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MINIREVIEWS

Obese children with fatty liver: Between reality and disease mongering

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Abstract

Following the current epidemic of obesity, the worldwide prevalence of nonalcoholic fatty liver disease (NAFLD) has increased with potential serious health implications. While it is established that in adults NAFLD can progress to end-stage liver disease in many cases, the risk of progression during childhood is less well defined. Since most obese children are not adherent to lifestyle modifications and hypocaloric diets, there is a growing number of studies on pharmacological interventions with the risk of disease mongering, the practice of widening the boundaries of illness in order to expand the markets for treatment. Here, we propose a critical appraisal of the best available evidence about long-term course of pediatric NAFLD and efficacy of treatments other than hypocaloric diet and physical exercise. As a result, the number of NAFLD children with a poor outcome is small in spite of the alarming tones used in some papers; large-scale longitudinal studies with long-term follow-up of pediatric NAFLD patients are lacking; the studies on ancillary pharmacological interventions have been performed in few patients with inconclusive and conflicting results.

Key words: Obesity; Children; Non alcoholic fatty liver disease; Non alcoholic steatohepatitis; Cirrhosis; Liver transplant; Disease mongering

Core tip: The number of obese children with nonalcoholic fatty liver with a documented poor outcome is small in spite of the alarming tones used in some papers. The available studies are insufficient to determine whether or not children with nonalcoholic fatty liver have an elevated risk of developing detrimental health conditions. Large-scale longitudinal studies with long-term follow-up of children with nonalcoholic fatty liver are desirable. Since most obese children are not adherent to lifestyle modifications and hypocaloric diets, there is a growing number of studies on pharmacological interventions with the risk of disease mongering, the practice of widening the

boundaries of illness in order to expand the markets for treatment. The studies on ancillary pharmacological interventions, in addition to diet and exercise, have been performed in few children with inconclusive and conflicting results. The proposal to the obese patient of an ancillary drug may divert his attention from the diet and exercise.

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INTRODUCTION

Childhood obesity can adversely affect nearly every organ system with increased mortality in adult life from a wide variety of systemic diseases[1]. Following the current epidemic of obesity, the worldwide prevalence of nonalcoholic fatty liver disease (NAFLD) has doubled during the last 20 years with consequent potential serious health implications[2].

In adults NAFLD has been reported to progress to fibrosis and end-stage liver disease in some 15%-20% of cases, sometimes with need of liver transplantation[1,3]. Data on fibrosis, evolution to cirrhosis and/or liver cancer in large cohorts of children with NAFLD followed up long-term are scarce[1]. Despite this lack of information, there is a widespread tendency to draw alarming scenarios also for childhood NAFLD[4-6], bordering on the phenomenon of so called "disease mongering", *i.e.* the practice of widening the diagnostic boundaries of illnesses and aggressively promoting their public awareness in order to expand the markets for treatment[7-9]. This concept is strictly related to medicalization, which implies an extension of medicine domain on three possible ways: qualitative (disease or not disease), quantitative (lowering threshold), temporal (antedating a diagnosis)[7-9]. It has been reported that the phenomenon of disease mongering is supported by informal alliances comprising drug company staff, physicians and consumer groups, which tend to promote a view of their particular condition as widespread, serious, and treatable[8]. In many cases these alliances are not maliciously preconceived and simply reflect the fear towards some conditions deemed dangerous to health[10]. Given the severe well-documented impact of obesity on health, for which it has been stated that we may see the first generation that will be less healthy and have a shorter life expectancy than their parents[11], it seems paradoxical to invoke the phenomenon of "disease mongering" for obesity-related liver disease. Nevertheless, in the case of obesity there are many myths and presumptions not scientifically supported[12]. Therefore, we think that the impact of pediatric NAFLD on morbidity and mortality must be critically evaluated.

