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Treatment of Nonalcoholic Fatty Liver Disease in Children: A Systematic Review

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Abstract

Context: Nonalcoholic fatty liver disease (NAFLD) is a chronic liver illness that results from exceeding fat cumulating in the liver. NAFLD can result in progressive fibrosis, which leads to end-stage liver disease. It has rapidly evolved into the most common liver disease seen in the pediatric and adolescent population, being an increasingly common indication for liver transplant even in youths. Best practices in the management of pediatric NAFLD have not been clearly defined.

Objectives: Due to increasing prevalence and the nature of the disease as well as importance of treatment plans and efficacy of each mode of treatment, all studies for pediatric fatty liver disease have been investigated for introducing definite or potential therapies.

Data Sources: This systematic review aimed to include and analyze all studies descry the effectiveness of lifestyle modification, pharmacological, non-pharmacological, and dietary supplement treatments in children suffered from fatty liver, NAFLD, or NASH. The PUBMED/MEDLINE for Controlled Trials, Scopus, and OVID databases were searched for articles published up to and including December 2016.

Study Selection, Data Extraction: All study in the pediatric group with diagnosis of fatty liver spectrum were included in this review. Adult studies were excluded. The results extracted and expanded.

Results: A total of 27 randomized controlled trials were identified after the complete search, deletion of duplicates, removal of irrelevant studies, and final assessment of studies. Treatment plans of interest in these pediatrics articles included: lifestyle modifications, fish oil, and omega-3 fatty acids, including docosahexaenoic acid (DHA), probiotics, vitamin E, metformin, ursodeoxycholic acid, vitamin D, and bariatric surgery.

Conclusions: Lifestyle modification is the only approved treatment modality for which evidence-based studies have documented benefits. Omega-3 fatty acids, particularly DHA, are probably effective. Probiotics likely have therapeutic effects in cases of fatty liver; however, further research is needed. Vitamin E and metformin have equivocal results. Ursodeoxycholic acid is recommended as an adjuvant; however, the data are insufficient for vitamin D. Bariatric surgery is not an acceptable plan in pediatric patients. Research of fatty liver diseases in children in all aspects of treatments is urgently needed.

Keywords: Non-alcoholic Fatty Liver Disease, Pediatrics, Child, Treatment, Life Style Body Modification, Probiotic

1. Context

Nonalcoholic fatty liver disease (NAFLD) is a chronic liver disorder resulting from exceeding fat cumulating in the liver. NAFLD can result in progressive fibrosis that leads to end-stage liver disease. Pediatric NAFLD has become a serious public health issue due to the striking increase in its spread (1).

NAFLD can be histologically divided into nonalcoholic fatty liver, which consists of bland steatosis, and nonalcoholic steatohepatitis (NASH), that is marked by steatosis plus lobular inflammation and hepatocellular damage (Table 1) (2).

The prevalence of NAFLD that can lead to end-stage liver disease is reportedly 3% - 10 % in all children in the US, 2.6% in Japanese children, 3.6% in boys, and 2.8% in girls in Korea with an increased alanine aminotransferase (ALT) level; the overall prevalence adjusted for race, ethnicity, sex, and age is 0.7% - 33% (1, 3).

Best practices in the management of pediatric NAFLD have not been clearly defined. Due to the increasing incidence of pediatric NAFLD and its serious consequences and distribution of treatment data, we performed a comprehensive search and systematic review of published articles of the treatment of pediatric NAFLD exclusively in pediatric group.

Although the causes of NAFLD are unknown, studies

Table 1. Definitions of the Spectrum of Nonalcoholic Fatty Liver

	Definitions
Simple steatosis	At least 5% of liver cells with micro or macrovesicular fatty infiltration
NAFLD	The more benign form of simple steatosis and mild inflammation Or The summarizing term for the entire spectrum of the condition
NASH	"Pediatric type": macrovesicular hepatocellular steatosis with portal inflammation, with or without portal fibrosis, in the absence of ballooning degeneration and perisinusoidal fibrosis; "Adult type": steatosis with ballooning degeneration and lobular inflammation, with or without perisinusoidal fibrosis, and without portal inflammation

have suggested that obesity, dyslipidemia, and insulin resistance are association factors (3-5). Although it can occur in normal-weight children, the prevalence of NAFLD in this group has been increasing in obese children (6). Indeed, genetic, environmental and epigenetic factors may also contribute to its onset and progression to liver disorder (7).

