Omega-3 for nonalcoholic fatty liver disease in children

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Abstract

Question An overweight 12-year-old male patient with nonalcoholic fatty liver disease has had little improvement in liver steatosis or triglyceride levels over the past 2 years. Is omega-3 supplementation useful in managing his condition?

Answer Nonalcoholic fatty liver disease in children is prevalent in the Canadian population and can lead to liver fibrosis, cirrhosis, transplant, and reduced life expectancy. There is no recommended pharmacologic treatment of nonalcoholic fatty liver disease. Omega-3 fatty acids are associated with small improvements in liver steatosis and triglyceride concentrations. There are conflicting results with regard to liver function test results and insulin resistance, and while there might be histologic improvement revealed on biopsy, there is little evidence that fibrosis is improved. In children who have struggled to be consistent with the changes needed in their diet, particularly those with elevated triglyceride levels, there might be a role for omega-3 supplementation while continuing to focus on the mainstays of treatment (diet and physical activity); however, further research is still needed.

Les oméga-3 pour la stéatose hépatique non alcoolique chez l'enfant

Résumé

Question Chez un garçon obèse de 12 ans atteint de la maladie du foie gras non alcoolique, peu d'améliorations ont été observées dans sa stéatose hépatique ou dans ses taux de triglycérides au cours des 2 dernières années. Un supplément d'oméga-3 serait-il utile dans la prise en charge de son problème?

Réponse La stéatose hépatique non alcoolique chez les enfants est répandue dans la population canadienne. Elle peut entraîner une fibrose, une cirrhose et une greffe du foie, de même que réduire l'espérance de vie. Aucune pharmacothérapie n'est recommandée pour le traitement de la maladie du foie gras non alcoolique. Les acides gras oméga-3 sont associés à de légères améliorations dans la stéatose hépatique et les concentrations de triglycérides. Les résultats sont contradictoires en ce qui concerne les tests de la fonction hépatique et de la résistance à l'insuline et, si des améliorations histologiques peuvent être constatées à la suite d'une biopsie, il y a peu de données prouvant que la fibrose est améliorée. Chez les enfants qui ont éprouvé des difficultés à maintenir les changements nécessaires à leur alimentation, en particulier ceux dont les niveaux de triglycérides sont élevés, un supplément d'oméga-3 pourrait être utile, tout en continuant à se concentrer sur les éléments principaux du traitement (régime et activité physique); par ailleurs, des recherches plus approfondies sont encore nécessaires.

Nonalcoholic fatty liver disease (NAFLD) has become a leading cause of liver disease in children and is related to the overweight and obesity epidemic.[1] Defined as hepatic fat seen in excess of 5% of hepatocytes in the absence of alcohol use and viral-, autoimmune-, and drug-induced liver disease,[2] it ranges in severity from fat infiltration and accumulation in the liver (steatosis), to nonalcoholic steatohepatitis, characterized by inflammation and risk of progression to fibrosis, cirrhosis, or hepatocellular carcinoma.[1,2] The pathogenesis of NAFLD is multifactorial, but hepatic steatosis ultimately develops from an imbalance between processes that increase intrahepatic fat content (eg, hepatic uptake of lipids from the diet or peripheral adipose tissue in the context of insulin resistance; de novo lipogenesis) and those that reduce it (eg, oxidation of fatty acids; synthesis and export of very low–density lipoproteins).

Nonalcoholic fatty liver disease is considered by some to be the hepatic manifestation of metabolic syndrome (a cluster of obesity, hypertension, hyperglycemia, hypertriglyceridemia, and dyslipidemia), as it often coexists with these comorbidities.[1,3] Pediatric NAFLD histologic features differ compared with adults and has milder lobular inflammation, ballooning, and perisinusoidal fibrosis but more severe steatosis, portal inflammation,[4] and possibly portal fibrosis.[5] While adult NAFLD has been thought to have little effect on mortality,[6] children might face faster progression,[7] as a retrospective study reported a standardized mortality ratio of 13.6 over a mean follow-up of 6.4 years.[8] Children with NAFLD are commonly asymptomatic even

while dealing with associated comorbidities such as liver damage, insulin resistance, and type 2 diabetes mellitus.[9]

