Assessment of Rapid Hepatic Glycogen Synthesis in Humans Using Dynamic $^{13}$C Magnetic Resonance Spectroscopy

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Carbon-$^{13}$ magnetic resonance spectroscopy (MRS) following oral intake of $^{13}$C-labeled glucose is the gold standard for imaging glycogen metabolism in humans. However, the temporal resolution of previous studies has been >13 minutes. Here, we describe a high-sensitivity $^{13}$C MRS method for imaging hepatic glycogen synthesis with a temporal resolution of 1 minute or less. Nuclear magnetic resonance spectra were acquired from the liver of 3 healthy volunteers, using a $^{13}$C clamshell radiofrequency transmit and paddle-shaped array receive coils in a 3 Tesla magnetic resonance imaging system. Following a 15-minute baseline $^{13}$C MRS scan of the liver, [1-$^{13}$C]-glucose was ingested and $^{13}$C MRS data were acquired for an additional 1-3 hours. Dynamic change of the hepatic glycogen synthesis level was analyzed by reconstructing the acquired MRS data with temporal resolutions of 30 seconds to 15 minutes. Plasma levels of $^{13}$C-labeled glucose and lactate were measured using gas chromatography–mass spectrometry. While not detected at baseline $^{13}$C MRS, [1- $^{13}$C]-labeled α-glucose and β-glucose and glycogen peaks accumulated rapidly, beginning as early as ~2 minutes after oral administration of [1-$^{13}$C]-glucose. The [1-$^{13}$C]-glucose signals peaked at ~5 minutes, whereas [1-$^{13}$C]-glycogen peaked at ~25 minutes after [1-$^{13}$C]-glucose ingestion; both signals declined toward baseline levels over the next 1-3 hours. Plasma levels of $^{13}$C-glucose and $^{13}$C-lactate rose gradually, and approximately 20% of all plasma glucose and 5% of plasma lactate were $^{13}$C-labeled by 2 hours after ingestion. Conclusion: We observed rapid accumulation of hepatic [1-$^{13}$C]-glycogen following orally administered [1-$^{13}$C]-glucose, using a dynamic $^{13}$C MRS method with a temporal resolution of 1 minute or less. Commercially available technology allows high temporal resolution studies of glycogen metabolism in the human liver. (Hepatology Communications 2020;4:425-433).
disorders, including obesity, diabetes, and nonalcoholic fatty liver disease. For example, patients with type 2 diabetes have an impaired rate of glycogen synthesis following a meal, likely due to hepatic insulin resistance and/or an altered insulin to glucagon ratio. \(^\text{(1)}\) Patients with poorly controlled type 1 diabetes can develop glycogenic hepatopathy, a rare disorder characterized by the accumulation of large amounts of hepatic glycogen that ultimately can lead to fibrosis and cirrhosis of the liver. \(^\text{(2)}\) Genetic mutations in enzymes responsible for the synthesis or breakdown of glycogen cause glycogen storage diseases, a family of recessive disorders characterized by an abnormal quantity or quality of glycogen in the liver, muscles, heart, and kidney, depending on the specific molecular defect.

Glycogen metabolism in human patients initially was explored using \(^\text{[3H]}\)- and \(^\text{[14C]}\)-labeled tracers. \(^\text{(3,4)}\) Because of the constraints of radiotracers for clinical research, the gold standard for studying in vivo hepatic glycogen metabolism in humans is \(^\text{13C}\) magnetic resonance spectroscopy (MRS) following oral intake of \(^\text{13C}\)-labeled glucose. Hepatic glycogen metabolism has been extensively studied using this method in both physiologic and pathologic settings and following intake of various diets and/or drugs. Early studies conducted in the 1980s and 1990s determined the steady-state kinetics of liver glycogen synthesis in fasting and fed healthy individuals. \(^\text{(5,6)}\) Since then, hepatic glycogen metabolism has been studied by MRS in humans with a wide spectrum of traits or diseases, including obesity, \(^\text{(7)}\) type 2 diabetes, \(^\text{(1)}\) and glycogen storage disease. \(^\text{(8)}\)

Due to limited sensitivity, however, these previous MRS-based studies of glycogen metabolism relied on relatively low temporal resolutions, averaging signals of 13 minutes or longer. \(^\text{(1,5,8-12)}\); that is, the earliest time point of hepatic glycogen assessment was 13 minutes after oral intake. \(^\text{(12)}\) The hormonal and neuronal responses to oral food intake are nearly instant. For example, insulin is secreted from the pancreas and glucose is transported from the gut lumen across the enterocytes into the hepatic vein within minutes after glucose ingestion. \(^\text{(11,13)}\) Measuring immediate changes in hepatic glycogen synthesis would therefore require a better temporal resolution than 13 minutes. A fine-scale temporal resolution might provide new insights into the earliest postprandial phase of hepatic metabolism.

