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Therapeutic strategies for pediatric non-alcoholic fatty liver disease: A challenge for health care providers

Valerio Nobili, Melania Manco

Valerio Nobili, Melania Manco, Liver Unit, Bambino Gesù Children's Hospital and Research Institute, Rome, Italy
Correspondence to: Valerio Nobili, MD, Liver Unit, Research Institute, Bambino Gesu' Children's Hospital, S. Onofrio 4 square, Rome 00165, Italy. nobili66@yahoo.it
Telephone: +39-66-8592243 Fax: +39-66-8592192
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Abstract

Non-alcoholic steato-hepatitis (NASH) is related to insulin resistance and, thus, frequently occurs as part of the metabolic changes that accompany obesity, diabetes and hyperlipidemia. In childhood, the overwhelming boost of obesity and its co-morbidities have lead to the extraordinarily increased prevalence of NASH. Establishing effective therapeutic strategies to treat the disease represents the challenge for hepatologists and gastroenterologists in the next decade. Therapeutic approaches have aimed at treating associated conditions (obesity, insulin resistance, hyperlipemia, *etc*) or reducing liver oxidative damage (vitamin E).

Key words: Insulin resistance; Non-alcoholic fatty liver disease; Non alcoholic steato-Hepatitis; Vitamin E, Diet; Thiazolidinediones

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TO THE EDITOR

Pediatric non-alcoholic fatty liver disease (NAFLD) is considered as a global problem, which has been reported in North America, Europe, Australia and Asia[1]. It is the most common cause of liver disease in preadolescents and adolescents. The increase in the prevalence of NAFLD has been observed along with a dramatic rise in obesity in children during the past three decades. Nevertheless, it cannot be excluded that this may partially represent increased recognition of this condition[1]. The disease is related to insulin resistance and, thus, frequently occurs as part of the metabolic changes that accompany obesity, diabetes and hyperlipidemia. The term NAFLD encompasses a spectrum of histological findings, ranging from simple steatosis to steatosis accompanied by inflammation and other evidence of cell injury (termed non-alcoholic steatohepatitis, NASH).

Diagnosis of NAFLD is usually suspected in presence of raised levels of aminotransferases and/or ultrasound liver brightness. Diagnosis of NASH requires liver biopsy, and the exact prevalence may be severely underestimated.

In large cohorts of preadolescents and adolescents, the National Health and Nutrition Examination Survey (NHANES III)[2] and the 1998 Korean National Health and Nutrition Examination Survey[3] have reported that NAFLD may be suspected in 3% of the general pediatric population as estimated by elevated alanine aminotransferases (ALT). In a study of 810 Japanese children, fatty liver was diagnosed in 2.6% of subjects[4]. In United States, prevalence of hypertransaminasemia varied from 10% to 23% in the NHANES III study[2,5] when obese children were considered. In particular, the latter study was a school-based trial that recruited third graders from public elementary school in California, Louisiana, Minnesota and Texas, and follow-up was made through the 12th grade[5]. The prevalence rises extraordinarily to 74% in obese Chinese children[6], and to 42%[7] and 53%[8] in two cohorts of Italian obese children, respectively. Among children with type 2 diabetes, the prevalence of elevated ALT was 48%[9]. In a cohort of biopsy proven NAFLD, NASH was diagnosed in 26% of the cases with increased body mass index associated with worsen liver histology[10].

NASH may result in cirrhosis, even though no longitudinal study has been conducted in children. Therefore, establishing effective therapeutic strategies to treat the disease represents the challenge for hepatologists in the next decade.