Patients with NAFLD might complain of nonspecific symptoms such as fatigue, malaise, or abdominal pain, and examination might reveal acanthosis nigricans and increased waist circumference.[1,10] While serum testing, ultrasound, and magnetic resonance imaging have been used to identify the presence of NAFLD, they are characterized by poor sensitivity (serum testing and ultrasound)[10,11] or require further research in pediatric NAFLD.[12] Liver biopsy remains the criterion standard for diagnosis.[10]

Epidemiology of NAFLD

The prevalence of NAFLD was found to be 9.6% in normal-weight children, based on 742 pediatric autopsies from the United States between 1993 and 2003.[13] A 2015 meta-analysis of 74 studies and nearly 47 000 children reported a prevalence of 7.6% in the general pediatric population and 34.2% in children managed clinically for obesity.[14] In Canada, NAFLD is prevalent in children; in one study 15% of previously healthy children undergoing abdominal computed tomography scans posttrauma were found to have hepatic steatosis.[15]

Management

The most effective intervention for NAFLD management is weight reduction through dietary and physical activity modifications.[9] Nutritional interventions commonly include reduction in total energy (portion control), fat, and fructose intake, as well as dietitian support and adoption of the American Heart Association diet strategies.[16] One study reported that after 1 year of lifestyle modifications, half of the 66 children aged 3.2 to 19.6 years had a weight loss of greater than 10%, and 86% of them demonstrated improvements in or normalization of aminotransferase levels.[8] While lifestyle interventions are successful, they are challenging to sustain. The same study revealed that 76% of children regained weight and 46% had aminotransferase levels return to baseline after a mean of 6.4 years.[8]

Currently, no pharmacotherapy is indicated for the treatment of pediatric NAFLD, but some practitioners recommend pharmacotherapy for children presenting with a more aggressive clinical course (eg, steatohepatitis and fibrosis). Vitamin E has been shown to ameliorate liver histology findings in children[17] yet is not superior to placebo in reducing serum alanine aminotransferase (ALT) levels,[18] and concerns regarding long-term safety have limited its use in practice.[19] Other medications such as insulin sensitizers,[20] statins,[21] and supplements (eg, ursodeoxycholic acid, vitamin D, probiotics)[9] have been shown to be ineffective or have been inadequately studied to support evidence-based use.[12] Use of omega-3 supplementation for the treatment of pediatric NAFLD has also been investigated.

Rationale for using omega-3 fatty acids in NAFLD

Omega-3 fatty acids can reduce hepatic de novo lipogenesis and increase fatty acid beta-oxidation, both of which improve hepatic steatosis and inflammation.[1] Additionally, they can suppress production and increase export of very low–density lipoproteins thereby reducing hepatic triglyceride levels.[22] Patients with metabolic diseases also see improvement in insulin sensitivity with omega-3 supplementation,[23] which is beneficial as most hepatic fat in patients with NAFLD originates from adipose tissue.[24] Beyond their effect on hepatic steatosis, omega-3 fatty acids have anti-inflammatory potential through effects on cell membranes and at the level of genetic transcription.[1]

A 2007 position paper from the Dietitians of Canada and the American Dietetic Association emphasized the importance of omega-3 polyunsaturated fatty acid consumption and recommended 2 servings of fish per week (approximately 500 mg/d of the omega-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid [DHA]) for healthy individuals 2 years of age and older.[25] Interestingly, a cross-sectional analysis of 223 patients recruited from the NonAlcoholic Steatohepatitis Clinical Research Network sites across the United States reported that children with NAFLD consumed only 10% of the recommended amount of fish and only 5% of the recommended omega-3 intake.[26] This suggests that omega-3 supplementation might have a beneficial effect on patients with NAFLD.

