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Research Article

Is Nonalcoholic Fatty Liver Disease Associated with Gastroesophageal Reflux Symptoms In Children And Adolescents?

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Abstract

Recently, nonalcoholic fatty liver disease (NAFLD) has been found to be associated with a high prevalence of symptoms of gastroesophageal reflux disease (GERD) in adults. Aims of this study were to assess the prevalence of GERD symptoms in children and adolescents with NAFLD, and to determine whether ectopic fat depots, including liver fat and visceral adipose tissue (VAT), are linked to GERD. This study included 108 overweight/obese children and adolescents aged 6-16 years. Fifty-four patients met the criteria for diagnosis of NAFLD [i.e. hepatic fat fraction (HFF)≥ 5% on magnetic resonance imaging (MRI)]. All enrollees underwent a detailed clinical history, a complete physical examination, laboratory tests, and phenotyping of abdominal and liver fat by MRI. GERD was evaluated using the Pediatric GERD Symptom and Quality of Life Questionnaire. There were no significant differences in age, gender, pubertal status, and body mass index-standard deviation score between the two groups. Children with NAFLD had a higher waist circumference, and VAT than those without liver involvement. GERD symptoms were significantly more frequent in NAFLD patients than in subjects without NAFLD (61.0% vs 31.5%; P< 0.01), and GERD symptom score resulted significantly higher [mean, 3.4 (SD, 2.6) vs 1.9 (1.4); P< 0.01]. In multivariate analysis, GERD symptom score was independently associated with VAT (P< 0.05) and HFF (P< 0.001). Conclusion: Our preliminary results indicate that NAFLD is a risk factor for GERD in children and adolescents, and that the risk of GERD symptoms rises progressively with the increase in both visceral and liver fat.

ABBREVIATIONS

NAFLD: Nonalcoholic fatty liver disease; NASH: nonalcoholic steatohepatitis; MetS: Metabolic syndrome; GERD: Gastroesophageal reflux disease; VAT: Visceral adipose tissue; SAT: Subcutaneus adipose tissue; BMI: Body mass index; MRI: Magnetic resonance imaging; HFF: Hepatic fat fraction; SDS: Standard deviation score; WC: Waist circumference; PQDQ: Pediatric GERD symptoms and Quality of Life Questionnaire; HDL-C: High-density lipoprotein cholesterol; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: Gamma-glutamyl transferase; HSCRP: High-sensitive C-reactive protein; HOMA-IR: Homeostasis model assessment of insulin resistance; SD: Standard deviation; IQR: Interquartile range.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a spectrum of fat-associated liver conditions that can result in end-stage liver disease and the need for liver transplantation [1]. Simple steatosis, or fatty liver, occurs early in NAFLD and may progress to nonalcoholic steatohepatitis (NASH), fibrosis and cirrhosis with increased risk of hepatocellular carcinoma [1]. Over the last two decades, the rise in the prevalence rates of overweight and obesity explains the emergence of NAFLD as the leading cause of chronic liver disease in pediatric populations worldwide [2,3]. The liver is one of the main ectopic sites where lipids may accumulate in obese subjects. Ectopic fat disposition occurs particularly when the energy storage capacity of the adipose tissue is exceeded, leading to increased net lipid flux to non-adipose organs, thereby

causing lipotoxiciy and insulin resistance [4,5]. As described in adults, children and adolescents with fatty liver display insulin resistance, glucose intolerance, and dyslipidemia [6,7]. Thus NAFLD has emerged as the hepatic component of the metabolic syndrome (MetS) [8] and a strong cardiovascular risk factor even at a very early age [9,10].

Gastroesophageal reflux disease (GERD) is a common condition, defined by the passage of gastric contents into the esophagus, causing troublesome symptoms and/or complications, affecting up to 20% of the general population [11]. Evidence has emerged suggesting a link between metabolic syndrome, especially obesity and visceral fat accumulation, and the onset of GERD [12-14]. Moreover, in recent studies, NAFLD has been found to be associated with a high prevalence of symptoms of GERD in adults [15-17]. NAFLD has never been investigated in children as possible risk factor for GERD. Therefore, the aims of this study were to assess the prevalence of GERD symptoms in children and adolescents with NAFLD, and to determine whether ectopic fat depots, including liver fat and visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT), are linked to GERD.

