Title

Obesity, Nutrition, and Liver Disease in Children

Journal

Clinics in Liver Disease, 18(1)

ISSN

1089-3261

Authors

Feldstein, Ariel E

Patton-Ku, Dana

Boutelle, Kerri N

Publication Date

2014-02-01

DOI

10.1016/j.cld.2013.09.003

Obesity, Nutrition, and Liver Disease in Children

Ariel E. Feldstein, MD[a,b,*], Dana Patton-Ku, MD[a,b], Kerri N. Boutelle, PhD[a,c,d]

KEYWORDS

• Obesity • Nutrition • Liver disease • Children

KEY POINTS

- One-third of children in the United States are overweight or obese.
- Overweight children can suffer from a host of comorbid conditions and should be screened appropriately.
- Making the diagnosis of nonalcoholic or metabolic fatty liver disease in children remains difficult, given the impracticality of liver biopsy and the lack of reliable biomarkers.
- The gold standard for childhood weight loss is family-based behavioral therapy, with 30% of children no longer overweight at 10-year follow-up.
- Pharmacologic intervention for weight loss is limited in children and for liver disease is limited to those children with nonalcoholic steatohepatitis.

SCOPE OF THE PROBLEM

Epidemiology of Obesity

Children have natural weight fluctuations as they grow, therefore defining overweight in youth requires standardized growth charts that account for sex and age. Currently, for children aged 2 to 18 years, overweight is defined as a body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters) in the

Funding: the work was funded by NIH (DK076852 and DK082451 to AEF), T32 DK007202-37 (DPK) and (DK075861, HL112042 DK094475 to KNB).
Disclosure of Financial and Competing Interests: Dr Feldstein reports that he is named as coinventor on pending and issued patents filed by the Cleveland Clinic and University of California San Diego that refer to the use of biomarkers in fatty liver disorders. Dr Patton-Ku and Dr Boutelle have no financial disclosures.
[a] Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Rady Children's Hospital, 3020 Children's Way, San Diego, CA 92123, USA; [b] Division of Pediatric Gastroenterology, Hepatology, and Nutrition, University of California, San Diego, 9500 Gilman Drive, MC 0984, La Jolla, CA 92093, USA; [c] Department of Pediatrics, University of California, San Diego, 9500 Gilman Drive, 0874 La Jolla, CA 92093-0874, USA; [d] Department of Psychiatry, University of California, San Diego, 9500 Gilman Drive, 0874 La Jolla, CA 92093-0874, USA
* Corresponding author. Division of Pediatric Gastroenterology, Hepatology, and Nutrition, University of California, San Diego.
E-mail address: afeldstein@ucsd.edu

Clin Liver Dis 18 (2014) 219–231
http://dx.doi.org/10.1016/j.cld.2013.09.003 **liver.theclinics.com**
1089-3261/14/$ – see front matter

85th percentile or greater and obesity is BMI in the 95th percentile or greater, adjusted for sex and age.[1] In children younger than 2 years, a weight-for-length value greater than 95th percentile for age and sex is categorized as overweight. There are no normative data for BMI in this age group. Recent data from the 2009 to 2010 National Health and Nutrition Examination Survey showed that 31.8% of children aged 2 to 19 years were overweight or obese and 16.9% of children were obese.[2] The prevalence of obesity in children has increased 3-fold from the 1960s and 1970s.[3]

Comorbid Conditions

With the increasing prevalence of obesity in children, there has been a concomitant increase in the medical consequences of obesity in children. Overweight and obesity have been associated with orthopedic complications (slipped capital femoral epiphysis and Blount disease), asthma, sleep apnea, diabetes mellitus type 2, dyslipidemia, liver disease, and hypertension.[4] In addition, obese children often become obese adults.[5] Overweight and obese children also incur greater medical costs from more frequent laboratory studies,[6] greater numbers of sick visits, and greater use of mental health services.[7] In terms of psychosocial comorbidities, obese children have reported lower health-related quality of life[8] and had lower self-worth compared with normal-weight children.[9] Studies on depression in obese children are mixed, with some studies linking obesity to depression and some showing no difference when compared with normal-weight peers.[10] Eating disorders may be more frequent among obese youth, with 1 cross-sectional study showing that 30% of severely obese adolescent girls manifested unequivocal binge eating.[11] There may also be higher rates of usage of diet pills, laxatives, and vomiting to control weight.[12]

Nonalcoholic or Metabolic Fatty Liver Disease

Nonalcoholic or metabolic fatty liver disease (NAFLD) has evolved as a key comorbidity associated with obesity.[13] The presentation and severity of NAFLD can vary significantly, from isolated hepatic steatosis (which represents fatty deposition without inflammation) to nonalcoholic steatohepatitis (NASH) (which encompasses steatosis, inflammation, and ballooning degeneration of hepatocytes) to liver fibrosis and end-stage liver disease. Because of increasing rates over the last few decades, NAFLD is now considered to be the most common form of chronic liver disease in most of the Western world, with a prevalence ranging from 20% to 35% in adults and 5% to 17% in children.[14] Children with NAFLD are usually obese and have associated features of metabolic syndrome; insulin resistance, impaired glucose tolerance, and type 2 diabetes may also be present at diagnosis.[15]

