



EDITORIAL

Pediatric nonalcoholic fatty liver disease^{☆,☆☆}

Doença hepática gordurosa não alcoólica em crianças



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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. Simple steatosis, or fatty liver, occurs early in NAFLD and may progress to nonalcoholic steatohepatitis, which is characterized by the presence of hepatocellular damage such as lobular inflammation and cellular ballooning. It may evolve to fibrosis, and to cirrhosis with increased risk of hepatocellular carcinoma (HCC) in a variable proportion of cases. NAFLD is considered to be the hepatic component of metabolic syndrome (MetS),¹ which also includes obesity, hypertension, dyslipidemia, impaired glucose regulation, and insulin resistance, and therefore represents a strong cardiovascular risk even at a very early age.^{2,3}

The global burden of NAFLD runs parallel to the prevalence of obesity, with the degree of hepatic triglyceride accumulation being proportional to the severity of each component of MetS.⁴ With over two billion individuals with overweight/obesity expected worldwide by 2030, NAFLD is undoubtedly becoming the most prominent chronic liver disease of the 21st century in both adults and youths.⁵ During the past few decades, obesity has shifted toward an onset earlier in life, with a dramatic rise in childhood.⁶ This finding represents a serious threat to the health state of youths

and raises the issue of how this earlier advent of overweight will affect the burden and management of NAFLD later in life. In a recent study, Hagström et al.⁷ showed that overweight in late adolescence is a significant predictor of severe liver disease, including HCC later in life. The researchers used register data from more than 1.2 million Swedish men enlisted for conscription between 1969 and 1996. During a follow-up of more than 34 million person-years, 5281 cases of severe liver disease including 251 cases of HCC were identified. An association with severe liver disease was found for overweight (Hazard ratio [HR] 1.49; 95% confidence interval [CI], 1.35–1.64) and for obese men (HR 2.17; 95% CI, 1.82–2.59). Development of type 2 diabetes mellitus (T2DM) further increases the risk for severe liver disease across all body mass index (BMI) categories. The study by Hagström et al.⁷ definitively establishes that the obesity-related risk of future severe liver disease starts early in life.

In addition to liver complications, patients with NAFLD also have a high risk of cardiovascular disease (CVD).² Indeed, NAFLD may be considered in adults as well as in children a multisystem disease affecting several extra-hepatic organs and involving a range of extra-hepatic chronic diseases, in particular T2DM, CVD, and chronic renal disease.^{8,9}

The exact prevalence of NAFLD is uncertain. Several studies have demonstrated a prevalence of 3–10% in general pediatric populations, which increases to up to 60–70% in subjects with metabolic comorbidities.¹⁰ Importantly, NAFLD prevalence varies widely depending on geographical area and diagnostic methods used.¹¹ Initial population-based studies, which estimated the prevalence of pediatric NAFLD by determining aminotransferases or by ultrasonography in several countries, have indicated a prevalence range of 3–7%.¹¹ In an autopsic study, conducted in unselected

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children who died in accidents in California, the prevalence of histological NAFLD ranged from 0.7% in 2- to 4-year-old to 17.3% in 15- to 19-year-old subjects, but increased to 38% in obese children.¹² In cohorts of children of various nationalities selected for overweight or obesity, the prevalence of elevated alanine aminotransferase was higher and ranged from 8% to 42%, whereas the prevalence of bright liver ranged from 1.7 to 77%.¹¹ A recent meta-analysis including 76 independent study populations of youths aged 1–19 years led to an estimate of NAFLD of 7.6% (95% CI, 5.5–10.3%) in the general population and 34.2% (95% CI, 27.8–41.2%) in obesity clinics.¹³ In both populations, there was marked heterogeneity ($I^2 = 98\%$), which was partly accounted for by sex distribution, difference in BMI, and ethnicity, with NAFLD prevalence being higher in males, individuals with more severe adiposity, and Asians. Notably, the use of liver enzymes to diagnose NAFLD led to a significant underestimation of disease prevalence.¹³