MATERIALS AND METHODS

Study design and patient

The study population consisted of obese children and adolescents [body mass index (BMI) above the 95th percentile for age and gender] who were recruited at the Hepatology outpatient Clinic of the Department of Pediatrics, Sapienza University of Rome, Italy. The diagnosis of NAFLD was based on magnetic resonance imaging (MRI) with high hepatic fat fraction (HFF ≥ 5%) [18]. Other causes of chronic liver disease, including hepatic virus infections (hepatitis A-E and G, cytomegalovirus, and Epstein-Barr virus), autoimmune hepatitis, metabolic liver disease, α-1- antitrypsin deficiency, cystic fibrosis, Wilson's disease, hemochromatosis, and celiac disease were excluded with appropriate tests. Other exclusion criteria were history of type 1 or type 2 diabetes, renal disease, total parenteral nutrition, smoking or alcohol consumption, and use of hepatotoxic medications. For comparative purposes, a group of control subjects, matched for age, gender, pubertal stage and as closely as possible for BMI-standard deviation score (SDS) was recruited at the Lipid and Nutrition outpatient Clinics of the Department of Pediatrics, Sapienza University of Rome, Italy. The control group was composed of obese children with normal levels of aminotransferases, and without MRI evidence of fatty liver (HFF <5%) as well as of other causes of chronic liver disease (see above). Controls were also excluded if they had history of type 1 or type 2 diabetes, renal disease, smoking or alcohol consumption. Finally, the use of anti-inflammatory drugs, antibiotics or probiotics was considered among the exclusion criteria for both cases and controls.

All enrolled subjects had a complete physical examination [including measurements of weight, standing height, BMI, waist circumference (WC), determination of pubertal status], laboratory tests, and detailed phenotyping of abdominal and liver fat by MRI. The degree of obesity was quantified using Cole's least mean-square method, which normalizes the skewed distribution of BMI and expresses BMI as SDS [19]. GERD was evaluated using the Pediatric GERD Symptom and Quality of Life Questionnaire (PGDQ) [20].

The research protocol was approved by the local Ethics Committee (Policlinico Umberto I Hospital, Rome, Italy) and written informed consent was obtained from the next of kin, caretakers, or guardians on behalf of the children enrolled in this study, in accordance with principles of Helsinki Declaration.

Metabolic studies

Blood samples were taken from each subject, after an overnight fast, for estimation of glucose, insulin, C peptide, total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglycerides, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and high-sensitive C-reactive protein (HSCRP). Estimates of insulin sensitivity were calculated using homeostasis model assessment of insulin resistance (HOMA-IR) , defined by fasting insulin and fasting glucose [21].

Abdominal MRI

Abdominal MRI studies were performed on a 1.5T Siemens Avanto magnet (Siemens AG, Erlangen, Germany). The amount of hepatic fat content (% HFF) was measured by MRI as previously described and validated [18]. The three-point chemical-shift-fat-water separation method (fat-only dataset) was used to measure abdominal fat mass distribution [22]. MRI results were interpreted by an experienced radiologist who was blinded to clinical, laboratory and/or histologic findings.

Biochemical analyses

All analyses were conducted by COBAS 6000 (Roche Diagnostics). Insulin and C peptide concentrations were measured on cobas e 601 module (Electrochemiluminescence Technology, Roche Diagnostics), while the remaining analytes on cobas e 501 clinical chemistry module (Photometric Technology), according to the instructions of the manufacturer.

Statistical analysis

Statistical analyses were performed using the SPSS v. 20 package (IBM SPSS, Chicago, Illinois). The data are expressed as frequencies, mean with standard deviation (SD), or median with interquartile range (IQR), as appropriate. The differences between cases and control children in quantitative variables were evaluated by t-test or Mann–Whitney U-test, as appropriate. Proportions were compared by the chi square test. The Spearman's correlation coefficient and linear regression analyses were used to evaluate the relationship between GERD symptom score and the other continuous variables. A *P* value of less than 0.05 was considered to be statistically significant.