EVALUATION OF OBESITY IN CHILDREN

The American Academy of Pediatrics (AAP) recommends yearly evaluation of weight status using BMI measurement and assessment of dietary and exercise patterns to provide opportunities to intervene on poor dietary habits and sedentary behavior.[16] Given that the medical consequences of obesity can involve every organ system, a thorough history and physical examination are paramount in the evaluation of overweight and obese children. Important considerations in the family history include the presence of obesity-related disorders and parental obesity. Genetic factors have a strong influence on the development of conditions such as type 2 diabetes mellitus and cardiovascular disease in childhood.[17] Sleep apnea can occur in severely obese adolescents[18] and usually presents with night-time snoring and daytime somnolence. Obese children should also be questioned on the presence of wheezing and

shortness of breath, because asthma seems to be more common in this group as well.[4] The American Diabetes Association recommends that overweight children (≥85th percentile BMI) with any 2 of the following risk factors be screened for type 2 diabetes mellitus: (1) family history of type 2 diabetes, (2) of Native American, African American, Hispanic American, or Asian/South Pacific Islander ethnic background, or (3) have signs of insulin resistance or conditions associated with insulin resistance. Screening should start at age 10 years, or at the onset of puberty if it occurs younger, and should be performed every 2 years.[19] There are no evidence-based guidelines on when and how to best screen for NAFLD in children. However, an AAP expert committee has suggested that aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels be measured biannually for children with BMI in the 95th percentile or greater and those with BMI in the 85th to 94th percentile with at least 1 other risk factor.[16] Screening for many of the psychological comorbidities of obesity can be accomplished using the HEEADSSS examination, which most pediatricians use in every adolescent visit. This is a series of questions regarding home environment, education and employment, eating, activities, drugs, sexuality, suicide/depression, and safety designed to identify adolescents having difficulties in any of these areas during this high-risk developmental period.[20]

Medical causes of obesity in childhood are rare; however, many pediatricians find themselves needing to address these causes because of parental concern. Hypothyroidism is among the more common causes of weight gain (acquired hypothyroidism has a prevalence of about 1.2% of children in the United States).[21] However, children with this disorder typically have a decrease in their linear growth and a decline in academic performance. Primary Cushing syndrome is another rare cause of obesity in childhood. However, these children also typically have short stature. There are some genetic syndromes associated with obesity, such as Prader-Willi syndrome. These children typically have developmental delay and other medical conditions that precede the obesity.

EVALUATION OF NAFLD IN CHILDREN

The diagnosis of pediatric NAFLD is commonly made after increased serum aminotransferase levels are found during a routine checkup. Many centers have adopted a screening program for NAFLD in high-risk individuals, particularly in those presenting with features of the metabolic syndrome. Liver biopsy, the current gold standard for the diagnosis of NAFLD, is the only way to distinguish between NASH and isolated hepatic steatosis, determine the severity of liver damage and the presence and extent of fibrosis, as well as to rule out other diagnoses, such as autoimmune hepatitis. However, routine noninvasive evaluation (biochemical parameters, imaging tests, and serum biomarkers) are used as the first step to confirm the diagnosis of fatty liver disease, especially in the typical patient with features characteristic of the metabolic syndrome.

Serum Biomarkers

In children with suspected NAFLD or NASH, baseline testing should include levels of AST and ALT, total and direct bilirubin, γ-glutamyltranspeptidase, fasting serum glucose, and insulin, as well as a lipid panel. Aminotransferases may range from normal to 4 to 6 times the upper limit of normal, but mild increases are usually seen, ranging between 1.5 and 2 times the upper limit of normal.[22] Generally, the ratio of AST to ALT is less than 1, but this ratio may increase as fibrosis advances.[23] Circulating levels of aminotransferases may fluctuate over time and may be normal in a large proportion of children with NAFLD and NASH.[15] Furthermore, normal aminotransferase levels do

not exclude the presence of fibrosis or even cirrhosis. Given that most patients with NAFLD have some components of the metabolic syndrome, lipid profiles as well as fasting glucose and insulin levels should be verified. Insulin resistance can be determined by fasting insulin levels or by further studies if necessary (glucose challenge or glucose tolerance test). Albumin, bilirubin, and platelet levels are usually normal unless the disease has evolved to cirrhosis. Similar to adults, some children with NAFLD may have positive autoantibodies (antinuclear and anti–smooth muscle antibody) in the absence of autoimmune hepatitis.[24] The significance of this finding is still unclear.