Hitherto, treatment strategies for NASH have revolved around (1) identification and treatment of associated meta-bolic conditions such as diabetes and hyperlipemia; (2) improving insulin resistance by weight loss, exercise or pharmacotherapy; and (3) using hepato-protective agents such as antioxidants to protect liver from secondary insults. Many molecules have shown promising results in preliminary pilot trials; however, there have been few treatment modalities examined in rigorous randomised double-blind placebo controlled trials with adequate statistical evidence. Furthermore, interpretation of trials using biochemical markers of liver injury (i.e. hepatic

aminotransferases) as treatment end-points needs to be done cautiously, particularly in the absence of a control group. The natural history of patients with non-alcoholic fatty liver disease and raised aminotransferases is characterized by improvement of aminotransferases regardless of whether hepatic fibrosis improves or not[11].

Both weight loss and regular physical exercise target to improve first insulin resistance, but it can ameliorate secondarily associated metabolic conditions, namely diabetes, hyperlipemia and hypertension[10]. To achieve longstanding results, the expertise of a multidisciplinary team is required. Apart from the hepatologist, skilled dietician, endocrinologist, cardiologist, dietician, psychologist and radiologist enter a well-designed case management system to ensure the best therapeutic approach for each patient[12].

Lifestyle advice is of benefit to improve levels of aminotransferases[10,13], inflammation and steatosis in both children (unpublished data) and adults[13]. As far as fibrosis concerns, in a two-year double-blind controlled study, we have observed that fibrosis does not ameliorate in children either compliant to the nutritional program or to the supplementation with 600 g/d vitamin E (unpublished data). On the other hand, in adult NAFLD, fibrosis has been proved to be reduced after weight loss only in 50% of subjects compliant to the diet, who had higher levels of insulin at the baseline and greater decrease of ALT during the follow-up as compared with patients with lower hyperinsulinemia at the enrolment and a modest decrease of liver enzyme throughout the study period[13]. Effects of drugs reducing blood lipids (i.e. fenofibrates or orlistat) have not been exhaustively investigated either in adults or children, despite these medications may reduce fatty overload to the liver, lipid peroxidation and insulin resistance with low cost and acceptable side effects. On the contrary, attention has been paid to the effect of antioxidant agents, specifically alpha-tocopherol, and insulin-sensitizer agents, such as metformin, both medications being safe, easy to be managed and inexpensive. The pilot study by Levine[14] encouraged studies in children[15,16] and adults[17,18], but in a recent double-blind placebo study we observed that a 1-year supplementation with vitamin E is not better than diet and physical exercise in amelioration biochemical parameters in children[16]. Unfortunately, our clinical experience suggests that the anti-oxidant molecule is not able to affect liver histology as compared with placebo (unpublished data).

Data on metformin are promising too in the treatment of adult NAFLD[18,19], but a pilot study alone has been conducted in ten children for six months and no result has been provided on histology[20]. With great expectation, we are waiting for the results of two large controlled trial sponsored by the National Institute of Health with the aim to evaluate the effect of metformin *vs* vitamin E or placebo on liver enzymes in 180 biopsy-proven NAFLD children[21] or those of pioglitazone *vs* vitamin E or placebo on liver histology of 240 adult NASH (PIVENS clinical trial)[22]. The new frontier for the treatment of NASH may be the thiazolidinediones (TZD). Pioglitazone (45 mg/d) was administered in dieting NASH patients with impaired glucose tolerance or overt type 2 diabetes mellitus for six months[23]. In the TZD treated group, the drug significantly improved liver enzymes, steatosis, necroinflammation and ballooning in liver histology. However, the drug seems not to reduce liver fibrosis causes warning side effects, and is expensive as compared to metformin.

In conclusion, any attempt to treat pharmacologically pediatric NAFLD has failed and even though the use of anti-oxidants (including vitamin E or ursodeoxycholic acid) or metformin seems to be safe and not so expensive, there is no rationale to prescribe these medications unless conclusive results are provided to support their use. On the contrary, as it has been widely done for pediatric obesity, national organizations that provide health care must enhance consciousness of the disease among pediatricians and general health care providers in schools and families to favour healthy life-style, low-fat diet and physical exercise. Diet and regular physical activity remain reasonable and effective therapeutic approaches to pediatric NAFLD also in non-obese patients.

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