The diagnosis of NAFLD is based on the histological criteria of liver biopsy specimens (2). Liver histology remains the gold standard for distinction and follow-up of NAFLD/NASH, however, commendations of when to apply a liver biopsy are lacking (8).

The following substitute markers are frequently applied to evaluate the grade of steatosis and liver fibrosis and possibility of progression to end-stage liver disease: ultrasonography, magnetic resonance imaging (MRI), liver function tests, and serum markers of liver fibrosis (2). Hepatic fat quantification MRI is a useful tool for monitoring treatment efficacy in pediatric NASH (4).

Limited data suggests that children diagnosed with NAFLD have increased morbidity and mortality rates in adulthood (9). NASH can cause severe complications such as cirrhosis (1). Treatment of NAFLED is a major challenge in this field. From one side, the definite route of confirmation of treatment is liver biopsy. In most cases this invasive procedure dose not done, therefore, the success of treatment is not clear. The actual successful therapy is not also clear, thus, this issue is challenging in liver disease especially in pediatric group.

1.1. Objectives

Due to increasing prevalence and the nature of the disease as well as importance of treatment plans and efficacy of each mode of treatment, we reviewed all studies for pediatric fatty liver disease investigated for introducing definite or potential therapies.

2. Data Sources

We planned to identify all RCTs published to date of the treatment of NAFLD in children exclusively or in children and adults. All studies assessing the efficacy of lifestyle modification and pharmacological, non-pharmacological, and dietary supplement treatment in children who suffered from fatty liver, NAFLD, or NASH were screened in this systematic review. The electronic search strategy used standard filters for the determination of RCTs. The PUBMED/MEDLINE for Controlled Trials, Scopus, and OVID databases were searched for relevant publications up to and including December 2016. We also performed backward citation tracking of the references lists of the original articles to identify additional relevant articles.

Our subject-specific strategy search contained the underneath:

No. 1: (nonalcoholic [All Fields]) and ("fatty liver" [MeSH Terms] or fatty liver [Text Word]) or (steatohepatitis [All Fields]) or (steatosis [All Fields]) and ("liver" [MeSH Terms] or liver [Text Word]) or (NAFLD [All Fields])

AND

No. 2: ("therapy" [Subheading] or ("therapeutics" or "therapeutics" [MeSH Terms] or
treatment [Text Word]) or management [Text Word])

AND

No. 3:" pediatric" [MeSH Terms] or "child" [MeSH Terms] or "children" [Text Word]

In PubMed we searched the keywords "fatty liver", "steatohepatitis", "NASH", "pediatric", "child", "children" "therapy", "therapeutics", "treatment", "management". The keywords were searched in the title and abstracts only. We found 27 items in which one was in the diagnostic plan, one in common with adults, one was a commentary, and one was only explaining the problem in treatment. Therefore, 23 articles were suitable for our study. This protocol was done for other data sources as well.

3. Study Selection

The eligibility criterion was the inclusion of pediatric patients. For trials including both children and adults, if the data were reported separately for children, we extracted them for the analysis. Every possible related articles were saved, and the full text of these surveys was assayed to define which trials satisfied the inclusion criteria. Studies that included both adults and children and did not report data separately were excluded. Non-English articles were evaluated for abstract and if there was an English abstract, data extracted from the abstract. There was no limitation for publication date and all studies up to

2017 were selected for analysis. The primary outcome measures for the included trials were different in conclusions and the criteria for evaluation of response in trials was based on changes in serum ALT and/or aspartate aminotransferase (AST) levels and/or histological conversions in a liver biopsy sample.

The risk of bias is present due to omitting some research in this field. Although in each step we repeated the strategy and it seems most of the study was collected by this method, we did not search in progress article and some loss of recent article is probable.

4. Data Extraction

The authors studied the titles and abstracts identified in the searches. We got the full texts of every possible related articles and then selected the trials that were compatible with our inclusion criteria. We excluded adult trials, and combined adult and pediatrics. Variables selected included diagnostic criteria for pediatric NAFLD (histologic or non-histologic), treatment modality had been done for pediatric (pharmacologic, non-pharmacologic), and criteria for treatment or disease improvement (histologic or non-histologic).

Risk of study bias: As we described in the diagnosis section, a major limitation in diagnosing fatty liver is the invasive nature of liver biopsy. Most studies of this issue complained of a lack of diagnostic certainty and treatment response. Unfortunately, there is no comparable substitute for liver biopsy.

