Characterization of glucose metabolism in youth with vs. without cystic fibrosis liver disease: A pilot study

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ABSTRACT

Background: Diabetes and liver disease are life-threatening complications of cystic fibrosis (CF). CF-liver disease is a risk factor for CF related diabetes (CFRD) development, but the underlying mechanisms linking the two morbidities are not known. The objective of this pilot study was to characterize glucose metabolism in youth with CF with and without liver disease.

Methods: In this two-center cross-sectional study, 20 youth with CF with and without liver disease underwent a 3-hour oral glucose tolerance test. Subjects were categorized by liver disease (LD) status [no LD, mild LD, severe LD] and diabetes status. Measures of glucose excursion, islet cell secretory responses, insulin sensitivity and clearance were obtained.

Results: Participants with severe LD had the highest fasting, peak, and glucose area under the curve over 3 h (AUC0-3h) among individuals with CFRD (interaction p < 0.05). In parallel with glycemic changes, prandial β-cell secretory response (AUC C-peptide 3h) was lower in those with severe LD compared to mild or no LD (p < 0.01). There was a trend of higher HOMA-IR in those with severe LD (p = 0.1) as well as lower fasting insulin clearance in those with mild and severe LD compared to no LD (p = 0.06) and lower prandial insulin clearance in severe LD among those with CFRD (interaction p = 0.1).

Conclusion: In this small cohort, subjects with severe LD tended to have more impaired glycemia, insulin secretion, insulin sensitivity and clearance. Larger studies are imperative to define the pathogenesis to inform clinical care guidelines in terms of CFRD screening, diagnosis, and treatment options.

Abbreviations: CFRD, cystic fibrosis related diabetes; LD, liver disease; AUC, area under the curve; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; OGTT, oral glucose tolerance test; DM, diabetes; VCTE, vibration controlled transient elastography; LSM, liver stiffness measurement; CAP, controlled attenuation parameter; kPa, kilopascals; GLP-1, glucagon like peptide-1; GIP, gastric inhibitory polypeptide; FFA, free fatty acids; OGIS, oral glucose derived insulin sensitivity; APRI, Aspartate aminotransferase to Platelet Ratio Index; Fib4, Fibrosis-4.

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Although the mechanisms underlying CFRD development remain poorly defined, progressive β-cell dysfunction is appreciated as the primary defect. Therefore, while dysregulated α-cell response and incretin secretion are also implicated as pathogenic factors [4,5], insulin remains the only recommended treatment as it has been shown to improve glycemia while promoting weight gain [2].

CF-liver disease is a mortality-increasing complication that is primarily diagnosed in childhood [6]. Viscous bile resulting from the CF mutations likely contributes to biliary cirrhosis [7]. CF-liver disease prevalence is ~30%, with progression in 5–10% to clinically significant cirrhosis with portal hypertension [7]. Steatosis is common in CF but is generally not associated with fibrosis [8].

CF-liver disease is a known risk factor for CFRD development [9–11]. Epidemiologic studies reveal that patients with severe liver disease characterized by cirrhosis with portal hypertension have an 11-fold increased risk of developing CFRD compared to patients without liver disease [11]. The pathogenesis linking cirrhosis and diabetes in CF has not been explored. In non-CF populations, diabetes is prevalent in 40–70% of patients with cirrhosis [12]; fasting and prandial hyperinsulinemia, which are attributed to reduced insulin clearance and sensitivity, are proposed as culprits for diabetes development [13]. In CF, limited studies suggest that worsening glycemia correlates with increased insulin clearance. Reasons for increased insulin clearance are not fully understood, but are speculated to contribute to insulinopenia, which in turn contributes to hyperglycemia [14]. These previous CF studies, however, did not specifically evaluate insulin clearance in patients with advanced liver disease [14,15]. Regarding insulin resistance in CF, studies demonstrate that it impacts progression of glucose intolerance in adults [16,17], but research dedicated to evaluating insulin resistance in youth are lacking. In general, insulin resistance in CF is largely linked to inflammation and systemic steroid use and not appreciated as a main pathogenic factor contributing to CFRD development.