NAFLD diagnosis currently requires proof of steatosis, which relies on imaging techniques in clinical practice. To address such diagnosis in a large number of putative patients, liver biopsy, an invasive test with some risk of complications, is neither feasible nor ethical to use as a screening tool. Moreover, liver biopsy is susceptible to sampling bias. At present, ultrasound is the most commonly used modality to determine hepatic steatosis because of its relatively low cost, availability, and safety. However, ultrasound is operator dependent, and has limited sensitivity and specificity for steatosis assessment. Among the currently available imaging modalities, magnetic resonance spectroscopy (MRS) is the most direct MR-based method to separate the liver signal into its water and fat components and calculate the fat-signal fraction.¹⁴ However, MRS demonstrates some limitations in that it is too time consuming for routine clinical practice, and requires a skilled operator to correctly perform the examination, process the data, and interpret the results. Because of these limitations, MRS still lacks general availability in current clinical practice for assessment and monitoring of hepatic steatosis. Unlike MRS, MRI has shown greater promise for the quantitative assessment of hepatic steatosis in adults¹⁴ and children.^{15,16} Different methods can be performed for the evaluation of liver steatosis by MRI, but the most used method is based on the modified Dixon method based on dual-phase gradient-recalled echo sequences.¹⁷ On in-phase echo-time, water and fat signals add up and therefore, the total signal intensity is higher. On out-of-phase echo-time, water and fat signals cancel out each other, and consequently the total signal intensity decreases. While a healthy liver has no difference in signal intensities between the in-phase and out-of-phase images, in the case of fat storage, the liver signal intensity diminishes on the out-of-phase image.¹⁷ This imaging method is reliable in the absence of magnetic field inhomogeneity. The main drawback is that the quantity of water and fat can affect their signals.¹⁷ This can be managed by acquiring new images with variable T1-weighting, through the application of two flip-angle-imagings, such as high-flip-angle for uncovering small amounts of fat in tissues that include mainly water, or low-flip-angle for revealing small amounts of water in fat-rich tissues. Furthermore, hepatic iron deposition, often coexisting with hepatic steatosis, causes increased T2* decay and lowers the

detection of liver fat.¹⁸ Other confounders of quantification include T1 signal, spectral complexity of fat, eddy currents, and noise bias.¹⁸ By addressing these confounding factors, recent improvements in MRI have provided measurement of the proton density fat-fraction ([PDFF]: the fraction of the liver proton density attributable to liver fat), which is an inherent property of tissue and a direct measure of liver fat content.¹⁴ MRI-PDFF is accurate, precise, and reliable for quantifying liver steatosis, having been validated against liver biopsy in both adults¹⁸ and children.¹⁷ Thus MRI-PDFF is emerging as a useful biomarker, in particular in patients for whom liver biopsy is contraindicated or impractical.¹⁸

Into this environment, Benetolo et al.¹⁹ have published an article in this issue of the Journal describing the prevalence of NAFLD among Brazilian children and adolescents followed at an obesity outpatient clinic. Using MRI, they found that the prevalence of NAFLD was 28%, lower than that reported in other studies from different countries, including Brazil. Based on the scarce available literature, the prevalence of NAFLD in South America seems to be higher than the rate reported for the United States. Specifically, NAFLD prevalence (as assessed by ultrasonography) in population-based studies for South America has been estimated to be ~30.45% (95% CI, 22.74–39.4%). Indeed, the majority of studies reporting the prevalence of NAFLD from South America have been performed in Brazil. Nevertheless, in a study reported from Chile, the prevalence of NAFLD (as assessed by ultrasonography) was estimated to be 23%.¹⁰ Another study from Columbia, also using ultrasonography, reported a prevalence of 26.6% in men.¹⁰ These rates can be influenced by genetic predisposition. An important finding, however, of the Benetolo et al. study¹⁹ is that among children younger than 10 years the prevalence of NAFLD was 31.8%, similar to that encountered in those older than 10 years. Hepatic steatosis was associated with male gender, triglycerides, transaminases, and acanthosis nigricans, while there was no association with insulin resistance and MetS. There were some limitations to the study by Benetolo et al., which may have contributed to the lack of association of NAFLD with insulin resistance. The small sample size may have caused a type 2 error.

In conclusion, the deleterious effects of obesity on liver health should not be overlooked, particularly during childhood. Children with a long duration of obesity should be screened for liver disease – the earlier the onset of obesity, the higher the risk of NAFLD. While waiting for the development of effective drug therapies for NAFLD, all health-care providers should combine their efforts at the population level to control and prevent childhood and adolescent obesity.

Conflicts of interest

The authors declare no conflicts of interest.

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