The summary of data selection described in the PRISMA chart (Figure 1) and Table 2 demonstrate the results of pediatric NAFLD treatment.

5. Results

Indecision exists regarding the best treatment of NAFLD/NASH, particularly in pediatric populations, for which the number of RCTs published to date is confined. The limitation in some trials was the absence of a biopsy sample. The invasive nature of this procedure made it unacceptable to parents and physicians.

We found 81 publications in sources based on our search strategy with deleting duplications. Again, after review of references in each study, we added 17 articles that were not present in our data. Some studies did not differentiated adults and children; therefore, they were excluded from the data. At last, all studies were evaluated and analyzed for results. Some studies have questions due to no definitive biopsy approved diagnosis. We included this search for explaining probable scope in this field.

Table 2. Treatment Plan and Recommendation in Pediatric NAFLED

Treatment Plan	Mode of Interaction	Effect	References
Lifestyle modifications	weight loss, Physical activity, diet	Positive, strongly recommended	(3, 10-14)
Omega-3 fatty acid	Fish oil	Potentially effective, recommended	(5, 7, 15-17)
DHA	250 mg and 500 mg-daily	effective, recommended	(7, 18-20)
Vitamin E	400 to 1200 IU per day	Conflicting results, not effective as adjuvant	(21, 22)
Metformin	500 to 1500 mg per day	Equivocal results, further study in TONIC trial upcoming	(21, 23-25)
Vitamin D	Concomitant use with DHA	Trials not enough,	(7)
Ursodeoxycholic acid	10–12.5 mg/kg/day	Effective as adjuvant, recommended	(13, 26)
Probiotics	lactobacillus GG, VSL#3	Promising results, recommendable, further trials needed	(27, 28)
Bariatric Surgery	laparoscopic banding	Routinely not operable and recommended in children	36

6. Discussion

The most common current treatment plans based on the strong evidence were as follows:

1 - Lifestyle modifications

Recently, because of changing in lifestyle and dietary habits, the incidence of fatty liver disorder has increased. Alteration in Lifestyle, the mainstay of treatment for NAFLD, have been shown to improve liver histology and associated markers (29).

Three basic principles of lifestyle modifications include weight loss, physical activity, and diet. Diet and exercise are commonly recommended to treat obese youth with NAFLD since it does not include unfavorable side effects and confers multiple cardiometabolic profits. Proper dietetic measures consist of reductions in fructose, sucrose, total fat, cholesterol, and Trans fat.

One study of weight-reducing diets found that glycemic load or dietary fat restriction modified hepatic steatosis in 6 months. An experimental low-glycemic-load or conventional low-fat diet was introduced to children for 6 months (10).