Studying the kinetics of hepatic glycogen synthesis during the earliest postprandial period (0-30 minutes) is technically challenging, in part due to the low signal to noise ratio (SNR), which typically requires longer acquisition times and averaging of the signal across many minutes. Alternative methods have been proposed to improve the sensitivity of detecting the glycogen signal. For instance, a novel method for detecting in vivo glycogen using water resonance in magnetic resonance imaging (MRI) was recently developed and validated in a mouse model. \(^\text{(14,15)}\) The method has been used in a proof of concept experiment in a recent human study at 3 Tesla (T), but further technological development is required for clinical usage. \(^\text{(16)}\)

Major advances have been made in radiofrequency (RF) technology during the past decades. The SNR has been improved by novel coil designs and by exploiting new MRI techniques, such as parallel imaging. \(^\text{(17)}\) In particular, the recent translation of
dissolution dynamic nuclear polarization (or hyperpolarization) using $^{13}$C-pyruvate accelerated the development of $^{13}$C RF coils optimized for imaging various human organs.\(^{(18-20)}\) In this study, we hypothesized that a state-of-the-art $^{13}$C coil array design (volume carbon transmit coil, designed for hyperpolarized $^{13}$C studies) may improve SNR of \textit{in vivo} $^{13}$C glycogen signals. We describe a highly sensitive $^{13}$C MRS method that makes it possible to use commercially available technology to observe hepatic glycogen synthesis during the earliest postprandial phase in humans.

## Participants and Methods

### PARTICIPANTS

We recruited 3 healthy volunteers (38-51 years old, 2 men and 1 woman, all of white European descent). The study was approved by the ethical committee at the University of Texas Southwestern (UTSW) Medical Center. All volunteers provided written consent after having received oral and written information about the study. The participants arrived at the imaging facility at 7 AM after an overnight fast. Before the MRS session, weight and height were measured, blood samples were drawn, and an intravenous access was established.

### MRS

We used a system designed for imaging hyperpolarized $^{13}$C MRS in human patients: a 3T wide-bore clinical MR scanner (750w Discovery; GE Healthcare), a clamshell $^{13}$C transmit coil for RF excitation, and 8-channel $^{13}$C receive array paddle-shaped coils for signal reception (dimension of each channel element, $5 \times 10$ cm; GE Healthcare).\(^{(19)}\) Independent studies on a corn-oil phantom (square bottle, 3.78 L) and a $^{13}$C-labeled HCO$_3^-$ sphere phantom (1 M; diameter, 40 mm) were performed to determine the sensitivity profile of each coil element. For human studies, $^1$H images that include three-plane fast gradient-recalled echo and two-dimensional (2D) fast imaging employing steady-state acquisition (FIESTA) (16 slices; breath-hold; echo-time, 1.452 milliseconds; time of repetition [TR], 3.242 milliseconds) were acquired over the liver from each subject, using the GE body coil equipped in the scanner to acquire structural references and to optimize the position of the $^{13}$C paddle array coils. Following the $^1$H scans, a series of pulse-and-acquire $^{13}$C MRS scans were performed to monitor metabolism of thermally polarized (not hyperpolarized) [1-$^{13}$C]-glucose. A baseline $^{13}$C MRS liver scan was first performed (TR, 0.5 seconds; flip angle [FA], 60-degree angle; number of scans, 1,800; acquisition time, 15 minutes; spectral width, 10,000 Hz; number of spectral points, 4,096). The $^{13}$C MRS scan continued with oral administration of a [1-$^{13}$C]glucose solution (98 g glucose, containing 20% [1-$^{13}$C]glucose in 240 mL). Nonslice-selective RF pulse (duration, 512 microseconds) was used for excitation, and the hepatic signal was localized by the paddle coil. $^{13}$C MRS scans started concurrently with glucose ingestion and were repeated in 15-minute blocks for up to 3 hours. All free induction decay signals of individual scans were stored for reconstructing the spectra with various temporal resolutions. To confirm the spatial distribution of $^{13}$C signals, $^{13}$C chemical shift imaging (CSI) (field of view [FOV], 32 × 32 cm; matrix size, 8 × 8; TR, 0.5 seconds; eight averages; slice selective; FA, 60-degree; acquisition time, 4 minutes 16 seconds; spectral width, 10,000 Hz; number of spectral points, 4,096) was performed in participant 2 after MRS scans.

