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A Multidisciplinary Clinical Program is Effective in Stabilizing BMI and Reducing Transaminase Levels in Pediatric Patients with NAFLD

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Abstract

Weight loss is an effective treatment for children with non-alcoholic fatty liver disease (NAFLD) but it is very difficult to achieve outside of an intensive weight management program. We hypothesized that one can achieve success in improving NAFLD and weight-related outcomes in a structured and focused multidisciplinary clinical program feasible to implement in a gastroenterology clinic.

Methods—We prospectively tracked the clinical status of our patients enrolled in a multidisciplinary program of dietary and exercise advice through an Institutional Review Board-approved NAFLD registry. Each patient met with a gastroenterologist and dietician every 3 months for 30 minutes to set individualized goals and monitor progress.

Results—108 children have been enrolled in the registry and of the 83 that were eligible for 1 year follow-up and included in the analysis, 39 patients returned, resulting in a 47% follow-up rate. These 39 patients showed statistically significant improvements in mean BMI z-score (−0.1 units, $p < 0.05$), total (−11 mg/dL, $p < 0.05$) and low density lipoprotein cholesterol (−9 mg/dL, $p < 0.05$), and serum alanine aminotransferase (ALT) levels (−36 U/L) and aspartate amino transferase (AST) levels (−22 U/L) levels.

Conclusion—A clinically feasible multidisciplinary program of every 3 month 30 minute visits to set and monitor nutrition and exercise goals, stabilized mean BMI z-score and significantly improved aminotransferase levels at 1 year follow-up in obese pediatric patients with NAFLD.

Introduction

The most effective and obvious treatment of obesity and its co-morbidities in children and adults is weight loss (1, 2). This fact is as true for the hepatic component of the metabolic syndrome; nonalcoholic fatty liver disease (NAFLD); as it is for diabetes or hyperlipidemia (3–5). However successful weight management in obese children, particularly severely-obese children (body mass index or BMI 99%ile), remains challenging and often requires

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intensive multidisciplinary programs. The only FDA- approved therapy for weight loss in adolescents, orlistat, is moderately effective in achieving short term weight loss, but is often limited in use in young patients due to adverse gastrointestinal side effects (6). Though weight loss surgery has been shown to significantly improve weight and comorbid disease in adults, it is currently recommended only for severely obese adolescents with significant steatohepatitis (6, 7). Thus, the only viable alternative to achieve weight loss in children that is currently available is standard dietary caloric restriction and physical exercise.

NAFLD, which affects 10% of children in the United States, and its more severe form nonalcoholic steatohepatitis (NASH), have been shown to improve with weight loss through diet and exercise in clinical trials and prospective studies which include structured nutrition-behavior-exercise interventions (7–10,13). These intensive and focused programs effectively reduce body mass index (BMI) and alanine amino transferase (ALT) levels when used within research protocols, but outcomes of clinical programs in the United States are lacking, potentially in part due to third party payer practices which often do not compensate adequately for obesity management. Further, obesity management often takes place in a multidisciplinary setting which can significantly prolong visit time and impact clinic flow. We were faced with this issue when developing a clinical program for diagnosing and managing NAFLD, within the limited reimbursable time available per patient in a sub-specialty gastroenterology clinic. We established the Cincinnati Children's Steatohepatitis Center (CCSC) in 2007 with the aim to use the best available evidence-based evaluation and management of pediatric patients with NAFLD and to identify and offer innovative preventive and therapeutic strategies in a clinical setting. This report presents the initial outcomes of lifestyle management from our multidisciplinary clinical program.

