Role of Exercise in Mitigating Pediatric Nonalcoholic Fatty Liver Disease

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Nonalcoholic fatty liver disease (NAFLD) represents a clinical spectrum of liver abnormalities resulting from excessive fat accumulation in hepatocytes. These abnormalities extend to simple steatosis and nonalcoholic steatohepatitis (NASH), which includes lobular inflammation and evidence of cell injury. This entity may lead to fibrosis, cirrhosis, and ultimately hepatic synthetic dysfunction. This problem is more common in those who are overweight and obese and who exhibit features of metabolic syndrome including abdominal obesity, insulin resistance, dyslipidemia, and hypertension (1).

Data suggest that children with NAFLD have increased morbidity and mortality in adulthood (2). Early occurrence likely indicates deleterious environmental exposures or genetic predispositions. Given the rising prevalence in children and adults, paralleling concomitant changes in lifestyle over the past three decades, there are emerging imperatives for screening, diagnosis, and intervention.

Background

Primary outcome measures in treating NAFLD vary. A commonly accepted goal of treatment is a decrease in hepatic steatosis and a decrease or resolution of inflammation and cell injury (i.e., NASH) and/or fibrosis, which may elude noninvasive assessment. A sustained decrease in serum alanine aminotransferase (ALT) from baseline is commonly used as a surrogate marker for histologic improvement and response to treatment (3,4). Evaluation of fibrosis requires histologic assessment obtained via liver biopsy. In children, NAFLD comorbidities (insulin resistance, dyslipidemia, and hypertension) are also important to mitigate to improve clinical outcomes.

There are currently no pharmacologics approved by the U.S. Food and Drug Administration for the treatment of NAFLD. Lifestyle modifications, including dietary interventions and a focus on increased physical activity, remain the first-line treatment options for pediatric NAFLD (5,6). There is limited evidence to support recommendations for one specific diet over another. While seemingly intuitive, the additive benefit of increased physical activity in conjunction with dietary modification has not been studied extensively, particularly in preadolescents.

Study Overview

The study conducted by Labayen et al. (7), reported in this issue of *Diabetes Care*, is a nonrandomized, prospective, controlled trial that included overweight and obese preadolescents residing in a single city in Spain and examined whether the addition of a supervised high-intensity aerobic exercise regimen, along with family-based lifestyle intervention and counseling, would result in a greater reduction of hepatic steatosis, adiposity, and cardiometabolic risk factors in 8- to 12-year-olds. The primary end point was a change in hepatic fat (HF) percentage measured by MRI. Secondary outcome measures evaluated changes in features of metabolic syndrome including BMI, fat mass index, abdominal fat, blood pressure, lipid profile, and glucose and insulin concentrations. ALT was not examined. A decrease in HF percentage, which was marginally elevated overall, was noted only in the group that participated in exercise in addition to lifestyle education and counseling. Both treatment groups demonstrated an improvement in adiposity and insulin resistance—features of the metabolic syndrome.

Study Strengths and Weaknesses

This is one of the first studies to examine the impact of exercise on HF percentage utilizing MRI in a preadolescent population. The authors report a nearly 20% reduction in HF in the intensive group as well as a reduction in LDL compared with the control group. Hepatic steatosis was defined as $\geq$5.5% HF as determined on MRI. It is important to note that study participants did not have an established diagnosis of NAFLD. The percentage of HF noted at the time of enrollment was low in both the control and intensive-exercise

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groups with a mean of 5.2% and 5.6%, respectively. These low baseline values call into question the clinical significance of minor changes in HF given the absence of relation to features of NASH involving cell injury and fibrosis and the likely minimal clinical significance of altering hepatic fat fractions by as little as 1%. When examining the effect of exercise on NAFLD in children, the changes observed in preadolescents with minimal or no NAFLD, and minimal or no elevation of ALT, are minimally significant.

Although γ-glutamyl transferase was included in study analysis, the authors chose not to report ALT, which has been regarded as a standard screening test for NAFLD, particularly NASH (5,8). Prior studies demonstrated a relation between change in ALT and histologic response (3,4). While ALT provides an indirect estimate of prevalence of NAFLD, it has limited sensitivity and specificity (8). The prevalence of NAFLD is underestimated using this measure, but the degree of underestimation depends in part on the ALT threshold used. These limitations highlight the need for other noninvasive screening modalities. The authors chose a change in HF percentage as measured by MRI as their primary outcome. Imaging modalities, including MRI, have not been sufficiently validated in children with NAFLD as surrogate markers of histologic improvement, though emerging data shows promise (9,10,11). Utility appears to be limited to patients with the highest and lowest degrees of steatosis, with need for improvement in the diagnostic accuracy pertaining to the mild to moderate range of HF content (9). MRI-estimated steatosis is also limited by fibrosis stage. Barriers to routine use include cost, lack of universal availability, and insufficient data to relate change shown in MRI to changes in NASH features. Percutaneous liver biopsy remains the clinical standard for the diagnosis of NASH and for assessing histologic improvement following treatment.

