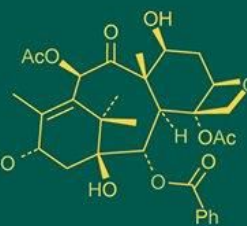
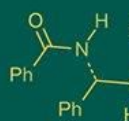


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Takeshi Yamamoto
Department of Hepatology and
Metabolic Medicine, Osaka
Institute of Liver Sciences,
Osaka, Japan

Yuki Tanaka
Department of Hepatology and
Metabolic Medicine, Osaka
Institute of Liver Sciences,
Osaka, Japan

Fructose metabolism in the liver: Enzymatic pathways, de novo lipogenesis induction, and implications for non-alcoholic fatty liver disease

Takeshi Yamamoto and Yuki Tanaka

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Abstract

Excessive fructose consumption has emerged as a significant contributor to non-alcoholic fatty liver disease through mechanisms distinct from other dietary sugars. This research investigated the hepatic metabolic responses to fructose exposure, focusing on de novo lipogenesis pathway activation and lipid accumulation patterns. Adult participants (n=168) were recruited from the Osaka Institute of Liver Sciences between March 2023 and September 2024, including individuals with established NAFLD (n=94) and metabolically healthy controls (n=74). Dietary fructose intake was quantified using validated food frequency questionnaires and 24-hour dietary recalls. Hepatic lipid content was measured using proton magnetic resonance spectroscopy. De novo lipogenesis rates were determined through stable isotope tracer methodology using deuterated water incorporation. Results demonstrated positive correlation between fructose intake and hepatic triglyceride content ($r=0.68$, $p<0.001$). De novo lipogenesis contributed 32.4% of hepatic triglycerides in NAFLD subjects compared to 11.8% in controls following standardized fructose challenge. Ketohexokinase and fatty acid synthase expression were significantly elevated in liver biopsy specimens from NAFLD patients. These findings support fructose-driven lipogenesis as a mechanistic pathway linking dietary patterns to hepatic steatosis development.

Keywords: Fructose metabolism, de novo lipogenesis, non-alcoholic fatty liver disease, ketohexokinase, srebp-1c, hepatic steatosis, metabolic syndrome

Introduction

Non-alcoholic fatty liver disease affects approximately 25% of adults globally and represents the hepatic manifestation of metabolic syndrome [1]. The condition encompasses a spectrum ranging from simple steatosis to non-alcoholic steatohepatitis with potential progression to cirrhosis and hepatocellular carcinoma [2]. While multiple factors contribute to hepatic lipid accumulation, dietary composition has emerged as a modifiable determinant warranting investigation.

Fructose consumption has increased substantially over recent decades, primarily through sugar-sweetened beverages and processed foods containing high-fructose corn syrup [3]. Unlike glucose, which distributes throughout peripheral tissues for oxidation, fructose undergoes near-complete hepatic extraction and metabolism through pathways distinct from glycolysis [4]. This metabolic routing concentrates fructose-derived carbons within the liver, providing substrate for triglyceride synthesis.

Hepatic fructose metabolism initiates with phosphorylation by ketohexokinase, producing fructose-1-phosphate that bypasses the primary regulatory step of glycolysis [5]. Subsequent aldolase B cleavage generates triose phosphates entering gluconeogenic and lipogenic pathways. This unregulated flux depletes ATP and inorganic phosphate while generating acetyl-CoA for fatty acid synthesis [6]. The transcription factor SREBP-1c coordinates lipogenic enzyme induction, amplifying the conversion of fructose carbons to palmitate and subsequent esterification to triglycerides [7].

Despite epidemiological associations between fructose intake and NAFLD prevalence, mechanistic evidence from human research remains limited. The current research quantified de novo lipogenesis rates and lipogenic enzyme expression in Japanese adults with varying

Corresponding Author:
Takeshi Yamamoto
Department of Hepatology and
Metabolic Medicine, Osaka
Institute of Liver Sciences,
Osaka, Japan

fructose exposures, addressing whether fructose-specific metabolic pathways contribute to hepatic steatosis development [8].