Establishing the diagnosis and disease severity as well as monitoring children over time remains a major challenge for pediatricians taking care of the increasing number of children with NAFLD. A liver biopsy is still considered the goal standard; however, this invasive procedure is not suitable for screening and risk stratification of children with this condition. There is a great need to develop noninvasive, simple, and reliable tests that can replace liver biopsy for these purposes. The currently available noninvasive tests as reviewed earlier have 2 central limitations: the inability to (1) distinguish NASH, from hepatic steatosis and (2) to stage the presence and extent of liver fibrosis. Thus, identifying and validating potential novel noninvasive biomarkers is a central area of research. Diagnostics development in NAFLD have been divided into 2 major groups: those aimed at detecting and quantifying the presence of fibrosis and those aimed at establishing the diagnosis of NASH. Regarding the former, the pediatric NAFLD fibrosis index (PNFI) which is obtained from 3 simple measures (age, waist circumference [WC], and triglycerides [TG]), was recently developed to predict liver fibrosis in children with NAFLD.[25] This index is easy to calculate, with no additional cost to the patient, and it has a good positive predictive value to rule in fibrosis; however, its negative predictive value is suboptimal. These limitations can be overcome when used in a sequential algorithm with the enhanced liver fibrosis (ELF) test. The ELF test uses a combination of 3 extracellular matrix components (hyaluronic acid, amino terminal propeptide of type III collagen, and inhibitor of metalloproteinase 1) and results in an accurate assessment of the presence of liver fibrosis in children.[26] Future studies are still needed to externally cross-validate these findings before the combination of PNFI and ELF can be recommended in children with NAFLD. Moreover, longitudinal studies measuring these panels serially against clinical outcomes will determine if they can be used to measure disease progression and regression.

Hepatocyte apoptosis has been found to be a prominent feature in patients with NASH, making it an interesting focus for biomarker development and for therapeutic intervention.[27] A large body of evidence has shown the usefulness of measuring plasma levels of caspase-generated cytokeratin-18 (CK-18) fragments, a specific by-product of apoptosis in liver cells, in the diagnosis of NASH in adult patients.[28] Recently, Fitzpatrick and colleagues[29] reported that children with biopsy-proven NAFLD also showed considerably increased levels of the CK-18 fragments compared with healthy controls. In addition, those with established NASH showed significantly higher numbers versus those with hepatic steatosis or borderline disease. These findings were further confirmed in a large study including more than 200 children with biopsy-proven NAFLD.[30] Numerous other biomarkers of inflammation, oxidative stress, apoptosis, and fibrosis are under investigation.[31] However, more studies are needed to validate the existing markers and techniques and develop other accurate noninvasive predictors of disease severity.

Imaging Techniques

Several radiologic techniques seem promising for quantifying hepatic steatosis (computed tomography, magnetic resonance imaging, or magnetic resonance

spectroscopy) as well as fibrosis (transient elastography). Liver ultrasonography (US) is the most commonly used imaging modality, largely because it is inexpensive, widely available, and user-friendly. Several studies in adults have reported that this technique is highly sensitive and specific for detection of NAFLD.[32,33] Moreover, liver US can provide a good estimate of the degree or extent of hepatic steatosis present based on a series of characteristics, including hepatorenal echo contrast, liver echogenicity, visualization of intrahepatic vessels, and visualization of liver parenchyma and the diaphragm. Based on these characteristics, it was recently shown that liver US is a useful tool for quantifying steatosis in pediatric patients who have suspected NAFLD, with US score strongly correlating with grade of steatosis on liver biopsy.[34] US sensitivity decreases when the liver contains less than 30% of fat. Furthermore, US cannot rule out the presence of steatohepatitis or fibrosis. Both computed tomography and magnetic resonance imaging studies, especially the new technique of magnetic resonance spectroscopy, are more sensitive techniques for the quantification of steatosis. However, they have been mainly used in the research setting, and their clinical usefulness is limited by their cost and the need for sedation in children. None of these imaging tools has sufficient sensitivity and specificity for staging the disease and cannot distinguish between hepatic steatosis and NASH with or without fibrosis.

Several investigators have reported that transient elastography provides a high level of accuracy for detecting significant liver fibrosis, advanced fibrosis, and cirrhosis observed in adult NAFLD.[35] Transient elastography has also been validated to assess liver fibrosis through tissue elasticity measured by US technology in several liver diseases and may be useful in pediatric NAFLD.[36]

Liver Biopsy

Liver biopsy remains the gold standard for establishing the diagnosis of NAFLD and grading and staging the severity,[37] distinguishing steatosis from steatohepatitis, and assessing the degree of fibrosis. Moreover, it is helpful in ruling out alternative causes such as chronic hepatitis C infection, Wilson disease, autoimmune hepatitis, and other metabolic liver disorders. In addition, histology permits the monitoring of disease progression and the response to therapy, because aminotransaminase levels may decrease during the course of the disease, regardless of whether fibrosis progresses or improves. A central limitation for the use of liver biopsy is its invasiveness and the potential for significant complications, such as bleeding. The histologic diagnosis of NASH in pediatric cases may also be challenging, because the features found in liver biopsy often differ from those commonly seen in adults.[38] The typical adult pattern (termed NASH type 1) is characterized by the presence of steatosis (mainly macrovesicular), with ballooning degeneration or perisinusoidal fibrosis (zone 3 lobular involvement), with the portal tracts being relatively spared. Pediatric type NASH (NASH type 2) is described as the presence of steatosis along with portal inflammation or fibrosis in the absence of ballooning degeneration and perisinusoidal fibrosis.[39]