Risk of progression of pediatric NAFLD toward end-stage liver disease

As recently reported[1], there is only one long-term outcome study on the natural history of NAFLD in children, which emphasizes the risk of an unfavorable evolution[4]. In this paper 66 children with NAFLD were enrolled and only 29 patients underwent a baseline liver biopsy, 5 of whom also had a follow-up histology. Moreover, a substantial proportion of the patients enrolled in this study, considered the reference paper for the natural history of children with obesity-related liver disease[1], were not obese (34%) and did not have metabolic syndrome (17%). Anyway, only two patients required liver transplantation: an 11-year-old Hispanic female, with a body mass index (BMI) of 26.9 kg/m^2, dyslipidemia, cirrhosis and esophageal varices at onset, transplanted at the age of 20 years for hepatopulmonary syndrome, with recurrence of NAFLD after 9 mo; and a 18.9-year-old female with a BMI of 33.6 kg/m^2, low HDL level and hepatopulmonary syndrome, transplanted at the age of 25 years, re-transplanted for recurrence of NAFLD 2.3 years after, who died from multiple organ failure at the age of 27 years.

Both cases had a very severe and atypical clinical course with early recurrence of NAFLD after liver transplantation, suggesting that they might have been affected by an unrecognized genetic metabolic disorder other than NAFLD. In this respect, very little information is provided in the paper on what investigations were done to exclude underlying chronic liver disease. It is to note that hypothalamic-pituitary axis dysfunction and lysosomal acid lipase deficiency (in which the recurrence of non alcoholic steatohepatitis (NASH) following liver transplantation is common) were not ruled out[13].

In Feldstein's study there were only two children with cirrhosis and these were the same two who required liver transplantation[4]. Overall, four children were included in the poor prognosis group: the two transplanted and two who died for complications related to bariatric surgery and whose death was not liver related. On the basis of the outcome of these four "atypical" patients with NAFLD, a standardized mortality risk of 13.6 was assigned to the category of the children with NAFLD in comparison with general population.

In the introduction of Feldstein's report[4], particular emphasis is attributed to some cases of cirrhotic stage disease in children with NAFLD previously reported in literature. If we analyze the relative references, we realize that overall a total of only 5 cases were reported. These 5 cases included a 12-year-old boy with craniopharyngioma with secondary obesity[14], and a patient who developed at the age of 30 years

hypertransaminasemia without evidence of metabolic syndrome with hepatic decompensation at 32 years[15]. Interestingly, though this patient had a low ceruloplasmin, Wilson disease was excluded only on the basis of urinary copper excretion[15]. The other two patients were drawn out of two case studies: one reported in 2003 by Schwimmer including 43 obese children[16] and the other reported in 1984 including 299 patients[17]. In these two studies further details about the two patients with cirrhosis were not provided.

Therefore, the critical analysis of the study[4] and its references shows that progressive liver disease is not a common complication of pediatric NAFLD[14-17].

Among the other reports of cirrhosis in children with NAFLD not cited in Feldstein's study[4], one showed 3 cases of cirrhosis and 8 cases of advanced fibrosis among 100 children with histologically documented NAFLD[18]. Unfortunately, further details about these patients with severe histology were not provided also in this study which, however, documented fibrosis absent or mild in about two thirds of cases[18]. Furthermore, an Italian study evaluating liver histology on a large sample of 203 children with NAFLD showed no case of stage 4 fibrosis and/or cirrhosis[19].

So far, the histologic evolution of children with NAFLD has been evaluated in few longitudinal studies[20,21]. In a cohort of one-hundred six children, 7 cases (6.6%) had a stage 3-4 fibrosis[21]. Paradoxically, these patients were significantly younger compared with those with mild or no fibrosis. Although the enrolled patients had an accurate histological evaluation, only 46 patients (43%) were investigated for metabolic syndrome[21].

At the present time, severe cases seem to be too few to refute the arguments on the generally favorable course of pediatric NAFLD as supported from the literature analysis performed here and elsewhere[1].