### BIOCHEMICAL MEASUREMENTS

Baseline blood samples were analyzed for plasma levels of lipids, lipoproteins, glucose, liver enzyme levels, and markers of kidney function, using standard clinical laboratory methods. Blood samples drawn every 15 minutes during the scan were analyzed for plasma levels of glucose and insulin (by enzyme-linked immunosorbent assay at the Metabolic Phenotyping Core of the UTSW Medical Center) and for $^{13}$C-enrichment of glucose and lactate, using gas chromatography–mass spectrometry (GC-MS) at the Metabolomics Facility of the Children’s Medical Center Research Institute at the UTSW Medical Center. The GC-MS analysis was performed on the upper phase of a Folch extraction, using 50 μL of plasma. Once dried, the sample was methoximated (10 mg/mL methoxyamine [226904; Sigma] in pyridine [270407; Sigma]) for 15 minutes at 70°C, then derivatized with N-(tert-butyldimethylsilyl)-N-methyltrifluoroacetamide (394882; Sigma) for 1 hour at 70°C. We injected 1 μL of the sample on an Agilent
7890 gas chromatograph coupled to an Agilent 5975 mass selective detector. The detected abundances for the mass isotopomers corresponding to glucose (608-614) and lactate (261-264) were corrected for natural abundance.

DATA ANALYSIS

All the $^{13}$C data were processed using MATLAB (Mathworks; Natick, MA). For MRS, the raw data were apodized with a 5-Hz Gaussian filter, zero filled by a factor of 4, and a fast Fourier transform (FFT) applied. The data were analyzed in several temporal resolutions (30 seconds to 15 minutes) by averaging every 60 to 1,800 measurements. After averaging the spectra over time, the zeroth- and first-order phases were corrected in absorption mode. The resulting rolling baseline of the spectra was corrected by fitting to a spline function. Each metabolite was quantified by integrating the peak. For $^{13}$C CSI, additional 2D apodization using a hanning filter, 2D zero filling by a factor of 4, and 2D inverse FFT was performed along the spatial domain. $^{13}$C metabolite maps were created by integrating the corresponding peaks and overlaid on top of the $^1$H FIESTA images for display purposes. SNRs of glucose and glycogen were measured from each time-averaged spectrum with 1-minute and 15-minute temporal resolutions by integrating the corresponding peaks. The SNRs are reported for nonoverlapping $[1-^{13}$C$]$-glucose (93.3 ppm) and $[1-^{13}$C$]$-glycogen (102.2 ppm) peaks only. All data are presented as mean ± SD.

Results

BASELINE CHARACTERISTICS

Baseline characteristics of the 3 volunteers are shown in Table 1. We included 2 men and 1 woman, aged 38, 51, and 46 years, respectively. No volunteer had obesity or diabetes, and all had normal plasma levels of lipids and liver enzymes.

SIGNAL SENSITIVITY OF PADDLE ARRAY COILS

A sensitivity profile of the 8-channel $^{13}$C paddle coils, using a bottle container of corn oil and a sphere phantom of 1-M $[^{13}$C$]HCO_3^-$, is demonstrated in

| Participant Number | 1  | 2  | 3  |
|-------------------|----|----|----|
| Age (years)       | 51 | 38 | 46 |
| Sex (F/M)         | M  | M  | F  |
| Body mass index (kg/m$^2$) | 28 | 22 | 23 |
| Glucose (mg/dL)   | 92 | 85 | 74 |
| Total cholesterol (mg/dL) | 305| 186| 157|
| HDL cholesterol (mg/dL) | 35 | 60 | 61 |
| LDL cholesterol (mg/dL) | 252| 103| 81 |
| Triglycerides (mg/dL) | 90 | 113| 81 |
| ALT (U/L)         | 22 | 30 | 11 |

Abbreviations: ALT, alanine aminotransferase; F, female; HDL, high-density lipoprotein; LDL, low-density lipoprotein; M, male.