TREATMENT

Goals

For obese children with or without NAFLD, lifestyle and dietary changes with resultant weight loss are the goals.[40] For both conditions, precipitous weight loss is generally not needed, and in the case of NAFLD, this approach can be detrimental. Therefore, the focus should be on instituting healthier behaviors, which over time result in weight loss. It has been shown that 5% reductions in BMI are associated with clinically meaningful changes in WC, and reductions in cholesterol, TG, and insulin resistance levels

in children.[41] Also, comparably small changes in weight result in significant improvement of liver enzyme levels in adults.[42] For children with NAFLD, there is an additional focus on treating the liver disease as well as the associated metabolic derangements. Pharmacologic therapy is limited to children with NASH, given that those with isolated hepatic steatosis generally have an excellent prognosis from a liver standpoint.

Interventions for Obesity

Family-based behavioral treatment

Family-based behavioral treatment (FBT) consists of nutrition and exercise education combined with behavior therapy techniques. It is an intensive program, in which the child and parent(s) meet weekly to biweekly over several months for group classes and also receive one-on-one meetings with a behavioral coach for individualized goal setting and problem solving. The behavior therapy curriculum consists of self-monitoring of diet and physical activity, stimulus control, positive reinforcement, parenting skills, goal setting, and relapse prevention.[43,44] Stimulus control focuses on setting up the child's environment to reduce food intake and sedentary activity and increase physical activity. Positive reinforcement includes positive parenting skills (praise) and motivation systems, in which the child earns points for participating in program-related behaviors. Parenting skills includes promotion of authoritative parenting style around eating and exercise and how to model healthy behaviors and set limits. Goal setting refers to contracting for immediate and long-term goals and the disbursement of rewards for achieving these goals (**Fig. 1**). The addition of these components to standard nutrition education has been shown to significantly improve weight loss.[45] The importance of behavioral therapy was also shown in another study comparing a behavioral weight reduction program with the same program plus a short course on general child management skills. Both groups lost weight, but children whose parents received general child management training in addition to the weight reduction program had improved weight maintenance at 1-year follow-up.[46] Golan

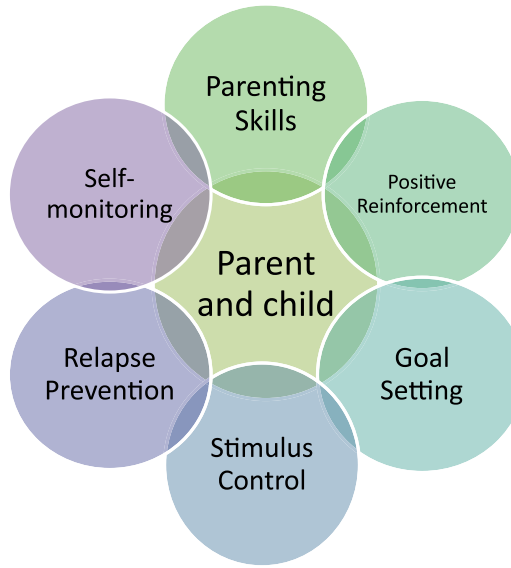

Fig. 1. Components of family-based behavioral therapy.

and colleagues[47] reported that the use of behavioral modification techniques explained 27% of the variance in the child's weight reduction.

One important difference in behavioral therapy for obese children compared with adults is the necessity of involvement of parents. One study compared the effect of targeting behavioral therapy toward the child, the child and parent, or a nonspecific target. Although all groups had similar weight reductions after treatment and at 2-year follow-up, the parent-child group had improved weight outcomes at 10-year follow-up compared with the other groups.[48] In addition, some studies have shown greater reduction in child percent overweight in parent-focused interventions when compared with child-focused interventions.[49,50] More recently, parent-focused programs that require the parent to master weight-control strategies and then teach these strategies to their child without the child attending any treatment sessions themselves have proved to be equally as effective as those including the child in treatment.[51,52]

Several studies have proved FBT an effective treatment of weight loss in children, and FBT is considered the gold standard for the treatment of childhood obesity. Long-term data have shown that 30% of children participating in FBT are normal weight after 10 years.[48] Unique to the treatment of childhood obesity is the need for parent involvement for treatment success.