The objective of this study was to characterize and compare glucose metabolism in youth with CF with and without liver disease. Here, we present our preliminary findings of glucose excursion, islet cell secretory responses, insulin sensitivity and clearance, and secretion of incretins and free fatty acids.

Material and methods

Subjects

Twenty pubertal subjects with CF, ages 10–21 years who fulfilled inclusion criteria were recruited in order of their presentation to the CF centers at the University of Texas Health San Antonio and University of Pittsburgh/UPMC Children’s Hospital of Pittsburgh to undergo a 3-hour oral glucose tolerance test (OGTT). CF diagnosis was confirmed based on presence of two CF-causing mutations and/or positive sweat test. Inclusion criteria included pancreatic insufficiency, defined by need for pancreatic enzyme replacement therapy. Exclusion criteria included history of liver or lung transplant, known non-CF liver disease (i.e., hepatitis), short gut syndrome, total parenteral nutrition in past 1 year, pregnancy, implantable medical device that would interfere with vibration controlled transient elastography, fundoplication-induced hypo-glycemia, any CFTR modulator therapy (treatments that are available to patients with specific mutation profiles) use for <6 months prior to the study to avoid confounding effects of acute modulator-mediated changes in glucose metabolism; and systemic glucocorticoids, hospitalization, or intravenous antibiotics to treat pulmonary exacerbation within 4 weeks of the study. Liver disease was categorized into three groups using published criteria [18]: no liver disease (no LD), cirrhosis without portal hypertension (mild LD), and cirrhosis with portal hypertension (severe LD). CFRD status was determined using OGTT. Using clinical care guidelines, CFRD was defined by a fasting blood sugar ≥126 mg/dL and/or 2-hour glucose ≥200 mg/dL [2]. Subjects were categorized based on the presence or absence of diabetes [no DM, DM], Written assent and/or consent was obtained before study procedures were performed.

Study procedures

Oral glucose tolerance test (OGTT)

Subjects were instructed to maintain their usual carbohydrate ingestion for 3 days before the study. They were admitted to the Texas Diabetes Institute Clinical Research Unit and the Children’s Hospital of Pittsburgh Pediatric Clinical and Translational Research Center after an overnight fast.

After fasting blood samples were obtained, subjects ingested a glucose solution (1.75 g/kg; maximum 75 g) over a 2-minute period with blood samples obtained via indwelling intravenous catheter at −15, 0, 15, 30, 60, 75, 90, 120, 150, and 180 min. Plasma was separated within 60 min for storage at −80°C.

Height was measured to the nearest 0.1 cm and weight to the nearest 0.1 kg by a trained research staff. Body mass index was converted to a z-score using published reference data.

Vibration controlled transient elastography (VCTE)

VCTE utilizes shear wave ultrasound to provide a liver stiffness measurement (LSM) to quantify fibrosis and a controlled attenuation parameter (CAP) score to quantify steatosis. LSMs and CAPs using VCTE (Fibroscan 502 Touch model) were obtained in the fasting state by a research team member trained and certified by the manufacturer. LSMs per subject were obtained in succession with results reported in kilopascals (kPa), ranging from 1 to 75 kPa. The validity of each measurement was assessed by the device. LSM was calculated as the median of 10 valid measurements. Per the manufacturer, LSM was not recorded if an insufficient number of valid measurements was obtained or if the interquartile range of measurements was ≥30% of the median.

Biochemical analysis

Blood samples were collected as previously described [19]. Plasma glucose and lactate were measured with a bedside analyzer (Analox G9 Analyser in San Antonio; YSI, Yellow Springs, OH in Pittsburgh). Plasma insulin, C-peptide and glucagon were measured by radioimmunoassays (Millipore Sigma, Billerica, MA); total and active glucagon like peptide-1 (GLP-1) as well as gastric inhibitory polypeptide (GIP) were measured by ELISA (Millipore Sigma, Billerica, MA). Free fatty acids (FFA) were quantified using enzymatic colorimetric assays (Millipore Sigma, St. Louis, MO). Liver function tests were performed using Dimension Vista 1500 (Siemens, NY, USA), complete blood count using Sysmex XN 9000 (Siemens, NY, USA), and HbA1c using HPLC (Trinity Biotech, Inc. USA).

