Indian Academy of Pediatrics (IAP)

nRICH

Newer **R**esearch and recommendations **I**n **C**hild **H**ealth

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UNDER THE AUSPICES OF THE IAP ACTION PLAN 2023

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Dear fellow IAPans,

nRICH

Newer **R**esearch and recommendations **I**n **C**hild **H**ealth-aims to bring you the abstracts of some of the breakthrough developments in pediatrics, carefully selected from reputed journals published worldwide.

Expert commentaries will evaluate the importance and relevance of the article and discuss its application in Indian settings. nRICH will cover all the different subspecialities of pediatrics from neonatology, gastroenterology, hematology, adolescent medicine, allergy and immunology, to urology, neurology,vaccinology etc. Each issue will begin with a concise abstract and will represent the main points and ideas found in the originals. It will then be followed by the thoughtful and erudite commentary of Indian experts from various subspecialties who will give an insight on way to read and analyze these articles.

I'm sure students, practitioners and all those interested in knowing about the latest research and recommendations in child health will be immensely benefitted by this endeavor which will be published online on every Monday.

Happy reading!

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HOW MUCH REDUCTION IN BODY MASS INDEX (BMI) SHOULD BE TARGETED TO REDUCE LIVER STEATOSIS IN CHILDREN?

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BASED ON ARTICLE

Khurana T, Klepper C, Fei L, Sun Q, Bramlage K, Arce-Clachar AC, Xanthakos S, Mouzaki M. **Clinically Meaningful Body Mass Index Change Impacts Pediatric Nonalcoholic Fatty Liver Disease**. J Pediatr. 2022; 250:61-6

SUMMARY

Authors, Khurana et al had a postulation that a reduction in body mass index (BMI) >0.25 is clinically a therapeutic target to reduce steatohepatitis in pediatric nonalcoholic fatty liver disease (NAFLD). They performed a retrospective study at Cincinnati Children's Hospital, United States of America in children with NAFLD under 18 years of age. Presumed NAFLD was diagnosed based on 1) elevated BMI (overweight or obese), 2) steatosis on imaging, 3) elevated liver enzymes and 4) absence of any other liver disease. Confirmed NAFLD was defined as all the above in addition to histological confirmation on liver biopsy. As per the guidelines of North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NSPGHAN), the therapy consisted of elimination of sugar-sweetened beverages; consumption of a portion-controlled, age-appropriate, well- balanced diet; and inclusion of physical activity with the goal of daily moderate-intensity exercise. The end-point for assessment was alanine transaminase (ALT) normalisation. The authors' recruited 784 patients aged 13±3 years, two - third were boys and a quarter were of Hispanic ethnicity. To document changes from baseline, 541 patients (69%) had a follow-up of >90 days. Of this group, 168 (31%) could achieve a reduction of BMIz score of >0.25 over a median of 367 days (IQR, 201-678 days). This group had a change in BMIz 0.42 (0.31-0.62).This cohort was the main subgroup the authors intended to evaluate. Hence two groups of patients were compared: those with reduction in BMIz >0.25 (group 1) vs. BMIz <0.25 (group 2). Group 1 patients were significantly younger (13±2.9 vs. 11.7 ±3.5 years, p<0.01) and had significantly lower baseline class II and III obesity (>120% of 95th centile) than group 2 (61% vs. 79%, p<0.01). Decrease in serum aminotransferase and lipid levels were observed in both groups; however, these reductions were more pronounced in group 1 children. The delta change (difference between baseline and follow-up) of various parameters were also compared between the two groups. ΔBMI (0.6 vs 0.1), ΔALT (-39 vs -14), ΔAST (-18 vs -10), ΔGGT (-12 vs -3), ΔALP (-49 vs -21), ΔHDL (2 vs 0). Multivariable modeling showed that young age (baseline age [OR 0.861; 95%CI, 0.81-0.92; P <0.01]) and non-Hispanic ethnicity (OR of non-Hispanic vs. Hispanic, 0.61; 95% CI, 0.38-0.97; P<0.04) were associated with a BMIz reduction of >0.25 over time. Sex and the presence of type 2 diabetes mellitus at baseline did not show a significant effect on BMIz reduction. In their study, the authors found that most optimal BMIz decrease required to achieve ALT normalization was 0.27. They

found that most optimal BMIz decrease required to achieve ALT normalization was 0.27. They concluded that their hypothesis of BMIz reduction of >-0.25 was correct and advocate the same for further clinical management of children with NAFLD.[1]