Dietary

There are few studies of specific dietary approaches to achieve weight loss in children. Many studies of behavioral therapy in children have used the traffic-light diet. This diet categorizes foods into green, yellow, or red, based on the energy density. Green foods are low in energy density and are allowed in unlimited amounts. Yellow foods are moderate in energy density and are to be approached with caution. Red foods are high in fat and simple sugar and should be eaten in limited amounts. Families are instructed to eat few red foods and eat as much green food as possible, but stay within a prescribed calorie range.[53] This diet has been shown to decrease BMI in several studies of behavioral therapy.[45,51,54]

There are few studies of altering carbohydrate content in children. In one of the few studies, a low-carbohydrate, high-protein diet was as effective as a standard portion-controlled diet in 102 children aged 7 to 12 years (ie, both groups had lower BMI z-scores at 12-month follow-up). However, the low-carbohydrate, high-protein diet had lower rates of adherence.[55] Other smaller studies comparing low glycemic index diets with a standard reduced-fat diet in adolescents have shown larger decreases in BMI among the groups with a low glycemic index.[56,57]

Pharmacologic

In adults, 2 appetite-suppressant drugs have been approved by the US Food and Drug Administration (FDA) for weight loss: lorcaserin HCl (Belviq) and phentermine/topiramate (Qsymia). However, the only FDA-approved drug for weight loss in adults and children is orlistat. Orlistat causes weight loss by decreasing fat absorption through inhibition of pancreatic lipase.[58] There have been few trials of this drug in children. A small, short-term study in obese adolescents showed modest reduction of weight (–3.8% $\pm$ 4.1% from baseline) when given orlistat in conjunction with a behavioral weight-loss treatment program.[59] In a larger, randomized controlled trial comparing the addition of orlistat or placebo with a diet, exercise, and behavioral therapy program in adolescents, the orlistat group had a mean reduction of BMI by 0.55, whereas the placebo group increased by 0.31. The orlistat group had more gastrointestinal side effects than the placebo group (9% to 50% compared with 1% to 13%).[60]

Interventions for NAFLD

Nonpharmacologic

As described earlier for obese children, gradual weight reduction and physical exercise continue to be the gold standard of treatment of NAFLD in children.[40] Weight reduction has been widely studied in adults and has been shown to improve not only the biochemical parameters but also the liver histology. Based on studies in adults, greater than 5% weight loss was associated with significant improvement in liver histology.[61] The relative efficacy of weight loss and degree of weight loss needed to induce histologic improvement in pediatric NAFLD is unknown, but rapid weight loss is not advised, because it may accelerate inflammation. In the context of evidence-based recommendations for patients with NAFLD, advice is based on the pathologic mechanisms of disease progression, favoring nutrients that have beneficial effects on the metabolic syndrome parameters as well as on inflammation. Consumption of carbohydrates should be limited (especially a high-fructose, high-glucose diet) and foods with a low glycemic index prioritized. Saturated fats are limited in favor of monounsaturated fatty acids as well as polyunsaturated fatty acids (omega-3). Recent pediatric studies evaluating lifestyle dietary changes and weight loss have suggested that in a selective group of children, effective intervention resulting in persistent weight loss is associated with improvement of serum AST and ALT levels and US liver brightness, as well as liver histology.[62]

Pharmacologic

Several drugs that improve insulin sensitivity, such as metformin, or glitazones (rosiglitazone, pioglitazone), lipid-lowering agents, such as clofibrate, or gemfibrozil, hepatoprotective agents, such as ursodeoxycholic acid (UDCA), and antioxidants, such as vitamin E, betaine, or *N*-acetylcysteine, have been proposed as potential agents for the treatment of NASH in both adults and children (**Table 1**).

Insulin-sensitizing agents Patients with NASH with diabetes are at higher risk of developing more aggressive disease.[63] Insulin-sensitizing agents such as peroxisome proliferator-activated receptor-γ agonists (glitazones) have been tested in adults with NASH, with mixed results.[64] The experience with glitazones in children and adolescence is limited, and there are no studies assessing this medication class in children with NAFLD. Metformin has been shown to be safe and effective in the treatment of diabetes in children and is the only insulin-sensitizing agent thus far evaluated in the treatment of NAFLD in children. Initial small pilot studies in pediatric NAFLD suggested improvement in serum ALT levels and reduction in hepatic steatosis as assessed by radiologic means.[65] However, a recently published large, multicenter, double-blind, randomized controlled trial of metformin or vitamin E in children (the Treatment of nonalcoholic fatty liver disease in children: TONIC trial) showed a complete lack of

Table 1
Various strategies for pharmacologic interventions for NAFLD in children

Strategy	Treatment
Insulin-sensitizing agents	Peroxisome proliferator-activated receptor-γ agonists (thiazolidinedione, rosiglitazone, pioglitazone); metformin
Antioxidants, hepatoprotective	Vitamin E, enteric coated cysteamine, *N*-acetylcysteine, pentoxifilline, caspase inhibitors
Others	Omega-3-fatty acids, carnitine, lipid-lowering agents

effect of metformin on both serum aminotransferase levels and liver histology.[66] The routine use of these agents in nondiabetic patients with NAFLD should be discouraged outside clinical trials.