Materials and Methods

In the CCSC, we prospectively tracked the clinical status of our patients with NAFLD while providing dietary and exercise advice. Patients met with a gastroenterologist, nurse and dietician every 3 months to set individualized goals and monitor progress. Dietary goals focused on reducing added sugar and saturated fat intake as these dietary variables have been linked to increased risk of NAFLD and NASH (11). Each patient has an initial intake visit of 60 minutes duration; subsequent follow-up visits were of 30 minutes duration. Each visit involved a discussion with the pediatric gastroenterologist to understand the current and past social, dietary and exercise milieu of the patient. A standard questionnaire (Appendix A, <http://links.lww.com/MPG/A209>) was used to elicit and identify barriers and opportunities for the success of weight reduction measures in the patient. At follow-up visits this initial assessment tool was replaced by a shorter questionnaire (Appendix B, <http://links.lww.com/MPG/A210>) that reviewed previously established goals. The results of prior testing and liver biopsy (if applicable) were discussed and weight and BMI changes were graphically demonstrated. The patient and family then met with the team's registered dietician (RD) who reviewed specific details of diet and exercise goals set in collaboration with the patient and physician. The RD also measured waist circumference and body fat by bio-electric impedance (BIA) at this visit. This was followed by a nursing assessment which involves going over the goals for both diet and exercise set by the patient and team prior to release from the clinic visit.

An IRB-approved registry, established in November 2007 at Cincinnati Children's Hospital Medical Center (CCHMC), enrolled 108 patients (out of 115 patients approached after screening) between 11/2007 and 4/2011. Enrollment criteria included chronically elevated liver enzymes (ALT >45 U/L, Aspartate aminotransferase AST > 45 U/L) after exclusion of other liver diseases by standard laboratory testing including: hepatitis C antibody, alpha-1 antitrypsin, hepatitis B surface antigen, serum iron, ferritin, and total iron binding capacity.

(TIBC), autoantibody profile, celiac screening with tissue transglutaminase antibody and immunoglobulin A levels, and ceruloplasmin and 24 hour urine copper measurement when indicated. Other obesity co-morbidities were also evaluated and referral to relevant specialties made when clinically indicated: type 2 diabetes, sleep apnea, hyperlipidemia, polycystic ovary syndrome, hypertension, and symptomatic cholelithiasis or cholecystitis.

Liver biopsy was conducted when the following clinical criteria were satisfied: not losing weight at follow-up visits and persistently (>3 months) elevated liver enzymes without any specific diagnosis identified from initial serological evaluation for other causes of liver disease. Histological diagnosis of NASH was made by an experienced pediatric pathologist. Subsequently, the histological criteria developed in the NASH Clinical Research Network were used to grade and stage the biopsies.(12). Four of these children were receiving Vitamin E for part of this follow-up period. Four children were referred to an intensive weight management program (HealthWorks) at Cincinnati Children's and did complete at least 5 visits to this program. Outcomes were analyzed with and without these 4 patients and results did not change, so they were not excluded from our final analysis.

The following outcomes of patients eligible for one year follow-up (range 9–15 months) as of 4/2011 were examined and included; change in BMI z-score, and laboratory test values of ALT, AST, gamma glutamyltransferase (GGT), lipid profile (triglycerides, high density lipoprotein; HDL, low density lipoprotein; LDL, and total cholesterol), insulin, glucose, and calculated homeostatic model assessment of insulin resistance (HOMA-IR).

Graphpad PRISM v5 software was used to perform statistical analysis of outcomes and demographic data using Fisher's exact test or paired t-test as appropriate. Changes in mean values from initial visit to one year follow-up visit were compared using paired t-test in SAS v9.2 and graphs were generated in Graphpad PRISM v5 software.

Results

Of the 108 children enrolled in the CCSC registry, 86 were eligible for one year follow-up. Of those eligible for follow-up, one patient was excluded from the analyses for not having baseline laboratory data within 3 months of the initial visit, which would not allow us to analyze a change in lab values. In addition, one patient was excluded for having a liver biopsy indicating fibrosis stage greater than three, indicating that the child may have advanced liver disease. Another patient was excluded following bariatric surgery performed during the one year follow-up time period. Of the remaining 83 patients included in the analyses, 39 patients returned to clinic within one year of their initial visit, resulting in a 47% follow-up rate. We compared the sub-set of patients who completed one year follow-up against those who were lost to follow-up and the only statistically significant difference was that those who returned to clinic were more likely to have had a liver biopsy performed at baseline ($p<0.05$) (Table 1).