Table 1[4,14-19,21-24] summarizes pediatric studies on NAFLD with indication of the cases of end stage-liver disease. Unfortunately, none of them provided long enough follow-up to assess long-term cumulative risk of severe outcomes. It is to note that almost all the evaluations were assessed in individuals under 20 years of age.

Risk of liver transplant for pediatric NAFLD

While NASH has become the second leading etiology of liver disease among adults awaiting liver transplantation, little information is available for children[1]. A recent paper from the States reports that NASH may be an important cause of transplant also in children and young adults[5]. The study included United States patients under 40 years of age transplanted for NASH (no information about the etiology of NASH was provided in the paper) and for cryptogenic cirrhosis associated with a BMI > 30 kg/m^2. The overall frequency of transplantation for NASH and cryptogenic cirrhosis associated with obesity was only 1.67% (330/19904), though this low percentage was not emphasized in the conclusions. Of interest, among these patients only 4.2% were < 18 years old, while 16.4% were between 18 and 29 years and 79.4 % between 30 and 40 years of age, suggesting that NAFLD is not a frequent indication for transplantation in children. Moreover, some 15% of the patients had a BMI < 25 kg/m^2 and therefore were not obese.

Despite this, the study is frequently cited to stress the high risk for liver transplantation in obese children[1]. To reinforce the concept that fatty liver due to obesity is rarely leading to liver transplantation is the observation that no children with NAFLD required liver transplant in large pediatric series in Europe and United States[25-28].

Risk of hepatocellular carcinoma among children with NAFLD

Though it has been frequently stated that NAFLD can progress to hepatocellular carcinoma in children, because of the role of obesity and insulin resistance in carcinogenesis, Nobili *et al*[1] reported that "only two cases have been described to date, in both cirrhotic and non-cirrhotic background". Is it reasonable to conclude that these cases of HCC are causally associated with obesity? Or, more likely, was it just a fortuity? In brief, given the paucity of data showing a direct correlation between the progression of NAFLD and hepatocellular carcinoma, currently, the risk estimates are not clear and NAFLD can be considered a risk factor likely but not certain. However, what is proved by the evidence is that childhood obesity by itself increases the risk of liver cancer in adulthood, as well as other carcinomas[12,29]. Therefore it appears more important to focus on the systemic impact of obesity in general rather than on the fatty liver.

Treatment of NAFLD in children

All studies accept the premise that the most effective treatment for patients with NAFLD, both adults and children, is lifestyle optimization, with a focus on nutrition and exercise. These measures have been proven to be able to revert liver damage[1]. Unfortunately, the majority of obese children are not adherent to lifestyle modifications and hypocaloric diets[30]. Therefore, there is a growing number of studies focused on pharmacological interventions, based on proven or perceived mechanisms involved in the pathogenesis of NAFLD. In children, most of these studies have been generally performed in small series of patients with conflicting and sometimes inconclusive results[31,32]. The evaluation of the effectiveness of the various drugs is based in most cases on serum levels of transaminases with few determinations after a short-term intervention[31,32]. Long-term results of these treatments and their ability to modify the natural course of NAFLD are not available.

Table 1 Studies with histologically documented cases of advanced liver disease in pediatric nonalcoholic fatty liver disease

Study	Yr	No. of patients	Age (yr)	Follow-up (yr)	Case of cirrhosis (*n*)	Progression of fibrosis (*n*)	Case of liver transplantation (*n*)
Cross-sectional studies							
Kinugasa *et al*[17]	1984	299	N/A	N/A	1	N/A	N/A
Schwimmer *et al*[16]	2003	43	N/A	N/A	1	N/A	N/A
Suzuki *et al*[15]	2005	1	12	N/A	1	N/A	N/A
Schwimmer *et al*[18]	2005	100	Range 2-18	N/A	3	N/A	N/A
Alkhouri *et al*[19]	2012	203	Mean 12.4	N/A	0	N/A	N/A
Longitudinal studies							
Molleston *et al*[14]	2002	2	10 and 14	N/A	2	2/2	None
Feldstein *et al*[4]	2009	66 (5 followed longitudinally)	Mean 13.9	6.4	2	4/5	2
A-Kader *et al*[21]	2008	106 (18 followed longitudinally)	Range 7-19	2.3	2	7/18	N/A
Lavine *et al*[22]	2012 (preliminary report)	58	Range 8-17	1.8	N/A	15/58	N/A
Brunt *et al*[23]	2014 (preliminary report)	102	Range 11-17	2.2	N/A	20/102	N/A
Alkhouri *et al*[24]	2015 (preliminary report)	330	4-40	N/A	N/A	N/A	14/330