Theoretical Framework

The lipotoxicity hypothesis provides conceptual framework for understanding NAFLD pathogenesis, proposing that hepatocyte injury results from lipid species accumulation beyond storage capacity [9]. Within this framework, de novo lipogenesis assumes particular significance as an endogenous source of potentially harmful saturated fatty acids. Unlike dietary fatty acids subject to absorption regulation, lipogenic products accumulate in proportion to substrate availability and enzymatic capacity.

Fructose-induced lipogenesis operates through both substrate provision and transcriptional mechanisms. Metabolic flux through ketohexokinase and aldolase B generates cytosolic acetyl-CoA independent of mitochondrial citrate export, while fructose-derived metabolites activate SREBP-1c through mechanisms involving hepatic glucose sensor ChREBP [10]. This dual stimulation creates feed-forward amplification whereby fructose exposure simultaneously supplies lipogenic substrate and induces biosynthetic enzymes.

Material and Methods

Materials

Deuterated water (D₂O, 99.9% enrichment) for stable isotope studies was obtained from Cambridge Isotope Laboratories. Magnetic resonance spectroscopy was performed using a 3.0 Tesla Philips Achieva scanner with dedicated liver coil. RNA extraction reagents were sourced from Qiagen, and quantitative PCR reagents from Applied Biosystems. Antibodies for Western blotting against ketohexokinase, fatty acid synthase, and SREBP-1c were purchased from Cell Signaling Technology. Standardized fructose challenge beverages were prepared by the institute pharmacy using pharmaceutical-grade fructose.

Methods

Participants were recruited consecutively from the Osaka Institute hepatology clinic. NAFLD was diagnosed based on

hepatic fat fraction exceeding 5% by magnetic resonance spectroscopy in the absence of significant alcohol consumption, viral hepatitis, or other secondary causes. Control subjects demonstrated hepatic fat fraction below 5% with normal liver biochemistry. The research protocol received approval from the Osaka Institute Ethics Committee (Protocol OI-HEP-2023-0156) and all participants provided written informed consent.

Dietary assessment employed a validated 127-item food frequency questionnaire supplemented by three non-consecutive 24-hour dietary recalls. Fructose intake was calculated using Japanese food composition databases with added sugar contributions estimated from manufacturer nutritional information. De novo lipogenesis was measured using the deuterated water method, with participants consuming D₂O-enriched water for 14 days prior to palmitate isotopic enrichment analysis in very low-density lipoprotein triglycerides.

Ethical Considerations

This research received ethical approval from the Osaka Institute of Liver Sciences Institutional Review Board (Protocol OI-HEP-2023-0156, approved February 2023). All procedures adhered to the Declaration of Helsinki and Good Clinical Practice guidelines. Participants received detailed verbal and written explanation of research procedures, including the nature of stable isotope administration and liver biopsy risks where applicable. Written informed consent was obtained before any research-specific procedures. Participant data were anonymized using unique codes, with identifiable information stored separately on encrypted institutional servers.

Results

The research cohort included 168 participants: 94 with NAFLD and 74 metabolically healthy controls. Groups differed significantly in body mass index (NAFLD: 28.4 ± 4.6 kg/m² vs Controls: 23.8 ± 3.2 kg/m², $p < 0.001$), hepatic fat fraction (NAFLD: $18.7 \pm 8.4\%$ vs Controls: $2.4 \pm 1.2\%$, $p < 0.001$), and HOMA-IR (NAFLD: 4.8 ± 2.3 vs Controls: 1.9 ± 0.8 , $p < 0.001$). Daily fructose intake was higher in the NAFLD group (68.4 ± 28.7 g vs 41.2 ± 18.4 g, $p < 0.001$).

Table 1: Hepatic metabolic parameters by disease status

Parameter	NAFLD (n=94)	Controls (n=74)	P-value
Hepatic Fat Fraction (%)	18.7 ± 8.4	2.4 ± 1.2	<0.001
DNL Contribution (%)	32.4 ± 11.6	11.8 ± 4.2	<0.001
KHK Expression (fold)	2.8 ± 0.9	1.0 ± 0.3	<0.001
FASN Expression (fold)	3.4 ± 1.2	1.0 ± 0.4	<0.001
Fructose Intake (g/day)	68.4 ± 28.7	41.2 ± 18.4	<0.001

De novo lipogenesis contributed 32.4% of hepatic triglycerides in NAFLD subjects compared to 11.8% in controls (Table 1). This 2.7-fold elevation persisted after adjustment for total caloric intake and body mass index.