Lifestyle intervention is the only established therapy

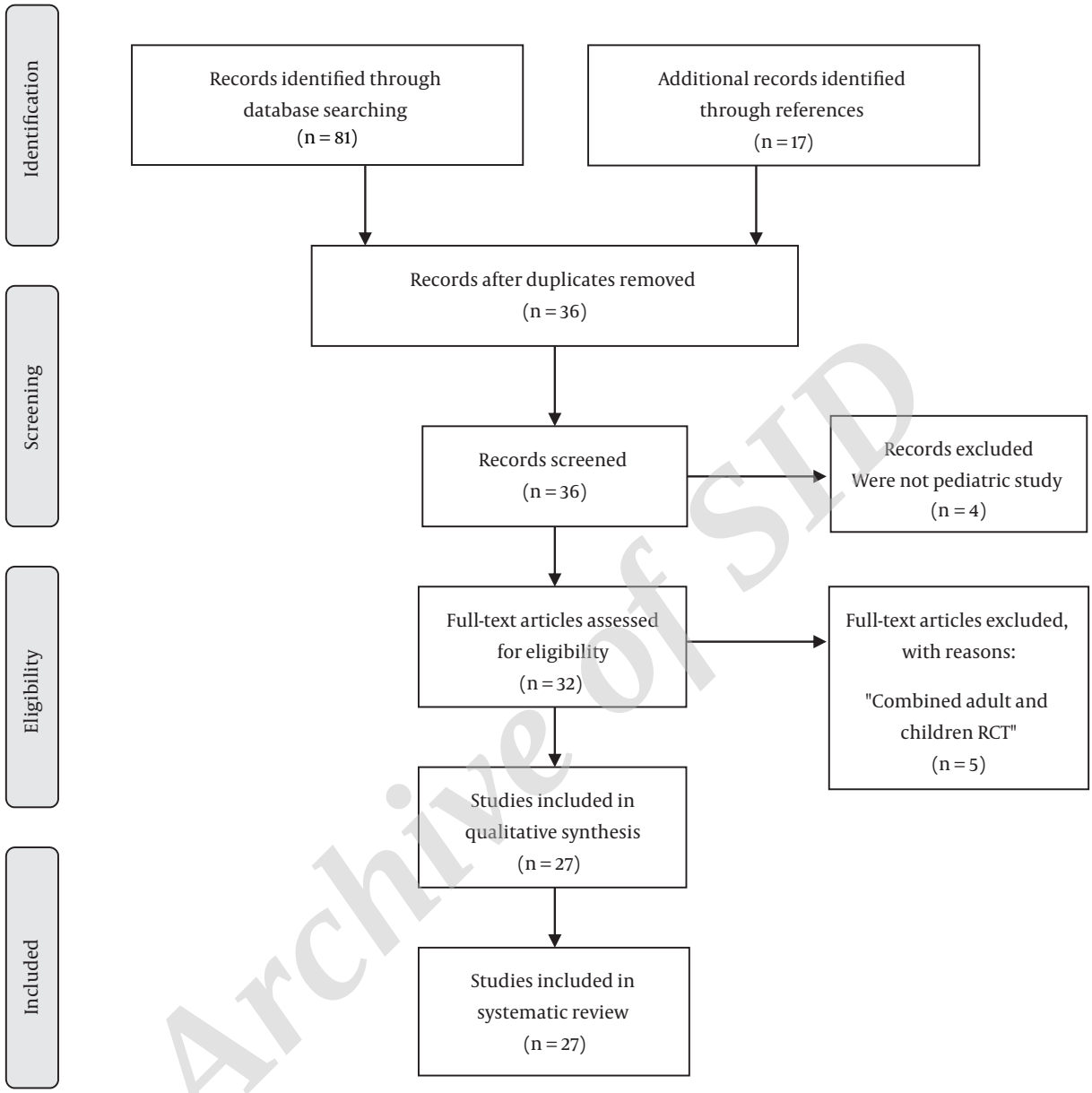

Figure 1. PRISMA Flow Diagram of Study Selection for Treatment of NAFLED in Children

for NAFLD. The best treatment plan and predictors of response to this program have not been established in pediatric group. A prospective research of 51 severely obese non-diabetic children with liver steatosis suggested that inpatient compared with outpatient intensive treatment did not increase treatment outcome (11).

Another study of lifestyle intervention combined with antioxidant therapy suggested that lifestyle intervention with increased physical activity and diet was associated with a meaningful improvement in histology of liver and abnormalities in laboratory in pediatric NAFLD. Ascorbic acid and α-tocopherol did not seem to increase the efficacy of lifestyle intervention (12).

In a different double-blind placebo study, lifestyle intervention with diet and physical exercise in children with obesity and NAFLD have induced weight loss and significant improvement in liver function, however, Vitamin E did not increase the efficacy of lifestyle intervention. The

diagnosis of fatty liver was based on liver function tests and ultrasonography findings (3).

Composition of 50% carbohydrates, 30% fat, and 20% protein in accordance with the American Heart Association diet was recommended. All obese patients were advised by restricting the daily caloric intake to 25 - 30 kcal/kg/day to lose weight. The lifestyle changes program consisted of 1 hour of exercise 3 times per week and the promotion of physical activities (5).

A body mass index (BMI) reduction combined with vitamin E and ursodeoxycholic acid (UDCA) showed a significantly higher rate of improvement in a clinical profiles study of 29 children and demonstrated that the first-line therapy should consist of BMI reduction (1).

Common recommendations for children are 30 - 60 minutes daily aerobic physical exercise at moderate to strong intensity in conjunction with age-appropriate muscle- and bone-strengthening for at least 3 days a week. However, rapid weight loss can lead to the onset of severe metabolic disease and promote further liver injury (13, 14).

2- Fish oil and Omega-3 fatty acid.

Very long-chain omega-3 or n-3 fatty acids are present in seafood, especially fatty fish, shellfish, and in nutritional complements (30).

Several studies have shown a benefit of omega-3 fatty acid treatment on lipid profile, insulin-sensitivity, and hepatic steatosis; it has also been suggested that Vitamin D treatment has potential antifibrotic properties in liver disease (7).