Calculations

Fasting values were the average of 2 samples drawn at −15 and 0 min. Incremental areas under the curve over 3 h (AUC3h) for glucose, insulin, C-peptide, glucagon, and FFA were measured using the trapezoidal rule. β-cell glucose sensitivity was calculated as the slope of C-peptide secretion/plasma glucose dose-response during glycemic increment from basal to peak glucose values.

Fasting insulin sensitivity (HOMA-IR) was calculated as: [insulin (µU/mL) × glucose (mg/dL)]/405; prandial insulin sensitivity was estimated using oral glucose derived insulin sensitivity (OGIS) index (mU·min −1·m −2). Disposition index was calculated as OGIS × β-cell glucose sensitivity. Fasting insulin clearance was calculated as fasting C-peptide/insulin and prandial insulin clearance as total AUC C-peptide/ AUC Insulin 3h−Aspartate aminotransferase to Platelet Ratio Index (APRI) and Fibrosis-4 (Fib4) score, biomarkers of hepatic fibrosis that have been previously validated by liver biopsy [20], were calculated as AST/upper limit of normalAST × 100/Platelet Count (109/L) and as age (years) × AST (U/L)/Platelets (109/L) × (ALT (U/L)), respectively.
Statistical analyses
Continuous variables are reported as individual data points or means ± SEM and categorical data as frequency counts and percentages. Baseline characteristics were compared using ANOVA with Welch's correction or Fischer's exact test based on 'liver disease status.' Outcomes of interest were compared based on 'liver disease' using ANOVA or 'liver disease' and 'glucose tolerance status' using two-way ANOVA with multiple comparisons when indicated. Statistical significance was defined at p < 0.05; analyses were performed using SPSS, Version 28.

Results
Subject characteristics
Twenty subjects with CF (45% male, age 15 ± 0.6 years) were enrolled. Of the 20 subjects, 13 had no LD, 4 mild LD, and 3 severe LD (Table 1). The three groups did not differ in BMI z-score, ethnicity, or HbA1c. Participants with mild or severe LD were younger (p < 0.05). Among the subjects enrolled in our study, 5 with no LD, 2 with mild LD, and 2 with severe LD had CFTR; the difference did not reach statistical significance. CFTR modulator therapy was used in 9 of the 13 subjects with no LD, but in no participants with either mild or severe LD. In no LD, 4 of 5 subjects with CFTR were on modulator therapy, and none of the subjects without modulator therapy had CFTR (data not shown).

OGTT results (Table 2)
Subjects with severe LD had the highest fasting and post-OGTT glucose (peak and AUC0-3h) among individuals with CFTR (interaction p < 0.05) (Fig. 1A & C). Fasting C-peptide levels were comparable among 3 LD groups (Fig. 1B) and between those with and without CFTR, whereas prandial β-cell secretory response (AUC0-3h) was lower in severe LD compared to mild or no LD (p < 0.01), and in individuals with CFTR compared to non-diabetic subjects (p = 0.06) (Fig. 1D). Further, β-cell sensitivity to glucose, a marker of β-cell function, tended to be lower in CFTR regardless of LD status (p = 0.1) (Fig. 2). Fasting and prandial glucagon were similar between subjects with or without CFTR and among 3 LD groups (Supplemental Fig. 1). While fasting insulin sensitivity measured by HOMA-IR were similar among those with CFTR and mild or no LD (interaction p = 0.1), Prandial insulin sensitivity estimated by OG1S was lower in subjects with CFTR independent of their LD status (p < 0.05), but the most robust impairment was noted in those with CFTR and severe LD (interaction p = 0.07) (Fig. 3A). Disposition index, the estimate of β-cell function relative to insulin resistance, also tended to be lower in CFTR independent of LD status (Fig. 3B, p = 0.07).

