METABOLIC, HORMONAL, OXIDATIVE, AND INFLAMMATORY FACTORS IN PEDIATRIC OBESITY-RELATED LIVER DISEASE

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Objective To examine the role of metabolic, hormonal, oxidative, and inflammatory factors in pediatric obesity-related liver disease.

Study design In 50 obese children (age 7 to 14 years) with (n = 20, group 1) or without (n = 30, group 2) hypertransaminasemia and ultrasonographic liver brightness, we studied insulin resistance (fasting glucose/insulin ratio [FGIR]) and serum levels of leptin, iron, transferrin, ferritin, C-reactive protein (CRP), white blood cell (WBC) count, tumor necrosis factor (TNF)-α, interleukin (IL)-6, C282Y and H63D mutations, and erythrocytic glutathione peroxidase (GPX) activity.

Results FGIR (6.7 ± 4.1 vs 9.2 ± 5.2; $P = .02$), serum ferritin (88.8 ± 36.0 vs 39.9 ± 24.0 ng/mL; $P = .0001$), serum CRP (5.4 ± 6.0 vs 1.1 ± 1.6 mg/dL; $P = 0.004$), and GPX (8.4 ± 0.9 vs 5.0 ± 0.5 U/g Hb; $P = .05$) were significantly higher and more frequently deranged in group 1 than in group 2. FGIR, ferritin, and CRP values were simultaneously deranged in 41% of the group 1 patients and in none of the group 2 patients ($P = .098$). Serum leptin, iron, and transferrin, WBC, TNF-α, IL-6, and C282Y and H63D mutations were similar in the 2 groups.

Conclusions Insulin resistance, oxidative stress, and low-grade systemic inflammatory status are implicated in pediatric obesity-related liver disease. These findings may be useful in planning pathophysiologically based therapeutic trials for hepatopathic obese children who are unable to follow hypocaloric diets. *(J Pediatr 2005;147:62-6)*

Liver involvement in obese individuals has become a leading cause of liver function test abnormalities.[1,2] It is classified within the abnormalities of nonalcoholic fatty liver disease (NAFLD), a condition ranging from simple hepatic steatosis (a putatively common and benign disease with an indolent course) to progressive necroinflammatory and fibrotic damage of the liver.[2,3] Although liver involvement is suggested by liver brightness on ultrasonography (US) and elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, the true prevalence of NAFLD remains obscure, largely because of the variability of definition criteria, including the threshold of hypertransaminasemia itself.[4,5]

NAFLD is being increasingly recognized in children.[6-16] The reported prevalence of hypertransaminasemia in obese children varies between 10%[11] and 24% to 25%,[10,12,13] and US liver brightness has been reported to vary between 22.5%[14] and 77%.[13]

The reasons underlying liver involvement and disease progression in only a proportion of obese individuals remain unclear. In adults and in animal models there is evidence that increased fat deposition within the hepatocytes of obese individuals results from augmented hepatic delivery of free fatty acids.[17,18] The latter is amplified by insulin resistance, which impairs suppression of lipolysis.[19] Excessive fatty acid oxidation in the liver generates free radicals, which damage hepatocytes and induce fibrogenesis through

ALT	Alanine aminotransferase	IL	Interleukin
AST	Aspartate aminotransferase	NAFLD	Nonalcoholic fatty liver disease
CRP	C-reactive protein	NASH	Nonalcoholic steatohepatitis
FGIR	Fasting glucose-to-insulin ratio	TNF	Tumor necrosis factor
FFA	Free fatty acid	US	Ultrasonography
GPX	Glutathione peroxidase	WBC	White blood cell
HFE	Hereditary familial hemochromatosis		

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cytokine production.[17,20] Two studies conducted in children that reported that the antioxidant vitamin E induced normalization of hypertransaminasemia but did not affect ultrasonographic liver brightness also support the concept that oxidative stress plays a pathogenetic role in obesity-related liver disease.[21,22] Although insulin resistance is considered pivotal to the development of fatty liver,[19] few data have been reported in the pediatric literature.[23,24] Similarly, abnormal iron handling and leptin levels are also implicated in the pathogenesis of fatty liver, but data in childhood are conflicting[19,25] and scarce.

Interleukin (IL)-6 produced by fat cells induces the synthesis of C-reactive protein (CRP) by the liver; thus, obesity is associated with low-grade systemic inflammation.[26] However, it remains to be established whether the inflammatory involvement is more severe in obese adults or children affected by liver disease.

Here we examine globally, and also in the same series of obese children, the role of metabolic, hormonal, oxidative, and inflammatory factors in pediatric obesity-related liver dysfunction.