Omega-3 fatty acids to treat steatosis

A meta-analysis of 4 randomized controlled pediatric studies showed improvement in liver steatosis with the use of omega-3 fatty acids.[27] **Table 1**[28-31] presents details of these studies. Nobili et al[32] reported that a greater number of patients improved from having severe steatosis to less severe steatosis with DHA supplementation. The reduction in severe steatosis persisted at 12, 18, and 24 months of consumption, and fewer patients progressed to more severe steatosis.[28] A similar study from Turkey[29] found that a greater number of children showed improvement of steatosis with omega-3 supplementation than with placebo (68% vs 40%, respectively). One study used magnetic resonance imaging–derived proton density fat fraction to document a reduction in steatosis.[30] The hepatic fat fraction decrease after 6 months was nearly double in the DHA group compared with the placebo group (53% vs 23%, respectively; $P=.04$). Also, there was a significant reduction in visceral adipose tissue and in epicardial adipose tissue demonstrated in the DHA group (7.8% and 14.2%, respectively) compared with the placebo group (2.2% and 1.7%, respectively) ($P=.01$ for both comparisons), which might indicate an improvement in overall metabolic risk.[30] In contrast, a multicentre trial from Poland found no reduction in steatosis with omega-3 supplementation compared

Table 1. Studies assessing the effect of omega-3 supplementation on hepatic steatosis

STUDY	COUNTRY	POPULATION	STUDY DESIGN	METHODOLOGY USED TO ASSESS NAFLD	OUTCOME
Nobili et al,[28] 2013	Italy	60 children with NAFLD confirmed on biopsy	Received 250 or 500 mg of DHA vs placebo for 24 mo	Ultrasonography	Lower odds of severe hepatic steatosis
Boyraz et al,[29] 2015	Turkey	108 obese children with steatosis revealed on ultrasound and with elevated transaminase levels	Received 1000 mg of PUFA (combination of 380 mg of EPA and 200 mg of DHA) per d vs placebo for 12 mo	Ultrasonography	68% vs 40% had improvement in steatosis in the PUFA and placebo groups, respectively
Pacifico et al,[30] 2015	Italy	51 overweight or obese children with NAFLD confirmed on biopsy	Received 250 mg of DHA vs placebo for 6 mo	MRI-PDFF	53% vs 23% had a reduction in fat fraction in the DHA and placebo groups, respectively
Janczyk et al,[31] 2015	Poland	64 overweight or obese children with steatosis revealed on ultrasound and with elevated transaminase levels	Received 450-1300 mg of omega-3 fatty acids (combination of 177.5-532.5 mg of EPA and 267-800 mg of DHA) vs placebo for 6 mo	Ultrasonography	No differences between the groups

DHA—docosahexaenoic acid, EPA—eicosapentaenoic acid, MRI-PDFF—magnetic resonance imaging–derived proton density fat fraction, NAFLD—nonalcoholic fatty liver disease, PUFA—polyunsaturated fatty acid.

with placebo.[31] This was the only study to give DHA in a weight-dependent manner and it found that a similar number of participants were present in each steatosis grade regardless of group. This result is consistent with the study on fish and omega-3 intake in NAFLD, which reported no decreases of steatosis with higher-dose intake.[26]

Histologic changes with omega-3 fatty acids

Nobili et al performed a study assessing the effect of long-term (18 months) DHA supplementation on histologic outcomes of 20 patients with biopsy-confirmed NAFLD; DHA use was associated with significant reductions in NAFLD activity scores (NAS) ($P<.001$), steatosis ($P<.001$), ballooning ($P<.001$), and lobular inflammation ($P<.05$) from baseline.[33] A subsequent randomized controlled study of children with biopsy-proven NAFLD and vitamin D deficiency assessed the effect of 24 months of DHA (500 mg) and vitamin D (800 IU) supplementation on liver histology findings; only those patients receiving treatment had repeat liver biopsies at the end of the study (n=18).[34] Treatment was associated with a decrease in NAS, steatosis, ballooning, and lobular and portal inflammation. Similar to the previous study, treatment did not lead to significant changes in fibrosis.

Indirect evidence of the effect of omega-3 fatty acids on histology findings has previously been provided by studies examining consumption of a Mediterranean diet (rich in omega-3) or a diet rich in fish. The Mediterranean Diet Quality Index for Children and Adolescents was used to measure adherence in 243 patients and the authors found that higher adherence was associated with lower NAS, grade 2 fibrosis, insulin resistance, and C-reactive protein levels.[35] Notably, all children diagnosed with nonalcoholic steatohepatitis had low adherence.[35] Likewise, St-Jules et al[26] reported that higher fish intake was protective against portal inflammation and was associated with a protective trend against lobular inflammation.