Long-term use of n-3 polyunsaturated fatty acids (PUFA) was evaluated in combination with the lifestyle for the treatment of NAFLD in children. The researcher concluded that this product is confident and effective in overweight children with NAFLD and can modify sonographic findings as well as liver enzyme levels (5).

Contrary to the mentioned study, in another research, Omega-3 fatty acid prescription has not effect in decreasing ALT levels and it did not affect the sonographic parameters of steatosis, however, it improved aspartate aminotransferase and gamma-glutamyl transpeptidase in patients with NAFLD as compared to the placebo. The limitation of this study was the exact confirmation of NAFLD, which was based on elevated alanine aminotransferase to more than 30% of the upper limit of normal and increased hepatic echogenicity on imaging such as sonography (31).

One study has assessed the relation of Fish and omega-3 fatty acid consumption, which concluded that Fish and omega-3 fatty acid intake was insufficient in children with NAFLD, which may increase susceptibility to hepatic inflammation. They suggested that children with NAFLD should be reinforced to use the planned amount of fish during weekdays (15).

In total, 4 studies with 263 subjects were identified. PUFA supplementation was associated with significantly improved hepatic steatosis grade on ultrasound and could decrease AST levels after 6 months, however, only reduce ALT levels after 12 months. In Conclusion, n-3 PUFA supplementation can improve liver steatosis and liver functions, and it is a potential food supplementation to treat NAFLD in children (16).

3- Docosahexaenoic acid (DHA).

Dietary N-3 LCPUFA have effects in decreasing serum lipids and have anti-inflammatory and insulin-sensitizing qualities, which can describe their effectiveness in decreasing hepatic steatosis (17).

In obese children with biopsy-proven NAFLD and vitamin D deficiency, DHA plus vitamin D treatment improved insulin-resistance, lipid profile, ALT, and NAS (NAFLD Activity Score) (7).

For studying the consequent of docosahexaenoic acid (DHA) use, the principle nutritive long-chain polyunsaturated fatty acids, in pediatric NAFLD, 20 pediatric patients with approved NAFLD were studied. Improvement of histopathological parameters and reduction of hepatic progenitor cell activation were seen. Based on these DHA, it could regulate activation of progenitor cell, hepatocyte survival and macrophage polarization, which showed a new and different crucial role in the regulation of the cell-to-cell cross-talk that drives inflammatory response (32).

Nobili et al. studied the effect of dietary supplementation with docosahexaenoic acid (DHA) on decreasing liver fat quantity in pediatric patient with NAFLD, that shows reduced liver fat content in NAFLD. There was no difference between doses of 250 or 500 mg per day of DHA and both dosing seems to be equally effective in reducing liver steatosis (18).

In addition, Nobili also tested consequence of supplementation with docosahexaenoic acid on hepatic steatosis and liver tests in children with NAFLD. DHA in both doses (250 or 500 mg) was found to reduce liver fat and insulin resistance; however, no effect was seen on ALT or body weight (19).

4- Vitamin E

The beneficial outcome of Vitamin E in patients with fatty liver has been assigned to its antioxidant function. Oxidative stress has a critical role in NAFLD pathogenesis.

There were contradictory data on the therapeutic value of vitamin E in 5 randomized trials. Neither vitamin E nor metformin were more effective than placebo in achieving the primary outcome of persistent reduction in ALT level in children with NAFLD (20).

In an Open-label pilot study, daily vitamin E supplementation stabilized serum aminotransferase and alkaline phosphatase in patients with NASH. They suggest

that overweight children with NASH should be enforced to decrease their weight with a comprehensive weight reduction plan and encouraged to supplemental alfa-tocopherol. In this study, diagnosis was based on excluding other disease and Liver biopsy was not performed (21).

Trials, have not demonstrated significant effects of adjuvant vitamin E over the placebo in decreasing serum ALT. Information regarding the long term results of adjuvant vitamin E on histological progress in children with NAFLD are still insufficient.

5- Metformin

Children with NASH are insulin-resistant and metformin is a possible treatment. A pilot metformin with a dose of 500 mg twice daily for 24 weeks was prescribed to children with documented non-alcoholic steatohepatitis who were non-diabetic. In this group, the Mean alanine aminotransferase and aspartate aminotransferase (AST) improved significantly ($P < 0.01$). ALT and AST normalized in 40% and 50% of subjects, respectively. The children then showed a dramatic decrease in hepatic steatosis defined with magnetic resonance spectroscopy (22).

