestyle interventions including diet and exercise for children with NAFLD. Because dietary supplements are often included in lifestyle treatment programs, we also reviewed the extant literature of clinical trials utilizing dietary supplements for pediatric NAFLD. Studies of diet alone did not indicate any one dietary approach that was superior to another for the treatment of pediatric NAFLD. Studies of exercise alone were performed in obese children, many of whom did not have NAFLD, but suggested that exercise may improve hepatic steatosis. Studies of the combination of diet and exercise suggested a potential for improvement in serum ALT and/or MRI with intervention. Dietary supplements were reported to have inconsistent effects on NAFLD in children.

Studying treatments for NAFLD in children is complicated by issues related to diagnosis, disease heterogeneity, and appropriate tools for and choice of outcome. One such challenge is knowing if the intervention is being applied to the correct population. An accurate diagnosis of NAFLD requires a combination of clinical history, detailed laboratory investigation, and review of liver histology [44]. Reliance on serum ALT or liver ultrasonography is likely to include children without liver disease as well as children with liver conditions other than NAFLD [8, 9]. Furthermore, NAFLD in children has several histologic subtypes which may represent different underlying pathophysiology and thus even different diseases [45]. Because of such heterogeneity, there also may be differences in response to therapies across the spectrum of NAFLD in children. An additional challenge is the choice of outcome to measure. Studies are more easily done using noninvasive measures, such as ALT or HFF, but it is unclear how well changes in these parameters reflect changes in liver histology. Moreover, the amount of change in any given histologic parameter that is most relevant to improvement in long-term outcomes for children is not known. These challenges have impacted studies of lifestyle intervention and dietary supplements to date and must be addressed in order to further advance the evidence base for the treatment of pediatric NAFLD.

Studies of diet alone in the treatment of pediatric NAFLD have focused on sugar and carbohydrate. The role of fructose in the pathophysiology of NAFLD remains interesting and controversial [46–48]. It is thought that fructose plays a role in de novo lipogenesis, which may be a critical contributor to the development of NAFLD. It is also possible that other monosaccharides and disaccharides play a role in the development of NAFLD when added to the diet. Notably, a low-fat diet was equally effective as a low-glycemic index diet in decreasing hepatic steatosis. In part, the confusion regarding the role of sugars and carbohydrates versus fats is confounded by the role of obesity in pediatric NAFLD. For children who are obese and have NAFLD, weight loss may have a beneficial effect regardless of the diet used. It is unknown to what extent any

specific diet may benefit the liver directly, independent of the effect of body weight. Because substantial weight loss is difficult to achieve, it is important to know whether diet can be useful for treating NAFLD without requiring weight loss. If this were proven to be true, it would reshape clinical goal setting for children with NAFLD. In addition, some children with NAFLD are normal weight, and thus weight loss is not indicated.

Exercise is widely believed to improve NAFLD because a sedentary lifestyle, poor aerobic fitness, and low muscle mass are all risk factors for NAFLD [49–53]. As such, guidelines recommend exercise as a primary form of treatment for NAFLD [5]. However, the guidelines do not provide any specifics for the prescription of exercise. This is because there is insufficient evidence regarding the efficacy of exercise as a treatment for NAFLD. To date, there have been no RCTs of exercise as a treatment for children with NAFLD. Multiple pediatric trials have treated obesity with exercise; however, most of the children in these studies did not have NAFLD. These studies suggest that liver fat can decrease in the context of exercise; however, the effect of exercise on children with NAFLD, who typically have liver fat fractions between 10 and 35 %, cannot be extrapolated from these studies. Moreover, most studies did not evaluate ALT, which is the most common measure in the evaluation and management of NAFLD. Thus, rigorous studies of structured exercise as a treatment for children with biopsy-proven NAFLD should be a high priority.