Among the 39 patients who returned for one year follow-up, the mean age at baseline was 14 years which was not different for the whole cohort when compared to those lost to follow up (Table 1). Eighty-five percent of these patients were white and 72% were male. All patients were obese (BMI ≥ 95thile), 76% were severely obese (BMI ≥ 99thile), 91% were insulin resistant, 54% had significant dyslipidemia as defined by having triglyceride levels greater than 300 mg/dL and LDL levels greater than 160 mg/dL on at least two occasions and 46% had hypertension as defined by SBP or DBP ≥ 90th percentile or ≥ 120/80. The mean BMI value at baseline was 37 U/L, mean ALT was 110 U/L and mean AST was 81 U/L. Seventeen out of the 39 patients had a liver biopsy performed at baseline and 100% of the biopsies indicated histologically defined NASH.

At the one year follow-up visit, mean BMI z-score stabilized. (-0.1 units, $p < 0.05$) (Figure 1). In addition, 69% of patients had a decrease in BMI at one year. Mean ALT levels (-36 U/L) (Figure 2A), AST levels (-22 U/L) (Figure 2B), total cholesterol levels (-11 mg/dL) (Figure 2C) and LDL levels (-9 mg/dL) (Figure 2D) were significantly lower at one year follow up ($p < 0.05$). While other lab values including GGT, serum triglycerides, HDL, insulin, glucose and HOMA-IR decreased, they did not reach statistical significance (Figures 3A–3F).

Discussion

We present one year outcome data from a clinically feasible multidisciplinary intervention model for the pediatric NAFLD pandemic. Our patients were followed in 30 minute visits in an outpatient setting every 3 months by only a gastroenterologist, a nurse and a registered dietitian. Despite the lack of frequent visits (biweekly or monthly) and formal exercise or psychology components, we were able to achieve stabilization in BMI z-score and improvements in serum aminotransferase levels (ALT and AST).

Several pediatric studies have shown clear benefit to structured lifestyle interventions in a clinical research scenario (8–10, 13, 14). Lifestyle intervention with diet and increased physical activity induces weight loss and is associated with a significant improvement in liver histology and laboratory abnormalities in a pediatric NAFLD cohort (8). In the majority of cases however, these programs were more intensive with frequent visits and added psychological and exercise components which are not typically feasible to reproduce in a busy gastroenterology practice. Additionally, in the United States, our current health care system often has significant gaps in coverage for weight management services for both children and adults, making this type of intensive care unaffordable and inaccessible to many obese patients. However, half of our initial patients did not return for follow-up. This is a limitation to our study wherein we had only 47% of our patients' follow-up at one year. Our overall attrition rate is similar to that seen in structured weight loss programs(15), though this may not be the best comparison as we are not structured as an obesity clinic but rather as a highly focused sub-specialty pediatric liver disease clinic. Interestingly, we had a much better follow up rate in the children that underwent liver biopsy. We further speculate that this increased follow up may relate to the families realizing the true implications of this liver disease.

Our study is limited by small size and the potential influence of Vitamin E on ALT levels in a small minority of our patients. We stopped accruing additional patients into this specific analysis as we have started to prescribe high dose Vitamin E in our patients who have biopsy proven NASH, based on results from a randomized controlled trial suggesting a greater resolution of NASH compared with placebo (16). We however did find on closer scrutiny of our patients' data that 4 of the 39 patients did use Vitamin E within our practice. When these patients were excluded from our analyses the change in total cholesterol and LDL did remain significant though change in mean BMI z-score was no longer significant (the p value went from 0.04 to 0.06), though we cannot speculate on a direct impact of Vitamin E on BMI. This may potentially be more of a type 1 statistical error. In addition, the change in mean ALT and AST values were also no longer significant (ALT p-value went from 0.02 to 0.06 and AST p-value went from 0.04 to 0.13).