Hepatoprotective, antioxidant therapy Several therapeutic agents believed to offer hepatocyte protection have been evaluated. Antioxidants have been hypothesized to decrease the oxidative stress and improve liver damage in NASH. A randomized controlled trial of vitamin E in adults[67] showed improvement in transaminases and fibrosis. Two pediatric studies with a small number of patients with NAFLD and no assessment in histology suggested an improvement of liver enzymes but no changes in liver brightness on US with vitamin E treatment. A large randomized controlled trial of pediatric NASH with changes in liver histology as the primary end point failed to show an additional benefit of vitamin E and C to a successful dietary weight-loss program.[68] Similarly, neither vitamin E nor metformin was superior to placebo in achieving sustained reduction in ALT level or in improving steatosis, lobular inflammation, or fibrosis scores in the TONIC trial. The only histologic feature of NASH that improved with both medications was ballooning. Compared with placebo, only vitamin E significantly improved the NAFLD activity score and was associated with improved resolution of NASH on the repeat liver biopsy (58% vs 28%; *P* value of .006). The investigators suggested that vitamin E should be considered in a subset of children with biopsy-proven NASH and evidence of hepatocellular ballooning degeneration, keeping in mind that the risk of biopsy may outweigh the benefits of therapy.[66]

SUMMARY

Childhood obesity is a serious and widespread problem, with one-third of children in the United States being overweight or obese. All of these children are at risk for a host of medical complications from their condition, including NAFLD. Screening for childhood obesity is important, and weight status should be evaluated via BMI at least yearly for all children. For overweight children, there are guidelines for screening for type 2 diabetes, but no evidence-based recommendations are available for screening for NAFLD and the other comorbidities. Furthermore, diagnosis of NAFLD remains difficult given the lack of reliable biomarkers and impracticality of liver biopsy. The gold standard for childhood weight loss is FBT. Pharmacologic therapy for weight loss in obese children is limited, and for liver disease, is limited to those children with NASH. Even modest weight loss in children can have a significant impact on their overall health.

REFERENCES

1. Kuczmarski R, Ogden C, Grummer-Strawn L. CDC growth charts: United States. Adv Data 2000;324:1–27.
2. Ogden CL, Carroll MD, Kit BK, et al. Prevalence of obesity and trends in body mass index among US children and adolescents, 199-2010. JAMA 2012;207(5): 483–90.
3. Ogden C, Carroll M. Prevalence of obesity among children and adolescents: United States, trends 1963-1965 through 2007-2008. Atlanta (GA): Centers for Disease Control and Prevention, National Center for Health Statistics; 2010. Available at: http://www.cdc.gov/nchs/data/hestat/obesity_child_07_08/obesity_child_07_08.htm.
4. Daniels SR, Arnett DK, Eckel RH, et al. Overweight in children and adolescents: pathophysiology, consequences, prevention, and treatment. Circulation 2005; 111(15):1999–2012.

5. Freedman DS, Khan LK, Serdula MK, et al. The relation of childhood BMI to adult adiposity: the Bogalusa Heart Study. Pediatrics 2005;115:22–7.
6. Hampl SE, Carroll CA, Simon SD, et al. Resource utilization and expenditures for overweight and obese children. Arch Pediatr Adolesc Med 2007; 161:11–4.
7. Estabrooks PA, Shetterly S. The prevalence and health care use of overweight children in an integrated health care system. Arch Pediatr Adolesc Med 2007; 161:222–7.
8. Schwimmer JB, Burwinkle TM, Varni JW. Health-related quality of life of severely obese children and adolescents. JAMA 2003;289:1813–9.
9. Braet C, Mervielde I, Vandereycken W. Psychological aspects of childhood obesity: a controlled study in a clinical and nonclinical sample. J Pediatr Psychol 1997;22(1):59–71.
10. Puhl R, Latner J. Stigma, obesity and the health of the nation's children. Psychol Bull 2007;133(4):557–80.
11. Berkowitz RA, Stunkard J, Stallings VA. Binge-eating disorder in obese adolescent girls. Ann N Y Acad Sci 1993;699:200–6.
12. Boutelle K, Neumark-Sztainer D, Story M, et al. Weight control behaviors among obese, overweight, and nonoverweight adolescents. J Pediatr Psychol 2002; 27(6):531–40.
13. Festi D, Colecchia A, Sacco T, et al. Hepatic steatosis in obese patients: clinical aspects and prognostic significance. Obes Rev 2004;5:27–42.
14. Schwimmer JB, Deutsch R, Kahen T, et al. Prevalence of fatty liver in children and adolescents. Pediatrics 2006;118:1388–93.
15. Feldstein AE, Charatcharoenwitthaya P, Treeprasertsuk S, et al. The natural history of nonalcoholic fatty liver disease in children: a follow-up study for up to 20-years. Gut 2009;58(11):1538–44.
16. Barlow SE. Expert committee and treatment of child and adolescent overweight and obesity: expert committee recommendations regarding the prevention. assessment, Report. Pediatrics 2007;120(Suppl 4):S164–92.
17. Fagot-Campagna A, Pettitt DJ, Engelgau MM, et al. Type 2 diabetes among North American children and adolescents: an epidemiologic review and a public health perspective. J Pediatr 2000;136:664–72.
18. Kalra M, Inge T, Garcia V, et al. Obstructive sleep apnea in extremely overweight adolescents undergoing bariatric surgery. Obes Res 2005;13:1175–9.
19. American Diabetes Association screening for type 2 diabetes. Diabetes Care 2003;26(Suppl 1):521–4.
20. Goldenring JM, Rosen DS. Getting into adolescent heads: an essential update. Contemp Pediatr 2004;21(1):64–92.
21. Rallison ML, Dobyns BM, Keating FR, et al. Occurrence and natural history of chronic lymphocytic thyroiditis in childhood. J Pediatr 1975;86(5):675.
22. Wieckowska A, Feldstein AE. Nonalcoholic fatty liver disease in the pediatric population: a review. Curr Opin Pediatr 2005;17:636–41.
23. Adams LA, Sanderson S, Lindor KD, et al. The histological course of nonalcoholic fatty liver disease: a longitudinal study of 103 patients with sequential liver biopsies. J Hepatol 2005;42:132–8.
24. Vuppalanchi R, Gould RJ, Wilson LA, et al, Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN). Clinical significance of serum autoantibodies in patients with NAFLD: results from the nonalcoholic steatohepatitis clinical research network. Hepatol Int 2011. [Epub ahead of print].