Fig. 1. Signal sensitivity of each channel decreased markedly with increasing distance to the phantoms. In particular, the sphere phantom signal measured by channel #5-8 was 10%-15% of that measured from channel #2, the channel closest to the phantom. The RF coils were, however, sensitive enough to detect $^{13}$C signals located approximately 20 cm away from each coil element.

MRS OF HEPATIC GLYCOGEN SYNTHESIS AFTER ORAL INTAKE OF $[1-^{13}$C$]$-LABELED GLUCOSE

While not detected at baseline $^{13}$C MRS, $[1-^{13}$C$]$-labeled α-glucose and β-glucose (93.3 and 97.2 ppm, respectively) and glycogen (98.5 and 102.2 ppm) peaks accumulated rapidly, beginning as early as ~2 minutes after oral administration of $[1-^{13}$C$]$-glucose (Fig. 2). Overall, the dynamic patterns of labeled glucose and glycogen were similar in the 3 participants. When reconstructed with 1-minute temporal resolution, the $[1-^{13}$C$]$-glucose signals peaked at 5.3 ± 1.5 minutes, whereas $[1-^{13}$C$]$-glycogen peaked at 23.7 ± 1.2 minutes after $[1-^{13}$C$]$-glucose ingestion, and both signals declined toward baseline levels over the rest of the MRS session. With 15-minute temporal resolution, however, the glucose and glycogen peaks were at 15 and 30 minutes, respectively. Maximum signal intensity varied somewhat between the 3 participants, likely reflecting differences in body composition and/or coil placements relative to the liver. The peak SNRs of glucose and glycogen were 76.4 ± 25.6 and 105.1 ± 49.7, respectively, with temporal resolution of 15 minutes, and 26.4 ± 25.6 and 30.3 ± 9.8,
Fig. 1. Sensitivity profile of the RF coils measured using a bottle container of corn oil (1.1% natural abundance of $^{13}$C) and a ball phantom of $^{13}$C-labeled 1-M HCO$_3^-$: (A) $^1$H MRI showing the positioning of the phantoms relative to the transmit clamshell and 8-channel receive paddle-shaped phased-array $^{13}$C RF coils. (B) Coil-wise reconstructed total $^{13}$C maps acquired using a free-induction decay chemical shift imaging sequence with a nonselective 90-degree angle RF pulse. (C) Spatially averaged coil-wise magnitude spectra. Abbreviations: ch, channel; RX, receive; TX, transmit.

Fig. 2. Real-time hepatic glycogen synthesis of a representative subject (participant 1), measured by dynamic $^{13}$C MRS followed by oral administration of [1-$^{13}$C]-glucose. (A) Axial $^1$H MRI showing the position of $^{13}$C paddle receive-array coils relative to the liver. Scale = 32 cm by 32 cm. (B) The first 15-minute averaged spectrum following glucose administration and (C) 30-second averaged spectra at 0-, 2-, 10-, and 15-minute time frames showed that glucose and glycogen started to build up rapidly. [1-$^{13}$C]-labeled glycogen (98.5 and 102.2 ppm) as well as $\alpha$-glucose (93.3 ppm) and $\beta$-glucose (97.2 ppm) could be resolved in each spectrum. Kinetics of [1-$^{13}$C] $\alpha$-glucose and $\beta$-glucose and [1-$^{13}$C] glycogen in temporal resolutions of (D) 15 minutes and (E) 30 seconds. Abbreviation: a.u., arbitrary unit.
respectively, with temporal resolution of 1 minute. Depending on the subject, the data could be reconstructed with a finer temporal resolution (< 1 minute). Clear $^{13}$C-glucose and $^{13}$C-glycogen signals from each spectrum when reconstructed every 30 seconds are shown, for example, in Fig. 2 (Supporting Fig. S1).

**SPATIAL LOCALIZATION OF [1-$^{13}$C]-GLYCOGEN PEAKS TO THE LIVER**

Although the spatial resolution was limited, separate $^{13}$C CSI data confirmed the spatial localization of [1-$^{13}$C]-glycogen peaks in the liver (Fig. 3). In contrast, [1-$^{13}$C]-glucose signals were primarily localized in the stomach area. The SNR of [1-$^{13}$C]-glucose and [1-$^{13}$C]-glycogen varied among the 3 participants, likely due to the different positioning of the paddle coils relative to the liver. However, glycogen peaks could be resolved even when reconstructed from 30-second-long segments (60 averages; Supporting Fig. S2).