RESULTS AND DISCUSSION

Fifty-four obese children with NAFLD and 54 obese children without evidence of liver disease were enrolled. The mean age of cases and controls was 11.06 (SD 2.8) and 11.03 (SD 2.9) years, respectively. Both cases and controls included 24 girls and 30 boys. The mean BMI-SDS of cases and controls was 2.07 (SD 0.40) and 2.0 (SD 0.35), respectively. The clinical and laboratory

characteristics for cases and controls are shown in Table 1. By definition, HFF values were significantly different between the two groups. WC and VAT were significantly greater in obese subjects with NAFLD than in those without NAFLD. NAFLD patients had higher values for triglycerides, HSCRP, fasting insulin, C peptide, and HOMA-IR values when compared to subjects with no liver involvement. As expected, children with NAFLD had higher liver enzymes when compared to those without NAFLD. There were no differences between children with and without NAFLD with respect to SAT, total cholesterol and HDL-C, and fasting glucose.

Figure 1 shows the type and prevalence of GERD symptoms in children and adolescents with and without NAFLD. In NAFLD group the prevalence of subjects who experienced at least one of GERD symptoms was significantly higher than that observed among obese without liver involvement (61.0% vs 31.5%; P< 0.01). In children with NAFLD, we found a higher prevalence of regurgitation, heartburn, and extraesophageal symptoms. Similarly, GERD symptom score resulted significantly higher in the NAFLD than in the control group [mean, 3.4 (SD, 2.6) vs 1.9 (1.4); P< 0.01] (Figure 2). Within the entire study population, GERD symptom score was not correlated to age, BMI-SDS, and SAT. GERD symptom score was associated with VAT (Standardized coefficient β, 0.193; P < 0.05) and HFF (Standardized coefficient β, 0.262; P < 0.01). When a multivariate regression analysis was performed with variables such as age, gender, VAT and HFF included in the model, both VAT (standardized β coefficient, 0.201; P < 0.05) and HFF (standardized β coefficient, 0.245; P < 0.05) retained statistical significance (Table 2).

Table 1: Characteristics of obese children by liver status.

	NO NAFLD (n= 54)	NAFLD (n= 54)	
Age, years*	11.03 (2.9)	11.06 (2.8)	
Male gender*	30 (55.5)	30 (55.5)	
BMI-SDS	2.0 (0.35)	2.07 (0.40)	0.56
Waist circumference, cm	85 (9)	90 (8)	0.046
Abdominal fat Visceral adipose tissue, cm2	278 (216-424)	396 (297-572)	< 0.0001
Subcutaneous adipose tissue, cm2	1363 (1068-2176)	1721 (1145-2195)	0.26
Hepatic fat fraction, %	1.7 (1.0-3.1)	11.0 (7.0-20.0)	< 0.0001
Triglycerides, mg/dL	81 (52-114)	96 (68-149)	0.049
Total cholesterol, mg/dL	158 (140-190)	151 (132-182)	0.11
HDL-C, mg/dL	49 (43-54)	45 (37-53)	0.31
Aspartate aminotransferase, U/L	25 (11)	34 (26)	0.037
Alanine aminotransferase, U/L	26 (17)	52 (41)	< 0.0001
γ-glutamyl transferase, U/L	15 (8)	23 (12)	< 0.0001
Fasting glucose, mg/dL	85 (6)	88 (8)	0.33
Fasting insulin, μU/mL	11 (8-15)	20 (15-28)	0.001
Fasting C peptide, pmol/L	780 (576-887)	1075 (816-1302)	< 0.0001
HOMA-IR values	2.24 (1.80-3.17)	4.11 (2.95-6.67)	0.003

Results are expressed as n (%), mean (SD), or median (IQR).
Matched variables.
BMI-SDS, body mass index-standard deviation score; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; HSCRP, high-sensitive C reactive protein.

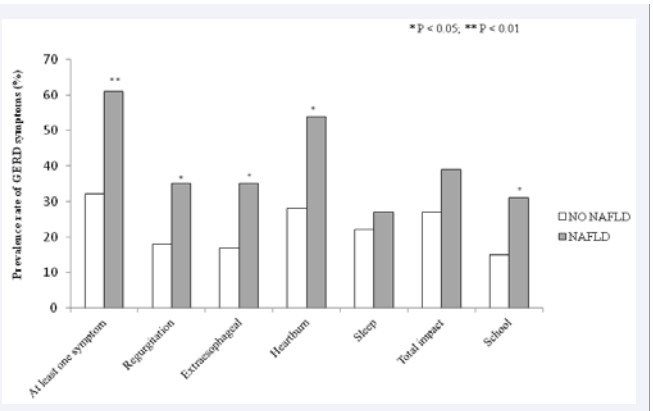

Figure 1 Type and prevalence rate of gastroesophageal reflux (GERD) symptoms in obese children and adolescents with and without nonalcoholic fatty liver disease (NAFLD).