METHODS

In the first stage of this study, we retrospectively recorded the anthropometric measurements and the results of liver function tests and US examinations contained in the clinical records of 256 obese (body mass index > 95th percentile) Italian children who had been monitored for at least 1 year at the pediatric obesity clinics participating in our project.

To ensure a distinct separation between individuals with and individuals without obesity-related liver disease, the study protocol was designed to evaluate only prepubertal patients (age > 6 years) who presented the following inclusion criteria: stable or increased percent of overweight due to poor compliance to a prescribed slimming diet and exercise program (n = 119), US liver brightness coupled with a persistent increase of ALT and/or AST levels > 1.5 times above normal values for age persisting for more than 6 months (hepatopathic obese patients), and normal US liver findings coupled with persistently normal ALT and AST levels (obese controls). Exclusion criteria were normalization of liver function tests after decrease in the percent overweight during follow-up, fluctuating transaminase levels reaching normal or near-normal values in the last 2 biochemical evaluations, and known causes of liver abnormalities other than obesity. Fever and respiratory tract infection during the acute phase of the disease were considered temporary exclusion criteria.

Of the 119 children identified from our pool of 256 obese children, 101 consented to a complete reassessment of anthropometric parameters, liver function tests, and a new US liver examination. Only 50 of 101 children met the more stringent inclusion criteria for the study of metabolic, hormonal, oxidative, and inflammatory factors involved in the pathogenesis of liver disease. Of these 50, 20 were hepatopathic obese children with chronic elevation of AST and/or ALT and US liver brightness (group 1). The other 30, who had persistently normal serum AST and/or ALT levels in the absence of US liver brightness at study entry, were assigned to the obese control group (group 2). All 50 patients were prepubertal, with a mean age of 9.0 ± 2.4 years; 26 were girls. None had previously been treated with hepatotoxic drugs, had undergone surgery, had received either blood or blood products, or had a history of alcohol consumption. No patient had a history of short gut syndrome, small bowel intestinal bypass, Cushing's disease, or diabetes mellitus, which could have caused hepatic steatosis. All were asymptomatic. None had arterial hypertension. The liver was slightly enlarged but of normal consistency in 6 patients of group 1. None had splenomegaly or other stigmata of portal hypertension.

In patients with liver involvement, causes of increased transaminase levels other than obesity (eg, muscular disease, viral hepatitis B and C, autoimmune hepatitis, α_1-antitrypsin deficiency, cystic fibrosis, Wilson's disease, hemochromatosis, hereditary fructose intolerance, amino acid disorders, atypical celiac disease) were ruled out by appropriate tests.

Routine liver function tests in addition to ALT and AST (ie, alkaline phosphatase, γ-glutamyltranspeptidase, bilirubin, total protein, protein electrophoresis) were also determined. Ultrasonography of the liver was carried out as described previously.[10] White blood cell (WBC) count, serum CRP level, lipid levels, glucose level, glycosylated hemoglobin level, fasting insulin and glucose levels, iron status (iron levels, percent of transferrin saturation), and ferritin level were determined by standard methods.

Samples of fresh sera and plasma for determining dosage of tumor necrosis factor (TNF)-α, interleukin (IL)-6, and leptin were collected from all subjects. Blood spots were also collected on filter paper for polymerase chain reaction analysis. Lysed red blood cells were obtained from all subjects for a glutathione peroxidase (GPX) assay.

Experimental Methods

The fasting glucose-to-insulin ratio (FGIR) was to measure insulin resistance, with insulin resistance diagnosed when values were < 7.[27] Blood cells eluted from filter paper were lysed and DNA was purified for polymerase chain reaction–single-strand conformation polymorphism analysis to detect the C282Y and H63D mutations causative of hereditary familial hemochromatosis (HFE), as described elsewhere.[28] Serum concentrations of TNF-α and IL-6 were determined by enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, Minn) in accordance with the manufacturer's instructions. A spectrophotometric reading was performed on microplates using 450-nm filters. The enzymatic activity of GPX was evaluated by an indirect colorimetric method (Bioxytech GPx-340; Oxis Research, Portland, Ore). Each sample was washed in 0.9% NaCl solution and lysed in sterilized bi-distilled frozen water. The ensuing oxidation of reduced nicotinamide adenine dinucleotide phosphate (NADPH) to NADP+ was photometrically measured by spectrophotometry (model DU 640; Beckman, Brea, Calif) at 340 nm for 180 minutes; data are expressed as U/g hemoglobin.

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