**PLASMA LEVELS OF GLUCOSE, LACTATE, AND INSULIN**

Following oral ingestion of 98 g glucose (20% [1-$^{13}$C]-labeled glucose), the fractional $^{13}$C enrichment of glucose and lactate rose gradually in the plasma. At 2 hours after ingestion, approximately 20% of all plasma glucose and 5% of plasma lactate were $^{13}$C labeled (data from participant 1 are shown in Fig. 4, top panels). Plasma levels of glucose and insulin rose in the 3 participants, reaching peaks at approximately 60 and 90 minutes after intake, respectively, and decreased toward baseline after 60 to 90 minutes (Fig. 4, bottom panels).

**Discussion**

In this study, we used $^{13}$C MRS to observe rapid accumulation of hepatic [1-$^{13}$C]-glycogen following orally administered [1-$^{13}$C]-glucose in 3 healthy adults aged 38 to 51 years. In all 3 participants, hepatic glycogen synthesis was detected by $^{13}$C MRS as early as 2 minutes after ingestion of labeled glucose. Hepatic glycogen synthesis increased rapidly and peaked at approximately 20 minutes after ingestion. The method uses commercially available technology that may be applied for clinical use. The improved sensitivity of the presented technology to the $^{13}$C-labeled glycogen signal allows *in vivo* assessment of dynamic glycogen synthesis every 30 seconds or longer, potentially allowing noninvasive assays and kinetic analysis of the enzymes associated with glycogen metabolism. Many drugs and hormones, such as glucagon and epinephrine, stimulate glycogenolysis with a timeframe of a few seconds. For instance, glucagon stimulates glycogenolysis and gluconeogenesis to raise plasma glucose, but the specific contribution of glycogenolysis versus gluconeogenesis is difficult to determine. Methods that measure glycogen on a minute to minute basis or even faster would allow exploration of such early response mechanisms.

FIG. 3. Spatial distribution of $^{13}$C signal after oral administration of [1-$^{13}$C]-glucose (participant 2). (A) Axial $^1$H MRI image that shows relative positions of the $^{13}$C paddle receive array coils and the slice prescription for $^{13}$C CSI. Fiducial markers indicate the location of each channel of the paddle coils. (B) Spatial distribution of the $^{13}$C metabolites at 90-110 ppm. The metabolite maps are overlaid over the $^1$H MRI. [1-$^{13}$C]-glucose and [1-$^{13}$C]-glycogen signals are mainly detected from where stomach (black arrow) and liver (white arrows) are located. Signals from the stomach area were dominant in channels #1-4 (B, left), whereas channels #5-8 (B, right) primarily detected signals from the liver. All images scale = 32 cm by 32 cm. Abbreviation: ch, channel.
Early studies have validated the use of nuclear magnetic resonance (NMR) techniques for measurement of $^{13}$C metabolic fluxes in animal model systems. The first study that reported natural abundance liver glycogen content in humans used a single 10-cm $^{13}$C-only coil and a 2.1T NMR spectrometer. The method was then further refined with the addition of a coplanar $^1$H-decoupler. The $^1$H/$^{13}$C concentric surface coil 11/8 cm configuration reached a time resolution of ~13 minutes and has been used since then in several studies.

In addition to measuring [1-13C]-glucose and [1-13C]-glycogen in the liver using 13C MRS, we used GC-MS to measure 13C-glucose and 13C-lactate in the circulatory system. These plasma measurements provide complementary information on the uptake and metabolism of the ingested bolus of [1-13C]-glucose. Following oral ingestion of 13C-labeled glucose, plasma 13C-glucose would be expected to stem from the following sources: (1) ingested [1-13C]-glucose that is not taken up by the liver and passes directly into circulation after uptake from the intestine, (2) 13C-glucose released from newly synthesized hepatic glycogen (i.e., [1-13C]-glucose that has been taken up by the liver, converted to glycogen, which subsequently undergoes glycogenolysis), and (3) from hepatic gluconeogenesis that used 13C-labeled substrates (e.g., amino acids or lactate) stemming from metabolites of the ingested [1-13C]-glucose bolus. Plasma 13C-lactate would be expected to derive from 13C-glucose taken up and metabolized in red blood cells and muscle cells. We observed that at 2 hours after ingestion, approximately 20% of all plasma glucose and 5% of plasma lactate was 13C labeled. The difference in glucose kinetics between 13C MRS and plasma GC-MS suggests a prompt and effective hepatic uptake of [1-13C]-glucose from the portal vein circulation during the early postprandial period (<30 minutes). Previous studies in animals and humans have estimated the net hepatic glucose uptake following ingestion of an oral glucose bolus.