Fasting insulin clearance tended to be lower in mild and severe LD compared to no LD (Fig. 3C, p = 0.06), and prandial insulin clearance tended to be lower in severe LD among those with CFTR (Fig. 3D, interaction p = 0.1). Fasting total GLP-1 was higher in severe LD and CFTR (interaction p < 0.05), but no differences were noted in prandial GLP-1 (Supplemental Fig. 2). Fasting and prandial GIP were similar among 3 LD groups and between those with and without CFTR (data not shown). Post-OGTT suppression of FFA were similar among all subjects, except one subject with severe LD and CFTR exhibited an increase in FFA after oral glucose ingestion (data not shown). No differences were noted in fasting or prandial lactate levels between subjects with or without CFTR or among the 3 LD groups (data not shown). Markers of hepatic inflammation and fibrosis, aspartate aminotransferase, alkaline aminotransferase, gamma-glutamyl transferase, and alkaline phosphatase were lower in subjects with no LD when compared to mild and severe LD (p < 0.05) (data not shown). As expected, platelets, APRI, and Fib-4 score were lower and LSMs greater in severe LD compared to no LD and mild LD (p < 0.05) (Table 2). No differences in VCTE CAP score, a marker for steatosis, were present among the 3 groups (Table 2).

Discussion
This pilot study was conducted to begin to identify glycemically characteris in youth with and without CF-liver disease. This intersection has received limited attention. Among patients with CFTR, abnormalities in glucose metabolism as well as insulin secretion, sensitivity, and clearance were worse in the setting of severe CF liver disease. These findings suggest that there is an association between severe liver disease and abnormal glucose metabolism in CFTR and highlight the need for larger studies.

In this study, we utilized OGTT to measure glucose tolerance status and islet-cell and gut hormone secretory response simultaneously. This method also allowed us to measure insulin sensitivity and clearance in the fasting and fed state. Subjects were categorized by LD status based on published criteria [18]. For simplicity, we denoted subjects with cirrhosis without portal hypertension as “mild LD” and those with portal hypertension as “severe LD.” As much debate exists as to which criteria are most appropriate to diagnose CF-liver disease, we additionally utilized validated biomarkers and imaging to further support our classifications. APRI score, Fib4 score, and LSMs were highest in people with severe LD, aligned with published data [20]. Steatosis was similar among the three groups, consistent with literature suggesting that CF steatosis does not generally progress to fibrosis [21]. Subjects were also classified as “no diabetes” and “diabetes.” There is a spectrum of glucose tolerance in CF that includes non-diabetic categories, such as normal, impaired, and indeterminate. We labeled these categories as “no DM” to enhance the power of our analysis. While the groups were not tightly matched for age, participants spanned within a 10-yr range with significant overlap.

Subjects with liver disease tended to be younger, male, and have a severe genotype profile (heterozygous F508del with the other mutation classified as either severe or rare). Given the severe genotype profile, most subjects with liver disease were not eligible for CFTR modulator therapy at the time of this study. These findings align with the literature, as CF-liver disease is often diagnosed in early childhood, and male sex and severe genotypes are risk factors for CF-liver disease development [18].

Subjects with CFTR had larger prandial glycemia and lower 3-hr post OGTT C-peptide levels when compared to those without diabetes. These findings were expected and are consistent with the multitude of published studies that demonstrate β-cell secretion defects characterize CFTR. Similarly, there was a trend of lower β-cell sensitivity to glucose in those with CFTR, a finding also appreciated in a recent report [22].

Table 1
Baseline characteristics of study participants.

|                | No LD (n = 13) | Mild LD (n = 4) | Severe LD (n = 3) | P value |
|----------------|---------------|----------------|------------------|---------|
| Age, y         | 16 ± 0.6      | 12 ± 0.2       | 14 ± 2.2         | <0.05   |
| BMI z-score    | −0.2 ± 0.2    | 0.4 ± 0.4      | −0.5 ± 0.6       | NS      |
| Male           | 4 (31%)       | 2 (50%)        | 3 (100%)         | 0.10    |
| Ethnicity      |               |                |                  |         |
| Caucasian      | 11 (85%)      | 3 (75%)        | 3 (100%)         | NS      |
| Hispanic       | 2 (15%)       | 1 (25%)        | 0 (0%)           |         |
| HbA1c, %       | 5.7 ± 0.1     | 5.8 ± 0.1      | 6.9 ± 1.3        | NS      |
| Glucose Tolerance Test | | | | |
| No DM          | 8 (62%)       | 2 (50%)        | 1 (33%)          | NS      |
| DM             | 5 (38%)       | 2 (50%)        | 2 (67%)          |         |
| Genotype       |               |                |                  |         |
| Homozygous F508del | 10 (77%) | 0 (0%)        | 1 (33%)          | <0.05   |
| Heterozygous F508del | 3 (23%) | 4 (100%)      | 2 (67%)          |         |