25. Nobili V, Alisi A, Vania A, et al. The pediatric NAFLD fibrosis index: a predictor of liver fibrosis in children with non-alcoholic fatty liver disease. BMC Med 2009;7:21.
26. Alkhouri N, Carter-Kent C, Lopez R, et al. A combination of the pediatric NAFLD fibrosis index and enhanced liver fibrosis test identifies children with fibrosis. Clin Gastroenterol Hepatol 2011;9(2):150–5.
27. Feldstein AE, Canbay A, Angulo P, et al. Hepatocyte apoptosis and fas expression are prominent features of human nonalcoholic steatohepatitis. Gastroenterology 2003;125(2):437–43.
28. Feldstein AE, Wieckowska A, Lopez AR, et al. Cytokeratin-18 fragment levels as noninvasive biomarkers for nonalcoholic steatohepatitis: a multicenter validation study. Hepatology 2009;50(4):1072–8.
29. Fitzpatrick E, Mitry R, Quaglia A, et al. Serum level of CK18 M30 and leptin are useful predictors of steatohepatitis and fibrosis in paediatric NAFLD. J Pediatr Gastroenterol Nutr 2010;51(4):500–6.
30. Feldstein AE, Alkhouri N, De Vito R, et al. Serum cytokeratin-18 fragment levels are useful biomarkers for nonalcoholic steatohepatitis in children. Am J Gastroenterol 2013;108(9):1526–31.
31. Wieckowska A, Feldstein AE. Diagnosis of nonalcoholic fatty liver disease: invasive versus noninvasive. Semin Liver Dis 2008;28:386–95.
32. Mazhar SM, Shiehmorteza M, Sirlin CB. Noninvasive assessment of hepatic steatosis. Clin Gastroenterol Hepatol 2009;7:135–40.
33. Dasarathy S, Dasarathy J, Khiyami A, et al. Validity of real time ultrasound in the diagnosis of hepatic steatosis: a prospective study. J Hepatol 2009;51:1061–7.
34. Shannon A, Alkhouri N, Carter-Kent C, et al. Ultrasonographic quantitative estimation of hepatic steatosis in children with nonalcoholic fatty liver disease (NAFLD): a prospective study. J Pediatr Gastroenterol Nutr 2011;53(2):190–5.
35. Piscaglia F, Marinelli S, Bota S, et al. The role of ultrasound elastographic techniques in chronic liver disease: current status and future perspectives. Eur J Radiol 2013. http://dx.doi.org/10.1016/j.ejrad.2013.06.009. [Epub ahead of print].
36. Nobili V, Vizzutti F, Arena U, et al. Accuracy and reproducibility of transient elastography for the diagnosis of fibrosis in pediatric nonalcoholic steatohepatitis. Hepatology 2008;48(2):442–8.
37. Adams LA, Feldstein AE. Nonalcoholic steatohepatitis: risk factors and diagnosis. Expert Rev Gastroenterol Hepatol 2010;4(5):623–35.
38. Schwimmer JB, Behling C, Newbury R, et al. Histopathology of pediatric nonalcoholic fatty liver disease. Hepatology 2005;42:641–9.
39. Carter-Kent C, Yerian LM, Brunt EM, et al. Nonalcoholic steatohepatitis in children: a multicenter clinicopathological study. Hepatology 2009;50(4):1113–20.
40. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. Hepatology 2012;55(6):2005–23.
41. Budd G, Hayman L, Crump E, et al. Weight loss in obese African American and Caucasian adolescents: secondary analysis of a randomized clinical trial of behavioral therapy plus sibutramine. J Cardiovasc Nurs 2007;22(4):288–96.
42. St George A, Bauman A, Johnston A, et al. Effects of a lifestyle intervention in patients with abnormal liver enzymes and metabolic risk factors. J Gastroenterol Hepatol 2009;24:399–407.