N/A: Not available.

Since many studies in humans have shown a relationship between gut bacterial overgrowth, enhanced gut permeability, increased paracellular leakage of gut luminal antigens and liver disease progression through an increased exposure of the liver to gut-derived bacterial products[33,34], modulating gut microbiota with probiotics, prebiotics, and synbiotics has become an attractive, safe and well tolerated treatment strategy of obesity and NAFLD. Nevetheless, also in adults, their therapeutic use is not supported by high-quality clinical studies[34,35]. Unfortunately, the only two pediatric RCTs, evaluating the influence of either single strain (*Lactobacillus rhamnosus* strain GG)[36] or multistrain VSL#3[37] probiotic supplementation on hepatic biomarkers in small groups of patients (20 and 40, respectively), gave different results. Vajro *et al*[36] reported no effect of *L. rhamnosus* strain GG on liver echogenicity, but a decrease in serum alanine aminotransferase levels in children treated with *L. rhamnosus* strain GG as compared to placebo. Conversely, Alisi *et al*[37] found that VSL#3 supplementation reduced the severity of steatosis as assessed by ultrasound. These findings were observed in short periods (2 and 4 mo, respectively) and with a single evaluation at the end of the study. From a pathophysiological point of view, it is difficult to understand how a short term intervention, as administration of probiotic for few months, could have such a long term impact on the composition of the intestinal microbiota (which is highly mutable and related to prenatal, perinatal and environmental factors)[38,39] to the point of affecting liver health. In particular, the problem is to hypothesize a lasting effect over time, given that the complications of NAFLD are expected in the long term.

Another critical point is the risk of stressing the beneficial effect of a drug on a limited aspect, albeit important, of a disease. This could be the case of vitamin E on ballooning degeneration, documented in TONIC trial, one of the best designed pediatric studies in a large sample of NAFLD patients[40]. This finding, although the Authors clearly stated that neither vitamin E nor metformin were superior to a placebo in attaining sustained reduction in ALT level (primary outcome) or improvement in fibrosis (secondary outcome) in patients with pediatric NAFLD, can encourage the use of vitamin E in patients with NAFLD. As stated before, it is important to understand if a therapeutic agent has an impact on a single parameter (liver enzymes) in a limited time interval or an impact on the long term course of disease. If we accept the hypothesis that a treatment with probiotics can really have a favorable impact on liver injury, as a result, probiotics should be prescribed, on a regular basis, to the patient in addition to the recommendation of reducing caloric intake and increasing physical activity. Given the long life expectancy of pediatric patients and the need of preserving obesity-related liver damage in the long term, for how many years (decades?) probiotics should be prescribed in addition to lifestyle modification? and with what economic cost? Furthermore, we must consider that the proposal to the obese patient of an ancillary drug, in addition to diet and exercise, may divert his attention from the diet and exercise.

Despite the absence of strong evidence and although the majority of the Authors is cautious in recommending the extensive use of these drugs[1], it is reasonable to fear a strong demand from parents who see the drug as a potential remedy for the liver disease of their child. Furthermore, it creates a favorable environment for the development of the phenomenon of disease mongering. Of course, with these considerations we do not deny the usefulness of research on the potential role of drugs and food

supplements in the therapy of this condition. What we hope however is that their effectiveness is documented with a robust methodology and on large series, that are actually missing.

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