**FIG. 4.** Temporal trends of plasma $^{13}$C-glucose and $^{13}$C-lactate and overall plasma levels of glucose and insulin after oral ingestion of [1-13C]-glucose in participant 1. Time of [1-13C]-glucose intake was set as 0. Abbreviation: m, mass.
We hypothesize that the decrease in \(^1^{3}C\)-glycogen pattern would be different in recently fed individuals. It is possible that the decreased \(^1^{3}C\)-glycogen after 30 minutes reflects gluconeogenesis to maintain euglycemia. It is possible that the hepatic uptake of orally ingested glucose is close to 100% in the early postprandial phase and that glucose only passes directly into circulation once the hepatic capacity for metabolizing or storing glucose is surpassed. Thus, the presented method may be used to clarify the percentage of glucose passing directly to the circulatory system postprandially.

We also found that hepatic \(^1^{3}C\)-glycogen decreased after approximately 30 minutes, whereas the fractional enrichment of \(^1^{3}C\)-glucose in plasma increased from 30 minutes and throughout the remaining scan period. A possible explanation for this pattern is that the participants had been fasting for >12 hours at baseline and were likely relying on glycogenolysis and gluconeogenesis to maintain euglycemia. It is possible that the decreased \(^1^{3}C\)-glycogen after 30 minutes reflects glycogenolysis of newly synthesized glycogen. We speculate that the last glucose residues incorporated (i.e., those derived from the labeled glucose load) are the first to be released during glycogenolysis. Studies in myofibroblasts support such a “last-in first-out” model of glycogenolysis. (25) It is possible that the pattern would be different in recently fed individuals. We hypothesize that the decrease in \(^1^{3}C\)-glycogen after 30 minutes would be blunted (or absent) in recently fed individuals after ingestion of labeled glucose compared to the fasting subjects included in our study.

It should be noted that the \(^1^{3}C\) spectra shown here can be further refined by proton decoupling, which was not available in the MR scanner that we used. For example, the SNR of \([1-{1^{3}C}]\)-glycogen peak can be significantly improved by decoupling the \(^1^{H}\) nuclei. (26,27) Moreover, a recent study showed that hepatic mitochondrial oxidative and anaplerotic fluxes can be measured from infused \([1-{1^{3}C}]\)-acetate by measuring \([5-{1^{3}C}]\)- and \([1-{1^{3}C}]\)-glutamate, using \(^1^{H}\)-decoupled \(^1^{3}C\) MRS. (27) Exploiting \(^1^{H}\) decoupling, however, requires caution as it increases substantial RF power deposition, which might easily exceed the specific absorption rate limit.

Our study has limitations that should be further investigated. First, we only studied 3 healthy middle-aged adults of white descent and without obesity. The results may therefore not necessarily be generalizable to subjects with different characteristics. For instance, coil placement relative to the liver appeared to majorly influence the sensitivity of the method. It is likely that sensitivity to detect glycogen will be lower in individuals with obesity in whom abdominal fat may hinder placement of the coil in proximity to the liver. Moreover, as the clamshell–paddle coil configuration samples \(^1^{3}C\) signals from a larger region than coplanar surface coils, the measured spectra likely contain signals from tissue regions other than the liver. In particular, muscle can convert glucose to glycogen under the experimental conditions. However, as the contribution of intracellular and vascular glucose in the liver is minimal, the \(^1^{3}C\) peaks detected in the liver by the CSI image is primarily glycogen in the liver (Fig. 3, white arrows). Another limitation is that we did not measure absolute levels of hepatic glycogen in our participants. This would have required the inclusion of phantoms with known glycogen concentrations during the scan. We suggest that future studies using the method should include glycogen phantoms, given that the absolute glycogen content of the liver is a biologically as well as clinically relevant measurement.

In conclusion, we observed rapid accumulation of hepatic \([1-{1^{3}C}]\)-glycogen following orally administered \([1-{1^{3}C}]\)-glucose, using a sensitive, high-resolution, time-resolved \(^1^{3}C\) MRS method. This method, which is based on commercially available and clinically used technology, may be useful for future studies of hepatic glycogen metabolism in humans.

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Supporting Information

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