ISSN: 3033-3504

Journal of Clinical Medicine and Regenerative Medicine

SCIENTIFIC Research and Community

Review Article

Open Access

Pediatric NAFLD - The Increasing Obstacle of The New World Retrospective Analysis of COVID-19 Pandemic

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Received: July 29, 2024; **Accepted:** August 08, 2024, **Published:** August 18, 2024

Introduction

Nonalcoholic fatty liver disease (NAFLD) is the presence of excess fat in the liver that occurs without significant alcohol consumption [1]. It is typical for the liver to have a small amount of fat. However, when fat makes up more than 5% to 10% of the liver's weight, it is called fatty liver (steatosis) [2,3].

NAFLD encompasses a variety of liver conditions, ranging from simple fat accumulation (steatosis) to severe scarring (cirrhosis) [4]. It is now the leading chronic liver condition globally, representing a significant shift in hepatic health over the last two centuries [5].

The rising numbers of obesity, reaching epidemic proportions in pediatric populations, have brought attention to the intricate relationship between obesity and NAFLD. Nonalcoholic fatty liver disease (NAFLD), commonly viewed as a silent companion of obesity, not only increases the likelihood of metabolic complications but also worsens the development of health issues associated with obesity. Despite the alarming surge in childhood obesity rates, the hepatic state has remained understudied due to the reliance on invasive diagnostic techniques. Therefore, it becomes imperative to explore and establish tools that can aid in comprehending the complex interplay between obesity and NAFLD. Such efforts are crucial for shaping a future where preventive strategies become the primary focus in combating these intertwined health challenges.

Chronological Milestones

In Oyekoya T. Ayonrinde's historical narrative, the author traces the evolution of our knowledge about fatty liver disease, from rudimentary explanations in the 19th century to the intricate understanding of NAFLD in the 20th and 21st centuries [6].

In the 19th century, fatty liver was primarily linked to alcohol consumption, malnutrition, and wasting diseases. As time passed, additional factors such as obesity, unhealthy diets, and sedentary behaviours were recognised. By the late 1800s, fatty liver was associated with liver scarring and cirrhosis, and by the early 1900s, it was also linked to diabetes. During the late 1900s, the terms NAFLD and NASH emerged, emphasising the metabolic origins of these conditions [6].

This historical account demonstrates the transformation in the perception of fatty liver disease, shifting from a focus on extreme nutrition or alcohol abuse to recognising it as a multifaceted metabolic disorder. This evolving comprehension and the primary shortcomings of terms like NAFLD and NASH, which relied on excluding certain factors and potentially stigmatising language, has resulted in the current emphasis and considerable scrutiny on NAFLD. In response, 236 experts from 56 countries engaged in four online surveys and two hybrid meetings to tackle these issues. The new term selected to replace NAFLD is metabolic dysfunction-associated steatotic liver disease (MASLD), reflecting its intricate metabolic origins [7]. It is essential to acknowledge that the observation of pediatric patients with obesity that initially inspired our research preceded the modification of terminology. Consequently, we will continue utilising the NAFLD designation.

NAFLD's Rising Tide

Although regional variances continue to impact the prevalence of the disease, its occurrence is on the rise in most nations in parallel with escalating rates of obesity and type 2 diabetes. Riazi et al. investigated 72 studies encompassing 1,030,160 individuals, revealing that the worldwide prevalence of NAFLD among adults is 32%. Over the years, this prevalence has surged from 26% in studies conducted pre-2005 to 38% in studies carried out in 2016 or later [8]. Moreover, a recent meta-analysis by Riazi et al. projected the annual incidence of NAFLD at 46.9 cases per 1,000 person-years. It is important to note that these observational cross-sectional or longitudinal studies pertain to study cohorts representative of the general adult populace, as opposed to children [8]. This distinction holds significance, particularly in light of the current epoch marked by escalating rates of obesity and fatty liver incidence, where children may potentially face heightened susceptibility to developing chronic liver ailments in the future.