43. Epstein LH. Family-based behavioural intervention for obese children. Int J Obes Relat Metab Disord 1996;20(Suppl 1):S14–21.
44. Epstein LH, Roemmich JN, Raynor HA. Behavioral therapy in the treatment of pediatric obesity. Pediatr Clin North Am 2001;48(4):981–93.
45. Epstein LH, Wing RR, Koeske R, et al. Child and parent weight loss in family-based behavior modification programs. J Consult Clin Psychol 1981;49:674–85.
46. Israel AC, Stolmaker L, Andrian CA. The effects of training parents in general child management skills on a behavioral weight loss program for children. Behav Ther 1985;16:169–80.
47. Golan M, Fainaru M, Weizman A. Role of behaviour modification in the treatment of childhood obesity with the parents as the exclusive agents of change. Int J Obes Relat Metab Disord 1998;22:1217–24.
48. Epstein LH, Valoski A, Wing RR, et al. Ten-year follow-up of behavioral, family-based treatment for obese children. JAMA 1990;264:2519–23.
49. Golan M, Weizman A, Apter A, et al. Parents as the exclusive agents of change in the treatment of childhood obesity. Am J Clin Nutr 1998;67:1130–5.
50. Golan M, Crow S. Targeting parents exclusively in the treatment of childhood obesity: long-term results. Obes Res 2004;12:357–61.
51. Boutelle KN, Cafri G, Crow SJ. Parent-only treatment for childhood obesity: a randomized controlled trial. Obesity (Silver Spring) 2011;19:574–80.
52. Janicke DM, Sallinen BJ, Perri MG, et al. Comparison of parent-only vs family-based interventions for overweight children in underserved rural settings: outcomes from project story. Arch Pediatr Adolesc Med 2008;162:1119–25.
53. Epstein LH, Wing RR, Penner BC, et al. Effect of diet and controlled exercise on weight loss in obese children. J Pediatr 1985;107(3):358–61.
54. Saelens B, Sallis J, Wilfley D, et al. Behavioral weight control for overweight adolescents initiated in primary care. Obes Res 2002;10(1):22–32.
55. Kirk S, Brehm B, Saelens BE, et al. Role of carbohydrate modification in weight management among obese children: a randomized clinical trial. J Pediatr 2012;161(2):320–7.
56. Spieth LE, Harnish JD, Lenders CM, et al. A low-glycemic index diet in the treatment of pediatric obesity. Arch Pediatr Adolesc Med 2000;154(9):947–51.
57. Ebbeling CB, Leidig MM, Sinclair KB, et al. A reduced-glycemic load diet in the treatment of adolescent obesity. Arch Pediatr Adolesc Med 2003;157(8):773–9.
58. Heck AM, Yanovski JA, Calis KA. Orlistat, a new lipase inhibitor for the management of obesity. Pharmacotherapy 2000;20(3):270–9.
59. McDuffie JR, Calis KA, Uwaifo GI, et al. Three-month tolerability of orlistat in adolescents with obesity-related comorbid conditions. Obes Res 2002;10(7):642–50.
60. Chanoine JP, Hampl S, Jensen C, et al. Effect of orlistat on weight and body composition in obese adolescents: a randomized controlled trial. JAMA 2005;293:2873–83.
61. Huang MA, Greenson JK, Chao C, et al. One-year intense nutritional counseling results in histological improvement in patients with nonalcoholic steatohepatitis: a pilot study. Am J Gastroenterol 2005;100:1072–81.
62. Nobili V, Marcellini M, Devito R, et al. NAFLD in children: a prospective clinical-pathological study and effect of lifestyle advice. Hepatology 2006;44:458–65.
63. Schuppan D, Schattenberg JM. Non-alcoholic steatohepatitis: pathogenesis and novel therapeutic approaches. J Gastroenterol Hepatol 2013;28(Suppl 1):68–76.

64. Mahady SE, Webster AC, Walker S, et al. The role of thiazolidinediones in non-alcoholic steatohepatitis–a systematic review and meta analysis. J Hepatol 2011;55(6):1383–90.
65. Schwimmer JB, Middleton MS, Deutsch R, et al. A phase 2 clinical trial of metformin as a treatment for non-diabetic paediatric non-alcoholic steatohepatitis. Aliment Pharmacol Ther 2005;21:871–9.
66. Lavine JE, Schwimmer JB, Van Natta ML, et al, Nonalcoholic Steatohepatitis Clinical Research Network. Effect of vitamin E or metformin for treatment of nonalcoholic fatty liver disease in children and adolescents: the TONIC randomized controlled trial. JAMA 2011;305(16):1659–68.
67. Sanyal AJ, Chalasani N, Kowdley KV, et al. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. N Engl J Med 2010;362(18):1675–85.
68. Nobili V, Manco M, Devito R, et al. Lifestyle intervention and antioxidant therapy in children with nonalcoholic fatty liver disease: a randomized, controlled trial. Hepatology 2008;48:119–28.