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Prevalence and Outcome of Nonalcoholic Fatty Liver Disease in Adolescents and Young Adults Undergoing Weight Loss Surgery

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Abstract

We evaluated the prevalence of NAFLD (nonalcoholic fatty liver disease) and NASH (nonalcoholic steatohepatitis) in 27 adolescents referred for weight loss surgery (WLS). On biopsy 18 patients (66.7%) had NAFLD, and of those, 10 patients (37.0%) had NASH and 11 (40.7%) had fibrosis. Insulin, HbA1C and homeostatic model assessment of insulin resistance (HOMA-IR) were significantly higher in patients with NASH than those without NASH. Following WLS, 40% of NASH patients had persistently elevated aminotransferase levels despite weight loss. We found that NASH is underdiagnosed in adolescents referred for WLS and hyperinsulinemia, HOMA-IR and HbA1c can aid in identifying high-risk patients.

Keywords

Non-alcoholic fatty liver disease; non-alcoholic steatohepatitis; Obesity; Adolescence; Roux-en-Y Gastric Bypass

Nonalcoholic fatty liver disease (NAFLD) is rising dramatically in adolescents and young adults and is now the most common cause of liver disease among adolescents in the US. NAFLD comprises a spectrum of hepatic pathology ranging from steatosis to nonalcoholic steatohepatitis (NASH). NASH in children can progress to cirrhosis and is associated with

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increased mortality when compared to the general population.[1, 2] However, clinicians infrequently evaluate adolescents for NAFLD despite guidelines recommending routine screening.[3, 4] The present study sought to evaluate the prevalence of histologically-proven NAFLD and NASH among adolescents and young adults presenting for WLS and to compare this to the frequency of NAFLD and NASH diagnosed before WLS referral. Further, we sought to evaluate metabolic differences in adolescents and young adults with NASH compared to those with steatosis and to evaluate the frequency of elevated aminotransferase levels after WLS.

This retrospective cohort study included all patients aged 22 years or less who underwent Roux en-Y gastric (RYGB) bypass at the Massachusetts General Hospital Weight Center (MGH-WC) between 2006-2012.

Subjects were assessed by treating physician for weight, height, BMI and co-morbid diseases including diabetes mellitus (DM), hypertension, obstructive sleep apnea (OSA) and dyslipidemia. Patients with other causes of chronic liver disease were excluded.

All subjects undergoing WLS at the MGH-WC have a wedge liver biopsy. Liver biopsies were reviewed by single blinded hepatopathologist (JM) and assessed for NASH and fibrosis stage as described by Kleiner et al. [5] As our subjects were adolescents, rather than prepubertal children, biopsies were assessed for Type 1 NASH (the histopathological type typically seen in older adolescents and adults).[6] NAFLD was defined by the presence of grade 1 or greater steatosis not meeting criteria for NASH. NASH was defined as lobular inflammation >=1, hepatocyte ballooning >=1 and steatosis grade >=1.[7] Non-NASH patients include both patients with normal liver histology and steatosis alone.

All statistical analysis was performed using SAS software, version V.9.2 (SAS Institute, Cary, NC). Continuous variables were analyzed using a Student's t-Test when normally distributed and paired Wilcoxon signed rank test was used when not normally distributed. Categorical variables were analyzed using a Chi square test or Fisher's exact test as appropriate. This study was approved by the Partners Health Care Human Research Committee.

Twenty-seven patients underwent WLS during the study period (Table 1). Only 2 subjects (7.4%) carried a diagnosis of NAFLD based on imaging at the time of presentation.

At our center seven of 27 patients (25.9%) were found to have abnormal ALT levels (>30U/L). All subjects underwent a wedge liver biopsy at the time of WLS. Based on histology, 18 subjects (66.7%) were found to have NAFLD and of those, ten subjects (37.0% of the total cohort) had NASH and 11 subjects (40.7%) had fibrosis stage 1a or greater. Two patients who did not meet criteria for NASH had stage 1a fibrosis. A single subject, who did not carry a diagnosis of NAFLD prior to referral, had advanced fibrosis (stage 3). Of the 2 patients previously diagnosed with NAFLD prior to referral, one had grade 2 steatosis only, and one had NASH with stage 1a fibrosis.

There were no significant differences between patients with or without NASH in ethnicity, age, BMI, prevalence of DM or hyperlipidemia. In addition, there was no significant

difference in aspartate aminotransferase (AST) or ALT levels, cholesterol, HDL, or triglyceride levels. There was a non-significant trend toward an increased prevalence of OSA in patients with NASH as compared to those without NASH (including simple steatosis and no steatosis) (47.1% vs. 80.0%, respectively; p=0.08).