Obesity vs. Compromised Liver Health - What Fuels Pediatric Metabolic Disease?

With the increasing prevalence of the obesity epidemic, a more significant challenge awaits the younger generation. By 2022, the number of overweight children under the age of 5 had reached 37 million. Moreover, there were over 390 million overweight children and adolescents aged 5-19 years, with 160 million individuals living with obesity [9]. Over the last four decades, the count of school-age children and adolescents struggling with obesity has surged more than tenfold, from 11 million to 124

million (2016 projections). Additionally, an estimated 216 million were identified as overweight but not obese in 2016, underscoring the swift escalation in obesity rates [10]. Various explanatory models posit environmental disruptors, food processing, and transgenerational metabolic memory as underlying factors, with compromised liver health emerging as both a significant contributor to and consequence of obesity.

There are several fascinating links between obesity and fatty liver disease. Apart from the fundamental principle of an imbalance between energy intake and expenditure, the Carbohydrate-Insulin Model of obesity (CIM) contends that a diet high in carbohydrates — including substantial quantities of refined starchy foods and sugar, as commonly consumed during the low-fat diet era — induces postprandial hyperinsulinemia, fosters calorie storage in fat cells instead of oxidation in lean tissues, and thereby predisposes individuals to weight gain through heightened hunger, diminished metabolic rate, or both [11-12]. Professor Ludwig introduces a distinctive perspective where overeating is viewed as a consequence of escalating adiposity rather than the primary cause. Through this lens, a compromised liver can be seen as a catalyst for obesity in future generations rather than a complication of obesity [11].

In addition to the direct association between obesity and liver health, various intermediate factors may serve as catalysts, significantly impacting the progression of NAFLD. An illustrative example is the altered physiological state associated with obesity, characterised by a relative deficiency in growth hormone (GH). Emerging evidence underscores the pivotal role of diminished GH levels and insulin-like growth factor-1 (IGF-1) in the pathogenesis of NAFLD. The physiological functions of GH within the liver encompass the inhibition of de novo lipogenesis (DNL) and the facilitation of lipid beta-oxidation, alongside displaying anti-inflammatory properties. Similarly, IGF-1 exerts its physiological influence by suppressing inflammatory and fibrogenic pathways crucial in the transition from hepatic steatosis to steatohepatitis and fibrosis. These intricate interactions shed light on the multifaceted mechanisms through which obesity impacts liver health, underscoring the importance of considering intermediary factors in the comprehensive understanding of NAFLD development [13]. Studying these complex physiological connections is essential because of the profound stigmatising impact of short stature and obesity on the mental health of a child.

Beyond obesity, another contributing factor to liver steatosis is insulin resistance. Given that the liver and kidneys are the primary sites for insulin clearance, with the liver playing a predominant role in metabolising endogenously released hormones, it has been proposed that insulin resistance may result from, rather than cause, reduced insulin clearance. Diminished insulin clearance contributes to hyperinsulinemia, hastening the progression of nonalcoholic fatty liver disease (NAFLD). In their review article "Hepatic Insulin Clearance: Mechanism and Physiology," authors Sonia M. Najjar and Germán Perdomo offer a compelling analysis linking insulin clearance rates, hyperinsulinemia, and liver steatosis [14]. They underscore the significance of carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1) in enhancing insulin clearance. Impaired CEACAM1 function diminishes insulin clearance, resulting in hyperinsulinemia and subsequent insulin resistance in the liver, leading to fat accumulation. This sequence underscores the pivotal role of the liver in developing metabolic syndrome. Najjar and Perdomo's study emphasises the importance of targeting hepatic insulin clearance and CEACAM1 function as therapeutic approaches against these metabolic disorders.

The diagnosis of NAFLD in children poses challenges due to factors like varied symptoms and the need for invasive tests. The COVID-19 pandemic worsened the situation by reducing physical activity and promoting overeating among kids. Our Institute observed an increase in cases of pediatric obesity following the pandemic and sought to establish the frequency of NAFLD in overweight and obese children aged 6-14 by utilising the fatty liver index (FLI) [15].