COMMENTARY

NAFLD in childhood is a global problem which is increasing in the recent years. A surge in pediatric NAFLD has arisen during the COVID-19 pandemic. During national lockdowns, there have been unprecedented school closures, restricted gathering, physical inactivity, obesogenic food intake and addiction to devices with increased screen time.2 NAFLD is a part of the metabolic syndrome and is hence associated with cardiovascular and endocrinal comorbidities. NAFLD is also higher in some ethnicities more than the others. Hispanics have highest predilection and progression as compared to Caucasians.3 There is a considerable under-reporting from Indian subcontinent. In NAFLD, the liver undergoes progressive phases of steatosis, inflammation (hepatitis), fibrosis, and cirrhosis, and end-stage liver disease necessitating liver transplantation. Uncontrolled and advanced fibrosis can also result in portal hypertension and its consequences. The first three stages (steatosis, inflammation, and fibrosis) are potentially reversible. Multimodality approach of dietary modification, lifestyle changes, physical activity and pharmacotherapy have been used with considerable success. Visceral adiposity closely correlates with the hepatic steatosis. Reduction of visceral adiposity is the cornerstone of management. In adults, a 5% weight loss reduces 50% intrahepatic fat and a 10% reduction shows complete resolution of stetatohepatitis and regression of fibrosis.4 Since children have dynamic growth related to age, sex and puberty, weight reduction in isolation is not a suitable benchmark for assessment. BMI is a better measure. The fundamental question that arises is, how much reduction in the BMI will reduce the steatosis or fibrosis in the liver? Xanthakos et al (an author in the present study) previously showed that of 122 children with NAFLD, 7% of their cohort achieved a reduction of BMIz >0.25. They concluded that for every 0.25 decrease in BMIz score, a 2 fold reduction in steatohepatitis is expected.5 However due to small numbers, the study had a limited impact in convincing for a meaningful practice. The study however provided a stepping stone for the present study.

In this light, Khurana et al could effectively demonstrate that the previous hypothesis was in fact correct. In their modest analysis, they showed that BMIz reduction >2.5 was associated with improvement in liver enzymes which were surrogate markers of steatosis. However in reality steatosis cannot be equated with steatohepatitis. Just like atherosclerosis, with increasing age, some amount of steatosis in liver is expected. However any amount of fat in liver at a young age is unacceptable and is considered a harbinger for liver damage. It should be noted that only 30% could achieve BMIz >2.5. Hence the larger question is whether this absolute cut-off is a truly achievable target for the majority? Will lower BMI targets also considerably improve liver steatosis? Khurana et al also showed improvements in lipid profile. They felt that the most optimal BMIz decrease required to achieve ALT normalization was 0.27.1 This raises the therapeutic benchmark higher. However in our opinion, BMIz 0.27 was not an optimal result as the receiver operating characteristic curve analysis shown was just 0.58. The ethnicity analysis in this study may not be applicable in Indians.

What does this study highlight? Among the many strengths, this study recruited large numbers and

reached a finite conclusion paving way for better therapeutic targets of management. However it is limited by one large drawback. Retrospective studies that analyse weight and BMI are often based on arbitrary dietary recalls and subjective end-points. That means, those with BMI reduction <0.25 may well not have received the correct therapeutic advice. Readers would also have been more appealed if there was an insight into the sub-analysis of the different obesity categories. A major setback in any dietary and lifestyle intervention is the compliance of caregivers and subjects, more so in adolescents. Old habits die hard. And it may be enduring to achieve targets in 90 days especially in patients who are morbidly obese. What is the way forward? For the time being, it may seem reasonable to push the patients harder to achieve a BMI reduction of 0.25 over 90 days. This requires patients' will power, dedicated dieticians, physical activity trainers and an active support group. For India, it is necessary to first document the prevalence of pediatric NAFLD in multiple urban centres. It is imperative to design a prospective time-point study with reasonable therapeutic end-points. Mere reduction of transaminases will not suffice. For a robust study, hepatic fat quantification by liver MRI, tissue elastography and histology are recommended.

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