Triglyceride levels and insulin resistance

Fish oil (omega-3 source) is a first-line treatment of choice for adult patients with hypertriglyceridemia.[36] In patients with NAFLD, omega-3 use lowers serum triglyceride levels.[11] Compared with placebo, supplementation with 250 mg or 500 mg DHA for 6 months was associated with a statistically significant decrease in triglyceride levels.[32] While the treatment group had consistently lower levels than the placebo group for 24 months, triglyceride levels increased over time. Two other studies found similar reductions in triglyceride levels at 6 months (17 mg/dL reduction vs 10 mg/dL reduction; $P=.041$) with 250 mg of DHA[30] and at 12 months (53.3 mg/dL vs 65.8 mg/dL) with 1000 mg of polyunsaturated fatty acid.[29] One study reported no significant difference in triglyceride levels.[31]

The literature to date suggests that there might be a benefit to using omega-3 fatty acids in patients with insulin resistance owing to the effects on fatty acid storage and hepatic lipogenic synthesis; however, this needs to be investigated further.[1] Nobili et al[32] showed an improvement in the insulin sensitivity index (improved insulin sensitivity) with 250 and 500 mg of DHA supplementation compared with placebo. In a follow-up study, the same group measured

homeostasis model assessment–insulin resistance (HOMA-IR) and found that levels were statistically significantly reduced at 6 and 12 months compared with placebo, and that levels were also reduced, but not significantly different, at 18 and 24 months; HOMA-IR levels were reduced with only the 250-mg dose of DHA and not the 500-mg dose of DHA in long-term treatment.[28] Boyraz et al[29] also found a greater improvement in HOMA-IR levels following 12 months of 1000 mg of polyunsaturated fatty acid supplementation compared with placebo. Two studies showed no difference after 6 months and found similar HOMA-IR levels in the omega-3 and placebo groups; however, one of these studies did report statistically significantly lower fasting insulin levels.[30,31] These differences in results could be due to the weight-dependent dosing in one study or regional differences in diet and activity (Italy, Poland, Turkey).

Omega-3 fatty acids and liver injury

While many studies include changes to serum liver enzyme levels as outcome measures, only the meta-analysis by Chen et al showed a statistically significant effect of omega-3 fatty acids in reducing ALT.[27] While ALT has been used as an outcome measure in studies investigating omega-3 supplementation in NAFLD, it does not adequately reflect disease severity[37] and for this reason the results should be interpreted with caution. Even patients with normal or low (<2 times upper limits of normal) ALT levels can have serious histologic findings and fibrosis, further underscoring the limitations of this biomarker as an indicator of liver disease severity.[38] Two studies did find statistically significant differences in aspartate aminotransferase and γ-glutamyl transpeptidase levels,[29,31] but these results have similar shortcomings.

Challenges in studying omega-3 fatty acids

Frequently, patients in the randomized controlled trials investigating omega-3 fatty acids underwent dietary and lifestyle changes, which are known to lead to weight loss and improvement in steatosis, serum aminotransferases, insulin resistance, and triglyceride levels, limiting the interpretation of omega-3 effect.[39] Furthermore, dietary consumption of fish and other sources of omega-3 were not recorded in those trials. Other limiting factors are the differing dosages given, ethnicity of participants, exclusion criteria, and sensitivity of ultrasound testing, which is considered more accurate when hepatic fat is more than 33%[40] and could underestimate the presence of steatosis when less than 20% hepatic fat is present.[41]

Conclusion

Omega-3 supplementation is associated with a small benefit for children with NAFLD based on surrogate markers such as steatosis, liver function test results, triglyceride levels, and insulin resistance, and its exact effect on clinical outcomes or long-term survival is difficult to determine with currently available data. Improvements in steatosis and triglyceride concentrations seem likely when omega-3 supplements are used in addition to appropriate lifestyle changes. Liver enzyme and insulin resistance changes are uncertain owing to the heterogeneity of results. Some evidence suggests that histologic changes might occur, but that fibrosis is not likely to be reduced. The latter might be challenging to assess owing to the natural history of fibrosis in the context of NAFLD, which is typically slow to progress and challenging to determine in short-term studies. In children who have struggled to be consistent with recommended dietary change, there is perhaps a role for omega-3 fatty acids. Continued focus on diet and lifestyle changes should remain the mainstay of treatment with a focus on long-term adherence.

Competing interests
None declared

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