Methods

A retrospective study was conducted on 126 children aged 6–14 with a BMI≥85th percentile for age and gender based on the CDC 2000 growth charts [16]. Data was obtained from medical records of children who underwent measurement of waist circumference, body mass index, and laboratory examinations of triglyceride and gamma glutamyl-transferase concentration during their ambulatory visit to the National Institute of Endocrinology, Georgia, during the Covid-19 pandemic.

BMI for age, waist circumference, triglyceride, and gamma-glutamyl transferase concentrations in serum measured in each participant were plugged into the algorithm to predict fatty liver. Exclusion criteria were concomitant liver disease, type 1 diabetes, and obesity due to iatrogenic causes.

Results

Most of the children examined who were found to be at a high risk of NAFLD, as indicated by the FLI, were obese. (Figure 1) (BMI to age > 95 % in percentiles). Interestingly, obese girls showed a higher prevalence of severe NAFLD than boys. (Figure 2)

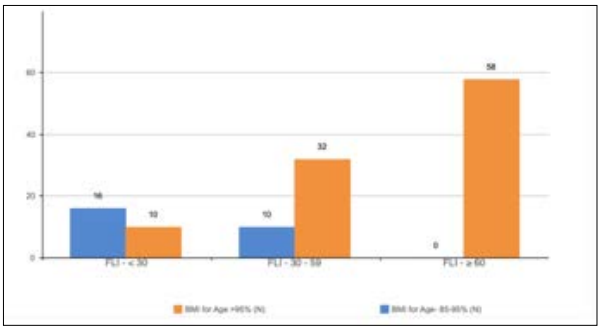

Figure 1

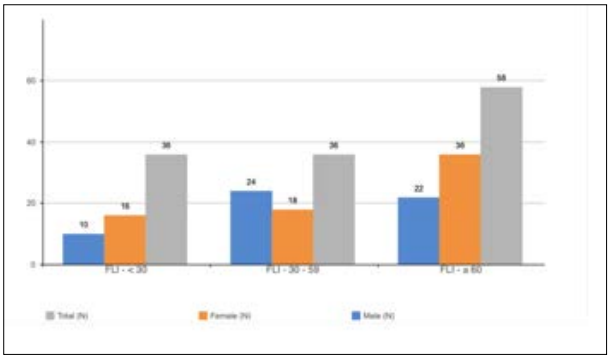

Figure 2

FLI score below 30 rules out NAFLD, 30 < FLI > 60 indicates an intermediate risk, and FLI≥60 indicates a high risk of NAFLD.

Conclusion

FLI emerges as a valuable tool for efficiently screening overweight and obese children for NAFLD in resource-limited community settings and epidemiological studies. This is particularly significant given the challenges of regions needing more sophisticated medical infrastructures. Children from various regions of Georgia seek appointments at the National Institute of Endocrinology, and the feasibility of conducting regular follow-up visits may be unsustainable. Therefore, leveraging accessible screening methods like the FLI becomes crucial in capturing the dynamic landscape of NAFLD prevalence in diverse populations.

Our findings suggest that utilising FLI to detect NAFLD in overweight and obese children is a cost-effective strategy that can assist clinicians in monitoring treatment progress.

Limitations

The study was limited by various factors that should be considered when interpreting the results. The nonlinear trajectory of pediatric growth highlights the potential for enhanced precision by evaluating percentile growth across multiple follow-up visits. Furthermore, regional exposure to endocrine disruptors, dietary preferences, the mother's health conditions during pregnancy and her nutritional intake, the family's socioeconomic status, and emotional stress within the household are important factors that could impact the study's outcomes.

We encourage researchers and clinicians to incorporate liver state evaluation equations in pediatric cohort studies. This inclusion would provide a more comprehensive understanding of the current liver health status and allow for tracking changes over time.

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