Application of ^{13}C Methacetin Breath Test in Longitudinal Monitoring of Metabolic Dysfunction-Associated Fatty Liver Disease Progression in Children, Adolescents, and Young Adults with History of Childhood Obesity

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Background

Metabolic dysfunction-associated fatty liver disease (MAFLD) represents an increasingly recognized spectrum of liver pathology associated with obesity, insulin resistance, and metabolic syndrome in pediatric and adolescent populations. The condition encompasses non-alcoholic fatty liver (NAFL), non-alcoholic steatohepatitis (NASH), and advanced stages such as compensated and decompensated cirrhosis.

In children and young adults, the progression of MAFLD can lead to chronic liver disease and elevated risks for hepatocellular carcinoma (HCC). Current tools for assessing disease progression and liver function, including APRI, FIB4, AST/ALT, GGT platelet ratio, and transient elastography have limitations in sensitivity and specificity. Liver biopsy remains the gold standard for diagnosing NASH and staging fibrosis. However, it's invasive nature carries potential risks, making it not feasible for frequent monitoring in children and adolescents.

^{13}C Methacetin Breath Test (^{13}C-MBT), a non-invasive test that measures liver function through exhaled breath after the administration of ^{13}C-labeled methacetin, may offer a promising solution. ^{13}C-MBT reflects metabolic capacity of cytochrome P450 1A2, potentially indicating subtle impairments in liver function before clinical symptoms manifest.

Objectives

1. To investigate the role of 13C-MBT in detecting functional liver impairment across the spectrum of MAFLD, from NAFL and NASH to compensated and decompensated cirrhosis.
2. To examine the potential of 13C-MBT have in monitoring longitudinal changes in liver function that may indicate progression or stabilization of disease.
3. To assess whether 13C-MBT values correlate with clinical, biochemical, and imaging markers (along with APRI, FIB4, AST/ALT, GGT Platelet ratio. HOMA-IR, AFP, shear wave elastography) of liver disease progression and can serve as an early screening tool for hepatocellular carcinoma in this population.
4. To develop predictive models that incorporate 13C-MBT results with other clinical parameters to enhance individualized risk stratification for disease progression.

Proposed Methodology: longitudinal cohort study over a 5-year period with biannual evaluations of disease progression

1. Study Population

Inclusion criteria:

- children, adolescents, and young adults (ages 8–25 years)
- MAFLD diagnosis confirmed by imaging, laboratory, and/or histology
- Willingness to undergo longitudinal follow-up

Exclusion criteria:

- Other chronic liver diseases (e.g. viral hepatitis)
- History of hepatocellular carcinoma
- Severe comorbid conditions that may independently affect liver function

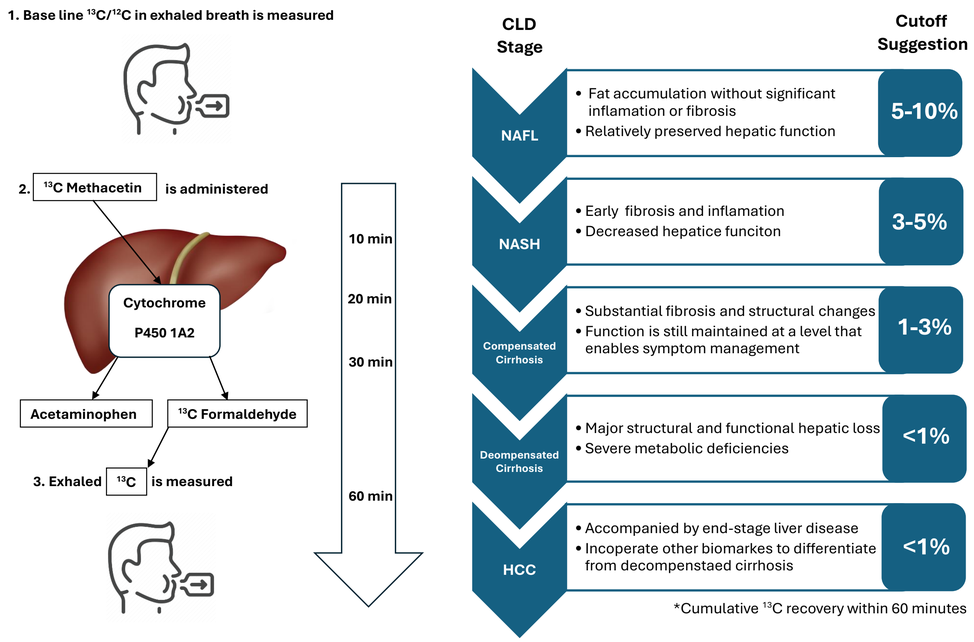
2. Baseline Assessment

- Anthropometric measurements
- Biochemical tests (liver function tests, lipid profile, fasting glucose, and insulin)
- Imaging assessments of fat content and fibrosis (ultrasound and transient elastography)
- Histological assessments (for patients with indications for liver biopsy)

3. Genetic Panel Screening

Variations of the PNPLA3, TM6SF2, . HSD17B13, GCKR, and MBOAT7 genes are screened in participants via genetic panels to identify high-risks individuals.

4. ^{13}C Methacetin Breath Test



Data from the breath test will be used to calculate metrics such as the elimination rate constant and cumulative recovery over time, which will be analyzed for trends over the course of the study.

5. Follow-up Evaluations

Every 6 months, participants will undergo repeated ^{13}C-MBT, liver function tests, and elastography . The progression to more advanced liver disease stages will be defined based on a combination of clinical parameters, imaging findings, and biochemical markers. Any patient showing evidence of decompensation (e.g., development of ascites, jaundice, or hepatic encephalopathy) or elevated alpha-fetoprotein (AFP) levels will undergo further evaluation for HCC.

- Primary outcome: association between changes in ^{13}C-MBT parameters and progression in liver disease stage as determined by clinical and imaging criteria.
- Secondary outcomes: correlations between ^{13}C-MBT values and standard biomarkers of liver function and the predictive value of ^{13}C-MBT for identifying patients at risk for decompensation or HCC development

7. Statistical Methods

Longitudinal mixed-effects models will be used to assess changes in ^{13}C-MBT parameters over time and to evaluate their associations with disease progression. Receiver operating characteristic (ROC) analysis will be employed to determine the sensitivity and specificity of ^{13}C-MBT as a predictor of disease stage transition or decompensation. Survival analysis techniques will also be applied to assess the utility of ^{13}C-MBT in predicting time to decompensation or HCC development.

Potential Impact

This study may establish ^{13}C Methacetin Breath Test as a practical and sensitive tool for routine monitoring of MAFLD progression. By providing a non-invasive method to evaluate real-time liver function, clinicians could be able to detect functional impairments that signify disease progression. Decompensation and progression to HCC could be distinguished in cirrhotic patients, potentially leading to timely interventions. The need for invasive liver biopsy may also be reduced, allowing for better individualized management of MAFLD in young patients.