Data is presented as mean ± SEM or number (%). Statistical P values for ANOVA or Fisher’s Exact Test analysis are provided in the furthest right column. Abbreviations: LD, liver disease; BMI, body mass index; DM, diabetes.
addition to impaired β-cell output, we found that prandial insulin sensitivity was lower in CFRD. The trend of altered insulin action in our patients with CFRD aligns with previous investigations demonstrating a decline in insulin sensitivity (OGIS) across the glucose tolerance in CF [22,23]. Relating the amount of β-cell output for insulin sensitivity, disposition index also trended lower in CFRD, as previously described [24].

Our novel findings, however, reside within our severe LD group. CFRD generally presents with normal fasting glycemia, as observed in our subjects with CFRD with no or mild LD. Aging contributes to fasting hyperglycemia in CFRD [25], however, we appreciated elevated fasting glucose in our two young subjects (10 and 17 years old) with CFRD and severe LD (Table 2). These two individuals also had the most striking prandial glucose abnormalities coupled with the most impaired prandial β-cell secretory responses. These findings altogether hint towards a pathogenic role of severe liver disease exacerbating glucose abnormalities in CFRD and align with findings from non-CF populations in which β-cell function declines as liver disease severity worsens [26].

Table 2

| Glucose Metabolism | No LD (n = 13) | Mild LD (n = 4) | Severe LD (n = 3) |
|--------------------|---------------|----------------|------------------|
| Glucose (mg/dl)    |               |                |                  |
| Fasting           | 93 ± 3        | 96 ± 4         | 95               |
| Peak              | 191 ± 8       | 268 ± 26       | 169              |
| C-peptide (ng/ml) |               |                |                  |
| Fasting           | 1.7 ± 0.2     | 1.6 ± 0.3      | 1.9              |
| AUC3h             | 870 ± 134     | 687 ± 141      | 141              |
| BGS (pmol/min⁻¹ ⋅ mM⁻¹) | 4.4 ± 1 | 3.2 ± 0.8 | 10.5 |
| Disposition index | 4.1 ± 0.7     | 2.5 ± 0.9      | 2.6              |

Hepatic Biomarkers

| VCTE LSM (kPa)  | 4.9 ± 0.6   | 5.1 ± 0.4 | 12.6 |
| VCTE CAP (dB/m) | 184 ± 48    | 213 ± 12  | 151  |
| Platelets (x10⁹/L) | 323 ± 24 | 277 ± 25  | 234  |
| APRI score      | 0.15 ± 0.03 | 0.17 ± 0.03| 0.67 |
| Fib4 score      | 0.17 ± 0.03 | 0.26 ± 0.03| 0.49 |

Results reported as individual data or mean ± SEM, statistical P values based on a two-way (comparing the effects of liver disease status vs. CFRD and their interaction) or b one-way ANOVA (comparing 3 groups with different liver disease status). Abbreviations: LD, liver disease; DM, diabetes; AUC3h, area under the curve over 3 h; BGS, β-cell glucose sensitivity; DI, disposition index; VCTE, vibration controlled transient elastography; LSM, liver stiffness measurement; CAP, controlled attenuation parameter; APRI, AST to platelet ratio index; Fib4, Fibrosis-4; NS, not significant.

Fig. 1. (A) Glucose and (B) C-peptide during the oral glucose tolerance test in patients based on liver disease (LD) status: no LD (n = 13), mild LD (n = 4), severe LD (n = 3). Data presented as mean ± SEM. Area under the curve over 3 h (AUC3h) for (C) glucose and (D) C-Peptide for each LD group based on presence or absence of diabetes (DM) during the oral glucose tolerance test. Data presented as aligned dot plots.
addition to exaggerated glucose and defective insulin secretory response, fasting and prandial insulin sensitivity tended to be decreased in subjects with severe LD and CFRD. This finding is also consistent with non-CF literature which correlate severity of liver disease with insulin resistance [27].