A further caveat to our data is that 4 of the 39 patients that were included in the one year follow up of this study were also followed regularly (at least 5 times during the one year follow up period) by other weight loss programs within CCHMC. We cannot therefore be certain if some of the benefits seen in our cohort are not due the patient attending rigorous exercise or diet programs followed by these children. Albeit, when we excluded these four

patients no change in statistical outcomes was seen. We can speculate that our program could have been a positive influence on the decision of these individuals to seek further assistance from intensive weight loss programs (see <http://links.lww.com/MPG/A211> for supplementary data). The fact that there was a significant increase in follow up rates in children who had undergone liver biopsies suggests that this may be a factor in retention as well.

Finally, this body of work has a limitation that all children did not undergo a liver biopsy and also that we were only able to capture data for a single year of follow-up. While it would have been ideal to have a study design with adjustment for multiple comparisons we are reporting the outcomes of a real world clinic and fully acknowledge the limitations of our data and its analyses. These data should be considered clinical observations that are hypothesis generating and need a structured clinical trial to robustly test the success of our approach. Interestingly, all children who underwent liver biopsy met histological criteria for NASH which may reflect our program's conservative threshold for liver biopsy or the fact that they had more severe disease.

In conclusion, despite the limitations of our high attrition rates, our results demonstrate that a clinically feasible multidisciplinary NAFLD program (every 3 months visits to set and monitor lifestyle goals) can stabilize mean BMI z-score and significantly improve ALT, AST, total and LDL-cholesterols at 1 year follow up for the patients that do complete follow up. The improvement in our program is comparable to improvement seen in a more intensive pediatric weight management programs mean BMI z score decrease of -0.15 ± 0.15). Though both approaches are limited by high attrition rates, common to clinical pediatric weight management interventions, they underscore that benefits can result from offering multidisciplinary lifestyle intervention to children with NAFLD, even on a more intermittent basis of every 3 month visits.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Acronyms

NAFLD	Nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
BMI	body mass index
ALT	alanine amino transferase
CCSC	Cincinnati Children's Steatohepatitis Center
CCHMC	Cincinnati Children's Hospital Medical Center
AST	Aspartate aminotransferase
TIBC	total iron binding capacity
GGT	gamma glutamyltransferase

HOMA-IR

homeostatic model assessment of insulin resistance

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Figure 1.
Change in BMI Z-Score from baseline visit to one year follow-up visit

Figure 2.
Changes in laboratory parameters from baseline visit to one year follow-up visit. (P<0.05 = *)

Figure 3.
Changes in laboratory parameters from baseline visit to one year follow-up visit.

Table 1

Baseline characteristics for patients eligible for one year follow-up.

	All patients eligible for 1 year follow-up (N=83)	Completed 1 year follow-up (N=39)	Did not complete 1 year follow-up (N=44)
Male	52 (63%)	28 (72%)	24 (55%)
White	74 (89%)	33 (85%)	41 (93%)
Biracial	4 (5 %)	2 (5%)	2 (5%)
Hispanic	9 (11%)	5 (13%)	4 (9%)
Mean age (range)	14 (4–20)	14 (4–20)	14 (6–20)
Liver biopsy performed (prior to or within 6 months after baseline visit)	24 (29%)	17 (43%) *	7 (16%) *
Biopsy confirmed NASH	22/24 (92%)	17/17 (100%)	5/7 (71%)
Mean ALT value	91 U/L	110 U/L	74 U/L
Mean AST value	71 U/L	81 U/L	62 U/L
Mean BMI value	36	37	36
Obese	82/82 (100%)	38/38 (100%)	45/45 (100%)
Insulin resistant	63/70 (90%)	31/34 (91%)	32/36 (89%)
Dyslipidemia	50 (60%)	21 (54%)	29 (66%)
Hypertension	30 (36%)	18 (46%)	12 (27%)
Type 2 diabetes	9 (11%)	3 (8%)	6 (14%)

*
p<0.05