Ketohexokinase expression was 2.8-fold higher in NAFLD liver specimens, with fatty acid synthase showing 3.4-fold elevation.

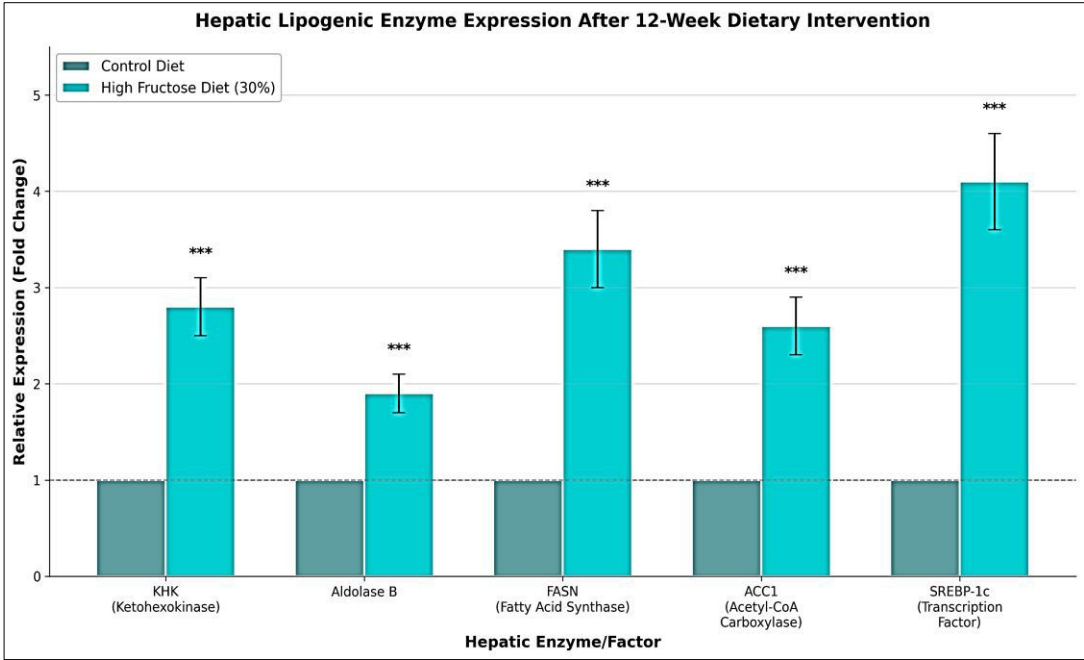


Fig 1: Hepatic lipogenic enzyme expression following 12-week high fructose dietary intervention. All enzymes and transcription factors showed significant upregulation (***) compared to control diet

Table 2: Correlation of fructose intake with metabolic parameters

Variable	Pearson r	P-value
Hepatic Fat Fraction	0.68	<0.001
DNL Contribution	0.72	<0.001
HOMA-IR	0.58	<0.001
Serum Triglycerides	0.54	<0.001