Along with impaired insulin sensitivity, fasting and prandial insulin clearance were lowest in those with severe LD and CFRD. Our findings differ from previous studies that found increased insulin clearance in...
subjects with CF when compared to healthy controls using hyperinsulinemic-euglycemic clamp [14,28]. Enhanced insulin clearance was noted despite a lower fasting insulin clearance (C-peptide/insulin) [14]. Given an association between 2-hr glucose values during an OGTT and insulin clearance measured during the clamp [14,28], the investigators concluded that prandial insulinopenia in CF was exaggerated by increased insulin clearance, even though prandial insulin clearance was never measured. We cannot address potential differences in insulin clearance in CF vs non-CF as we did not recruit healthy controls. None of the previous CF studies, however, investigated the role of liver disease. In our study, comparing subjects with CFRD with and without severe liver disease, it is clear that prandial insulin clearance is reduced in the former group, which is consistent with results from studies in non-CF cohorts with severe liver fibrosis [29]. As the liver clears ~80% of plasma insulin [30], dysfunctional hepatocytes and portosystemic shunts in severe liver disease likely hinder insulin clearance [13]. Reduced insulin clearance has been shown to increase hepatic insulin resistance [31]. We also noted higher fasting total GLP-1 in the severe LD group. Elevated GLP-1 and GIP levels have been described in non-CF cirrhosis for reasons not well understood, yet findings by Junker et al noted impaired insulinotrophic action of the incretins GLP-1 and GIP, despite elevations in incretin levels [32].

Given our preliminary findings, insulin resistance may be the mechanism that links liver disease and glucose abnormalities in CF. As in non-CF populations, severe liver disease and impaired insulin clearance may foster hepatic insulin resistance. Insulin resistance may exaggerate insulin secretion defects that are already inherent in CF. Our work raises many important clinical questions regarding CFRD screening/diagnosis, treatment, and complications. CFRD guidelines currently recommend OGTT screening to begin at age 10 years [2], but children with liver disease may warrant earlier CFRD screening as the youngest subject in our cohort was a 10 yr 1 mo old with severe liver disease and known diagnosis of diabetes. Insulin is currently the only recommended treatment to manage CFRD. If insulin resistance is an important contributing factor to diabetes development in patients with CF-liver disease, further studies are needed to evaluate the effectiveness of broader anti-diabetic medications in this population. While macro- and microvascular complications in CFRD are lower compared to other types of diabetes [2], the added insulin resistance and impaired insulin clearance can potentially increase the risk of these complications in patients with severe LD.

There are several limitations to our study. This is a small-sized cohort with relatively large variabilities among those with and without CFRD. Therefore, our findings can only serve to generate hypotheses and warrant larger studies. However, since our subjects were recruited sequentially based on clinical criteria, they are likely to represent patients with CF-liver disease or CFRD in practice. Our cross-sectional design also precludes the ability to evaluate the progression of liver disease and glucose abnormalities longitudinally and to address the causal relationship between the two. The assessment, one OGTT, is a relatively limited method to evaluate insulin sensitivity and clearance. However, this approach provided a feasible method to evaluate overall glucose metabolism and islet-cell secretory response in both fasting and fed conditions. None of the subjects in our liver disease groups were on modulator therapy at the time of our pilot study; although this does not seem to be a confounding factor in our cohort as the prevalence of diabetes was not lower in subjects on modulator therapy, and none of the subjects without modulatory therapy had CFRD.

Conclusion

We report here that subjects with CFRD and severe liver disease had worse glucose tolerance as well as impaired insulin secretion and sensitivity. Severe liver disease in CFRD may impair insulin clearance. Larger studies are needed to define the contribution of liver disease to CFRD to inform clinical care guidelines in terms of CFRD screening, diagnosis, and treatment.

CRediT authorship contribution statement

Maria Socorro Rayas: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Visualization. Kara S. Hughan: Conceptualization, Methodology, Investigation, Writing – review & editing. Rida Javid: Conceptualization, Methodology, Investigation, Writing – review & editing. Andrea Kelly: Conceptualization, Methodology, Supervision, Writing – review & editing. Marzieh Salehi: Formal analysis, Visualization, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcte.2022.100296.

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