Fasting insulin levels were significantly higher in subjects with NASH than in those without NASH (42.8μU/mL vs. 21.9μU/mL, p=0.02). HOMA-IR was significantly higher in NASH patients (5.9 vs. 5.4, p=0.02) as was HbA1C (5.9% vs. 5.4%, p=0.01).

Ten patients had NASH on liver biopsy. Eight of 10 patients (80%) had follow-up of their NASH in the form of liver function tests (n=8), imaging (n=1) and/or repeat liver biopsy (n=1) between 6 months and 2 years following surgery. The single patient who had a repeat biopsy two years after surgery had normal liver histology. Likewise, the patient who underwent a CT scan one year after surgery had no radiographic evidence of steatosis. Both patients had normal liver function tests before and after surgery. However, in four of the six patients who had only liver function testing between 1 and 2 years after surgery, 4 patients (40% of total cohort) had ALT > 30 U/L and 3 patients (30% of total cohort) had AST>32 U/L. There was no difference in pre and post-surgical mean ALT (30.3U/L vs 39.3 U/L, p=0.52) or mean AST before and following surgery (23.9 U/L vs. 32.4 U/L, p=0.58) or in the percentage of patients with elevated ALT (30.0% vs 40.0%, p=0.48) or AST (10% vs. 30.0%, p=0.63) before and after surgery. Thus, while 4 patients (40% of NASH cohort) had evidence of NASH resolution by biopsy, imaging or normalization of aminotransferase levels, 4 patients (40% of NASH cohort) had persistently abnormal aminotransferase levels despite weight loss.

In conclusion, we found that NAFLD is underappreciated but highly prevalent in adolescents and young adults with obesity referred for WLS. Insulin, HbA1C, HOMA-IR were significantly higher in patients with NASH and may help clinicians identify which patients warrant comprehensive evaluation. Finally, we found that despite significant weight loss, 40% of patients with NASH had persistently elevated aminotransferase levels up to 2 years after surgery, suggesting ongoing liver injury.

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What is already known about this subject?

- NAFLD is the most common cause of liver disease among adolescents.
- NASH is associated with elevated aminotransferase and glucose levels in adolescents.
- Weight loss surgery in adults leads to the resolution of NASH in a large proportion of patients.

What this study adds?

- NAFLD is underappreciated in adolescents with obesity referred for weight loss surgery.
- NASH is all associated with elevated insulin, HbA1AC and HOMA-IR.
- NAFLD, as evidenced by persistently elevated aminotransferase levels, may not resolve after weight loss surgery.

Table 1
Baseline Patient Characteristics Prior to Weight Loss Surgery

	Entire Cohort (N=27)
Age (years)	19 (15-22)
Gender	5M/22F
Race/Ethnicity	
Asian	2 (7.1%)
Black	3 (11.1%)
Hispanic	7 (25.9%)
White	13 (48.2%)
Other	2 (7.4%)
Weight (kg)	148.7 (105.2-249.1)
BMI (kg/m2)	52.7 (38.8-71.8)
Type 2 Diabetes	3 (11.1%)
Obstructive Sleep Apnea	16 (59.3%)
Hyperlipidemia	8 (29.6%)
NAFLD Diagnosed Before Surgery	2 (7.4%)

Table 2
Metabolic Characteristics of NASH and Non-NASH Patients

	Non-NASH (n=17)	NASH (n=10)	p-value
Age, (years)	19.4 (16-22)	18.3 (15-22)	0.27
Gender	3M/14F	2M/8F	0.88
Race/Ethnicity			0.24
Asian	0 (0%)	2 (20.0%)	
Black	3 (17.6%)	0 (0%)	
Hispanic	4 (23.5%)	3 (30.0%)	
White	8 (47.1%)	5(50.0%)	
Other	2 (11.8%)	0 (0%)	
BMI, (kg/m2)	51.5 (42.6-71.8)	54.7 (38.8-67.2)	0.35
ALT, (U/L)	26.4 (11.0-69.0)	30.3 (17.0-53.0)	0.52
Glucose, (mg/dL)	87.1 (74-107)	98.4 (74-134)	0.06
Insulin, (uU/mL)	21.9 (6-37)	42.8 (16-83)	0.02
HOMA-IR	4.6 (1.3-8.0)	11.3 (3.3-26.2)	0.02
HbA1C (%)	5.4 (4.7-6.3)	5.9 (5.3-7.4)	0.01
HDL, (mg/dL)	41.2 (26-73)	36.3 (28-47)	0.29
Triglycerides, (mg/dL)	126.9 (53-309)	122.8 (44.0-245.0)	0.90
LDL, (mg/dL)	109.3 (69-172)	79.0 (42-132)	0.02
Type 2 Diabetes Mellitus, (%)	1 (5.9%)	2 (20.0%)	0.12
Obstructive Sleep Apnea, (%)	8 (47.11%)	8 (80.0%)	0.08