Recommendations for lifestyle interventions include both dietary and exercise components. Therefore, most studies have included multimodal interventions. Studies of combination lifestyle interventions relevant to pediatric NAFLD have included a total of 832 children of whom 59 % were known or suspected to have NAFLD [22–32]. Moreover, only 65 % of participants completed the recommended interventions. Study duration ranged from 4 to 52 weeks. Some children in these studies had normalization of ALT or MRI hepatic fat fraction. Thus, one can anticipate a decrease in ALT and liver fat if a child receives moderate to intensive counseling and support, follows recommendations, and follows up on a regular basis. However, the nature of differences in inclusion criteria, intervention, duration of treatment, and outcomes measured makes it impossible to generalize about the effect of any specific lifestyle intervention on the liver and liver-related outcomes for pediatric NAFLD.

There is great enthusiasm for the use of dietary supplements as complementary and alternative medicine. Studies in children have shown inconsistent effects of vitamin E, fish oil, and probiotics. Moreover, no supplement has been shown to benefit a majority of children with NAFLD. The effect of vitamin E appears to be limited to improvement in ballooning in a minority of children who take it. Additionally, taking vitamin E supplements has been shown to prevent health-promoting effects of physical exercise [54]. Moreover, in adults who consume treatment doses of vitamin E, there is a potential for increased risk of cardiovascular disease and cancer [55–57]. Thus, the decision to use vitamin E for any individual patient requires a careful risk versus benefit analysis. An important lesson can also be learned from the arc of enthusiasm for fish oil in the prevention of cardiovascular disease in adults. In the USA, over 1 billion dollars is spent on fish oil annually [58]. This is despite high-quality studies disproving any role in the prevention of myocardial infarction or stroke [59, 60]. In addition, studies of fish oil in adults with NASH have been disappointing with one study showing no benefit and a second study shown worsening of insulin resistance [61, 62]. Due to the small numbers of children with NAFLD treated to date and the concerns raised by larger studies in adults, omega-3 fatty acids should still be considered experimental for children with NAFLD. Similarly, due to the increasing data suggesting a role for the microbiome in the development of NAFLD, there is excitement about probiotics as potential therapy for children with NAFLD. Studies to date support a need for additional clinical trials to be done. However, the need for investigational new drug approval by the FDA in order to properly test a probiotic as a therapy for a disease such as NAFLD has been an important stumbling block [63]. Clinicians should insist that studies of dietary supplements follow the same rigor as studies of medications before they recommend them to children with NAFLD.

Children with NAFLD may have a distinct physiology that is different from obesity alone and has the potential to influence lifestyle treatments. The majority of children who are obese do not have NAFLD [1]. Moreover, not all children with NAFLD are obese [1, 64]. When compared to peers matched for age, sex, and BMI, children with NAFLD are much more likely to have insulin resistance, dyslipidemia, and hypertension [65, 66]. After controlling for obesity, these alterations can cause harm in adolescents such that those with NAFLD, and are also more likely to have abnormal cardiac physiology including left ventricular dysfunction compared to adolescents without NAFLD [67–70]. In addition to altered physiology, children with NAFLD are more likely to have impaired quality of life and anxiety than matched peers [71]. Thus, the physiological and psychological status of children with NAFLD may impact the ability to initiate changes and hinder the response to these changes.

In conclusion, there is a lack of randomized controlled trials with evidence that shows that lifestyle interventions or supplements are effective for the treatment of NAFLD, and there is a need for large randomized controlled trials

that investigate specific dietary interventions and exercise regimens with the goal to have specific evidence-based recommendations for the treatment of NAFLD.

Key Messages

- Lifestyle interventions are uniformly recommended for the treatment of NAFLD in children
- The evidence base for any specific dietary and/or exercise intervention in the treatment of NAFLD in children is limited

Future Unmet Needs

- Rigorous studies of lifestyle interventions as a treatment for children with biopsy-proven NAFLD are an urgent need
- Studies are needed to identify the duration, frequency, and intensity of exercise that yields the optimal benefit for children with NAFLD

Implications for the Clinician

- The clinician should work with the child and family to individualize the lifestyle goals taking into consideration the severity of NAFLD, the presence and degree of obesity, and other associated co-morbidities
- Dietary supplements should be considered as experimental with potential risks

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Compliance with ethical standards

Conflict of interest None.

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