It is also interesting to note that the authors did not observe a significant change in percentage of HF in the control group that underwent lifestyle intervention and counseling. Schwimmer et al. (12) published a randomized clinical study in adolescent males with NAFLD and found that a diet low in free sugars resulted in significant improvement in hepatic steatosis compared with usual diet as assessed by MRI. Again, these differences may be attributed to the relatively low baseline HF content in the current study population.

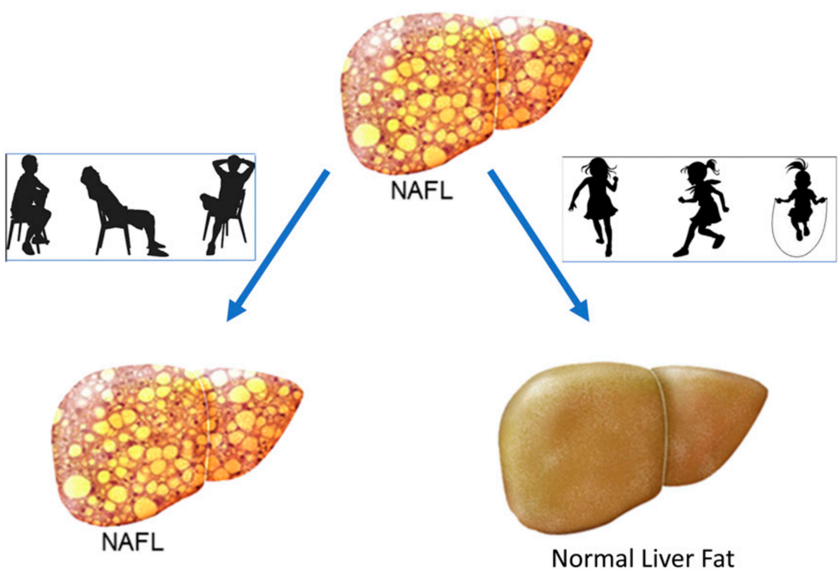

Figure 1—Exercise reduction of hepatic steatosis in children.

The results of this study (7) should be viewed in light of study limitations, including the nonrandomized and nonblinded study design, the homogeneous population, and the lack of a minimum HF cutoff to assess clinically meaningful response. It is also important to recognize that the study was of relatively short duration. Future studies should consider increasing the length of follow-up in order to more accurately assess the sustained benefits of exercise intervention.

Importance of the Work and Future Directions for the Field

The study by Labayen et al. (7) highlights several of the inherent difficulties in the management of pediatric NAFLD, namely, long-term monitoring and difficulty with adherence to current treatment. It is unknown whether the degree of steatosis in children with NAFLD impacts health outcomes or prognosis. Further studies are needed to delineate the natural history of pediatric NAFLD. To achieve this, we must establish noninvasive methods for diagnosis and monitoring to grade and stage steatosis, inflammation, hepatocellular injury, and fibrosis. In this study, the authors demonstrate that lifestyle intervention with exercise and dietary counseling can reduce hepatic fat in those who may or may not have fatty liver (Fig. 1).

Strict adherence to both dietary and lifestyle modification with the inclusion of high-impact aerobic exercise, while effective, may also be cost prohibitive and time intensive. Lifestyle modification is essential but difficult to maintain in the long term. Several families declined to participate in the intensive intervention at study onset due to the time commitment. Though not reaching statistical significance, the dropout rate was $>2\times$ higher in the exercise group (mean attendance rate 72%) compared with the control group. Likely, a number of socioeconomic factors play a contributory role in the underlying etiology of obesity and resultant NAFLD. Future efforts must continue to develop pharmacologic treatment adjuncts to employ in conjunction with lifestyle intervention for the treatment of pediatric NAFLD.

Duality of Interest. J.E.L. is an ad hoc consultant to Allergan, Novartis, Novo Nordisk, Janssen, and Madrigal and has a grant for a clinical trial with Genfit. No other potential conflicts of interest relevant to this article were reported.

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