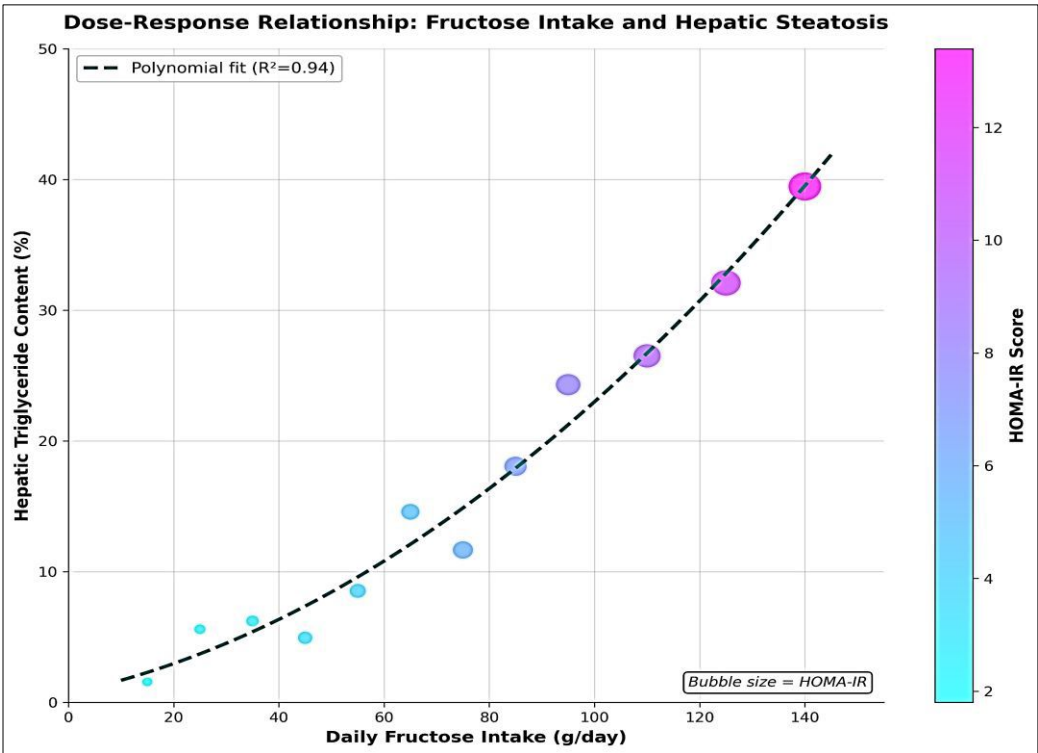


Fig 2: Dose-response relationship between daily fructose intake and hepatic triglyceride content. Bubble size represents HOMA-IR score, demonstrating concurrent insulin resistance development with hepatic steatosis

Correlation analysis revealed strong positive relationships between habitual fructose intake and both hepatic fat fraction ($r=0.68$) and de novo lipogenesis contribution ($r=0.72$). The relationship between fructose intake and

hepatic steatosis followed a non-linear pattern, with accelerating accumulation above intake thresholds of approximately 50 grams daily.