Nobili et al. planned a study to define the effect of metformin plus lifestyle intervention and alteration in pediatric NAFLD. In conclusion, they showed that metformin did not appear more effective than lifestyle intervention in improving aminotransferases level, steatosis, and liver histology in pediatric NAFLD (23).

To evaluate if metformin or vitamin E are effective in pediatric NAFLD, the nonalcoholic steatohepatitis clinical research network (NASH CRN) constructed a multicenter, double-blind, double-dummy, placebo-controlled study entitled "Treatment of NAFLD in Children: (TONIC)". TONIC is managed by the 10 children Clinical Centers and a central Data Coordinating Center of the NASH (24).

In this report of TONIC trial, neither vitamin E nor metformin was superior to placebo in decreasing ALT level, which is the primary outcome and aim of sustained improvement in children with NAFLD (20).

6- Vitamin D

There is no relation between vitamin D deficiency and the severity of steatosis on the biopsy (25).

One trial had been done for the effect of Vitamin D combined with DHA and the results showed that an improvement in insulin-resistance, lipid profile, ALT, and NAS (NAFLD Activity Score) (7).

7- Ursodeoxycholic acid

Treatment with vitamin E and UDCA in combination with body mass index (BMI) reduction was displayed and significantly higher rate of improvement in clinical presentations as well as Children who's BMI were successfully reduced showed favorable clinical improvements without any medication. The authors recommended that the primary recommendation should be the BMI reduction, however pharmacological treatment plus BMI reduction could have a more therapeutic effect in this children with NAFLD. Although Urso administration without BMI reduction did not demonstrate any improvement in disease process (1).

Another trial in children confirmed no efficacy of UDCA. The UDCA without lifestyle intervention group showed no major improvement in liver aminotransferase or echogenicity, while the group had received both interventions showed definite improvement in ALT and liver ultrasound findings.

8- Probiotics

Despite the scarcity of trials, probiotics have evolved as a possible role in the treatment of adult and pediatric non-alcoholic fatty liver disease (26, 33).

Only 2 studies in children have examined this issue.

In an RCT performed by Vajro et al. on obese children treated with Lactobacillus GG for 8 weeks, a significant decrease in ALT was reported (34). In RCT of VSL#3, "a mixture of eight probiotic strains" compare to placebo in overweight children with biopsy-proven NAFLD, administration of VSL#3 for 4 months significantly improves NAFLD in children (27).

In fact, priority for further RCTs is necessary, the data from the current searches proposed that enteric floral changes might have effects as a therapeutic plan to control obesity-related hepatic dysfunction.

9- Bariatric Surgery

Children with the diagnosis of fatty liver are younger and have lower levels of obesity compared to adolescents that undergo bariatric surgery, therefore, trials in pediatric groups rarely allowed performing.

A trial showed improvement in serum aminotransferases, fasting insulin, HbA1c, and lipids (28). These promising results warranted further research and confirmation of bariatric surgery benefits in pediatric NAFLED.

10- Unproven or undone medication in pediatrics:

There was another list of medications or modalities.S ome are beneficial in adults, however, any recommendation in children needs to be documented trials in future. This group comprised of: orlistat, Pioglitazone, Cysteamine bitartrate, Pentoxifylline [a phosphodiesterase inhibitor that antagonizes effects of TNF-a], and obeticholic acid [Farnesoid X receptor agonists].

Studies in this area are not numerous in children. Even a definitive diagnostic method is also controversial. Therefore, weaknesses of done works are different routes for diagnosis, which some of them are not decisive. After completing the trials, there are yet again complaints in confirming of improvement. The mentioned note can affect the outcome and resulting.

7. Conclusions

Based on limited trials in this issue, some of the different treatment plans were effective. Some treatment protocols, although not definitely approved, are recommendable. Lifestyle modification is the only treatment modality for which evidence-based studies have documented its benefits in the treatment of pediatric fatty liver. Omega-3 fatty acids, especially DHA, are probably effective and recommendable due to their benefits for cardiovascular disease and other useful aspects. Probiotics have therapeutic effects in fatty livers, Vitamin E and metformin have shown equivocal results but further research is needed. UDCA is recommended as an adjuvant, however, sufficient evidence is lacking for vitamin D. Bariatric surgery is not an acceptable plan in pediatric and adolescent patients.

In other words, further research in all aspects of pediatric fatty liver disease treatments is urgently needed.

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