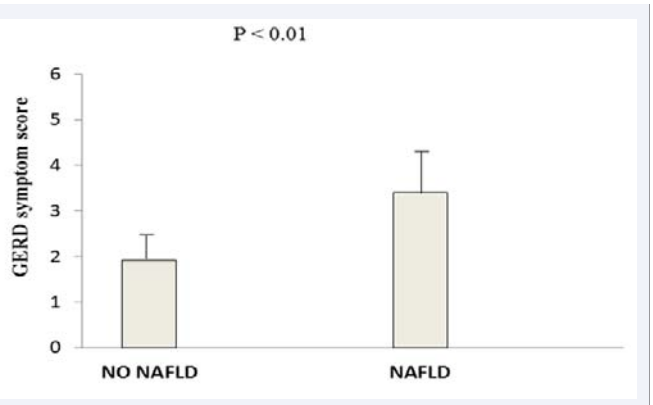

Figure 2 Gastroesophageal reflux (GERD) symptom score in obese children and adolescents with and without nonalcoholic fatty liver disease (NAFLD).

The few data available on the prevalence of GERD in patients with NAFLD are from the adult population [15-17]. Miele et al. [15], in a cross-sectional, case-control study of patients with NAFLD and age- and gender-matched control group, found that the prevalence of GERD symptoms is markedly higher in NAFLD patients than in the general population. In multivariate analysis, heartburn and belching were associated with NAFLD independently of BMI, MetS, increased WC, and GER medication. Fujikawa et al. [16] showed that the prevalence and severity of GERD symptoms are high in Japanese patients with NAFLD and the related risk factors are serum levels of triglycerides and total cholesterol but not BMI. Yet, Catanzaro et al. [17] showed that the prevalence of GERD typical symptoms is higher in patients with NAFLD, and that GERD is associated with higher BMI and MetS, but not with age and diabetes type 2.

As there are no pediatric studies on the association between GERD and NAFLD, the aims of the present study were to investigate in a series of obese children and adolescents with

Table 2: Multivariate linear regression analysis of the variables associated with GERD symptom score in the entire study population.

	GERD Standardized coefficient	score P
Age, years	0.097	0.343
Gender	0.134	0.175
VAT, cm^2	0.201	0.045
HFF, %	0.245	0.012

GERD, Gastroesophageal reflux disease; VAT, visceral adipose tissue; HFF, Hepatic fat fraction

NAFLD the prevalence of GERD symptoms, and to determine whether ectopic fat depots, including liver fat and abdominal visceral fat, are linked to GERD. Previous studies in children have investigated the relation between GERD symptoms and total [23,24] and central body fatness [25]. In a study involving overweight and obese children in comparison with a general normal-weight pediatric population, Quitadamo et al. [25] showed that both total and abdominal obesity are risk factors for the development of GERD symptoms. Moreover, the risk of GERD symptoms rised progressively with increasing BMI and WC, even in normal-weight children. Our data are therefore unique in showing that (A) GERD symptoms are significantly more frequent in NAFLD children than in obese subjects without NAFLD and (B) GERD symptom score is independently associated with visceral adipose tissue and hepatic fat, as measured by MRI.

Adipose tissue may play a pivotal role in the pathogenesis of GERD through different mechanisms as recently reviewed by Tilg et al. [26], increasing abdominal pressure with consequent esophageal acid irritation, increasing number and extent of reflux episodes [27], high fat diet or excessive caloric intake, that are long-term responsible for obesity and fatty liver, can determine frequency and severity of esophageal exposure to acid [28], release of adipokines and proinflammatory mediators which have direct effects on the stomach by facilitating gastrin release and on esophagogastric junction [29].

CONCLUSIONS

Our results indicate that NAFLD is a risk factor for GERD in children and adolescents, and that the risk of GERD symptoms rises progressively with the increase in both visceral and liver fat. Our findings may have important implications for future studies, which are asked to confirm, by the use of objective parameters such as impedance measurements, that ectopic fat accumulation may cause or exacerbate reflux symptoms.

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