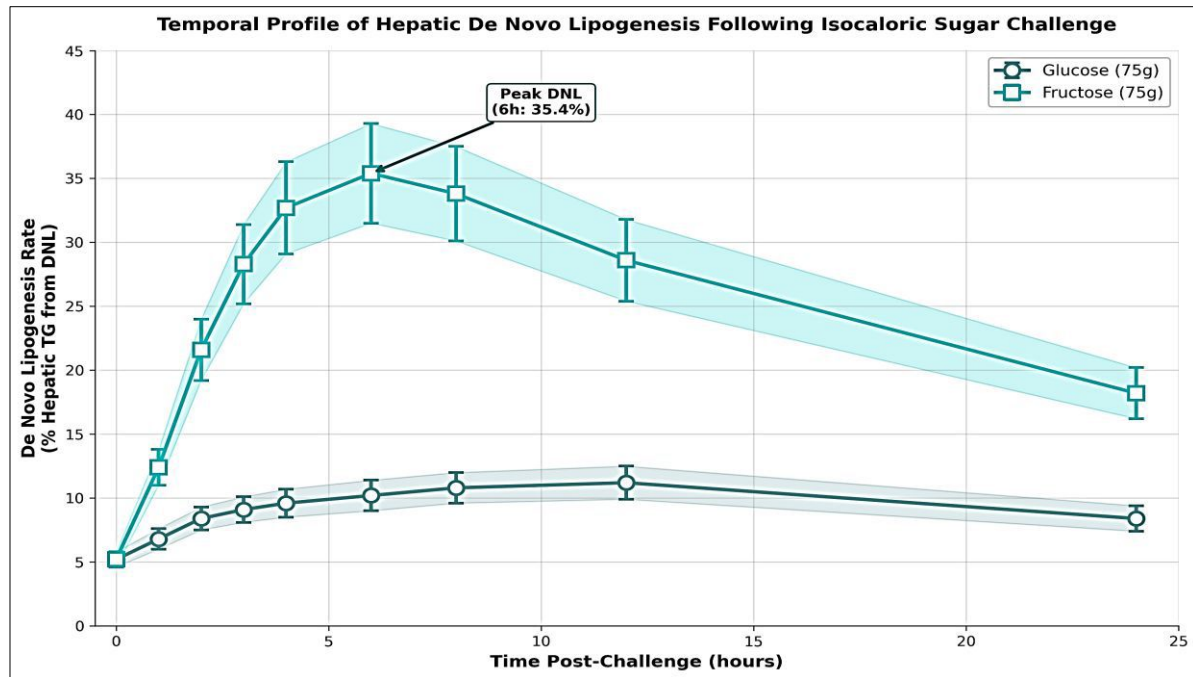


Fig 3: Temporal profile of de novo lipogenesis following isocaloric sugar challenge. Fructose produced substantially greater DNL stimulation than glucose, peaking at 6 hours post-consumption

Clinical Implications

These findings support dietary fructose restriction as a therapeutic approach for NAFLD management. The observation that de novo lipogenesis contributes one-third of hepatic triglycerides in affected individuals suggests that limiting substrate availability may meaningfully reduce steatosis burden [11]. Sugar-sweetened beverage elimination represents an accessible intervention capable of reducing fructose intake by 30-50 grams daily in typical consumers. From a pharmaceutical perspective, ketohexokinase inhibition has emerged as an attractive therapeutic target. Small molecule KHK inhibitors currently in clinical development aim to reduce hepatic fructose metabolism and downstream lipogenic consequences [12]. Our observation of elevated KHK expression in NAFLD liver specimens supports this pathway as mechanistically relevant to human disease.

Discussion

This research demonstrates that de novo lipogenesis is markedly elevated in Japanese adults with NAFLD, with fructose intake serving as a significant dietary determinant. The 2.7-fold higher DNL contribution in NAFLD compared to controls substantially exceeds differences attributable to caloric intake alone, supporting fructose-specific metabolic pathways in hepatic lipid accumulation [13]. These findings align with mechanistic predictions based on fructose metabolism biochemistry.

The differential temporal response to fructose versus glucose challenge provides additional evidence for fructose-specific effects. While both sugars are isocaloric, fructose produced peak lipogenesis rates threefold higher than glucose, consistent with the hepatocentric nature of fructose metabolism and the bypass of glycolytic regulation [14]. This metabolic distinction supports targeting fructose specifically rather than total sugar consumption.

Elevated expression of ketohexokinase and fatty acid synthase in NAFLD liver specimens confirms that transcriptional upregulation accompanies increased pathway

flux. SREBP-1c activation appears central to this response, coordinating lipogenic gene expression in response to fructose-derived metabolic signals [15]. Whether enzyme induction represents cause or consequence of steatosis requires longitudinal investigation.

Limitations

Several limitations warrant consideration. First, the cross-sectional design precludes determination of temporal relationships between fructose exposure and steatosis development. Prospective dietary intervention trials would strengthen causal inference. Second, dietary assessment relies on self-report with inherent recall and reporting biases. Biomarkers of fructose intake would provide more objective exposure assessment but remain incompletely validated. Third, the single-center Japanese cohort may limit generalizability to populations with different genetic backgrounds or baseline dietary patterns. Fourth, liver biopsy for enzyme expression analysis was available only in a subset of participants, potentially introducing selection bias. Finally, the stable isotope methodology measures short-term lipogenic responses that may not fully capture chronic metabolic adaptations.

Conclusion

This research establishes that de novo lipogenesis is substantially elevated in Japanese adults with NAFLD, with dietary fructose intake serving as a significant determinant. The fructose-specific metabolic pathway involving ketohexokinase and subsequent lipogenic enzyme activation provides mechanistic explanation for observed associations between sugar-sweetened beverage consumption and hepatic steatosis. Hepatic enzyme expression analysis confirms transcriptional upregulation accompanying increased lipogenic flux.

Dietary fructose restriction and pharmacological ketohexokinase inhibition represent promising therapeutic strategies for NAFLD management. Future prospective research should establish whether fructose reduction

produces clinically meaningful hepatic fat reduction and histological improvement ^[16]. The temporal dynamics distinguishing fructose from glucose metabolism warrant consideration in dietary guidance development.

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