## ORIGINAL RESEARCH

# Hepatic Steatosis in Patients With Single Ventricle and a Fontan Circulation

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**BACKGROUND:** Hepatic steatosis, caused by nonalcoholic fatty liver disease, is a leading cause of chronic liver disease. The interplay between hepatic steatosis and the development of liver disease following the Fontan procedure is not well understood. This study examined the prevalence and associations of hepatic steatosis in patients with a Fontan circulation.

**METHODS AND RESULTS:** This was a single-center retrospective study of 95 patients with a Fontan circulation with liver magnetic resonance imaging performed between 2012 and 2019. The average age at magnetic resonance imaging was 21.5±8.5 years. The percent liver fat signal was determined using magnetic resonance chemical shift-encoded proton density fat fraction imaging. Hepatic steatosis was defined as liver fat ≥5% and was present in 10.5% of the cohort. The presence of hepatic steatosis was associated with higher body mass index (29±4 versus 24±6 kg/m$^2$, $P$=0.006), a higher frequency of obesity (50% versus 12%, $P$=0.015), lower high-density lipoprotein cholesterol (35±9 versus 43±14 mg/dL, $P$=0.050), and greater subcutaneous fat thickness (2.6±0.7 versus 1.8±1.0 cm, $P$=0.043). There was no association between hepatic steatosis and cardiovascular imaging or hemodynamic variables from cardiac catheterization.

**CONCLUSIONS:** Risk factors for hepatic steatosis in patients with Fontan circulation include obesity and dyslipidemia, similar to what is seen in the general population. Fontan hemodynamics were not associated with hepatic steatosis.

**Key Words:** abdominal fat ■ adult congenital heart disease ■ Fontan associated liver disease ■ Fontan operation ■ hepatic steatosis ■ nonalcoholic fatty liver disease ■ obesity

The Fontan procedure is the final stage of palliation for patients with single ventricle congenital heart disease. Although the Fontan procedure has enabled survival into adulthood, persistently elevated central venous pressure and lymphatic obstruction can lead to long-term sequelae involving multiple organ systems.[1] The liver develops Fontan-associated liver disease (FALD), which can lead to fibrosis, and progress to cirrhosis in some patients. The Fontan circulation is also associated with ectopic fat deposition, but its association with fatty liver disease is unknown.[2] Fatty infiltration of the liver has the potential to be a "second hit" to a liver that is already at risk, given the unique hemodynamics of the Fontan circulation. In the general population, hepatic steatosis is most commonly attributed to nonalcoholic fatty liver disease (NAFLD), which is the most prevalent chronic liver disease in the United States.[3–6] Significant risk factors for NAFLD include dyslipidemia, insulin resistance, and increased adiposity, all of which are common in the aging patient with a Fontan circulation.[7–9]

Liver magnetic resonance imaging (MRI) has become an important tool in the diagnosis of hepatic steatosis and NAFLD, and it is also used in patients with a Fontan circulation to screen for parenchymal liver lesions as the Fontan circulation increases the risk

for hepatocellular carcinoma.[10] NAFLD is diagnosed on the basis of hepatic steatosis without alternative known causes. The objectives of this study were to (1) assess the prevalence of hepatic steatosis in a relatively large cohort of patients with Fontan circulation who had abdominal MRI as part of routine screening and (2) identify risk factors associated with increased liver fat in these patients.

## METHODS

The data for this study are available from the first author upon request. This was a single-center retrospective study of 95 patients with a Fontan circulation who had liver MRI examinations performed for routine surveillance between 2012 and 2019. The study was approved by the Cincinnati Children's Hospital Medical Center Institutional Review Board and was conducted in compliance with the Health Insurance Portability and Accountability Act. Informed consent was waived because of the retrospective nature of the study. Medical records (Epic Systems Corporation, Verona, WI) were reviewed to obtain clinical and outcome information for each patient.

Clinical variables collected included age, sex, date of Fontan operation, date of liver MRI examination, body mass index (BMI), type of Fontan pathway, and dominant ventricle. Being overweight was defined as having a BMI $\geq 25$ kg/m$^2$ in adults ($\geq 18$ years) and between the 85th and 94th percentiles in children. Obesity was defined as a BMI $\geq 30$ kg/m$^2$ in adults and $\geq$ the 95th percentile for age and sex in children. Laboratory data collected included serum aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, albumin, gamma-glutamyl transferase, cholesterol levels, and platelets.

Liver MRI examinations had been obtained for clinical purposes and included magnetic resonance elastography and complex chemical shift-encoded MRI for determination of MRI proton density fat fraction. Patients were instructed not to eat or drink for at least 4 hours before all MRI exams. MRI examinations were performed on 1.5-T MRI scanners (Ingenia; Philips Healthcare, Best, the Netherlands; and Signa HDx or Optima MR450w; GE Healthcare, Waukesha, WI). Liver stiffness was measured using the Cincinnati Children's Hospital institutional protocol.[11] Splenomegaly was defined as a spleen length $\geq 13$ cm, and radiologic portal hypertension was defined as the presence of at least 2 of the following 3 findings: (1) ascites, (2) varices, and (3) splenomegaly. Hepatic steatosis was defined as percentage of liver fat $\geq 5\%$.[12]

Subcutaneous and visceral fat thicknesses were measured at the L2 vertebral level via liver MRI as previously described.[13] The subcutaneous fat thickness was measured between the skin and linea alba, and the linear thickness of the visceral fat was measured between the linea alba and the anterior surface of the L2 vertebral body (Figure). Measurements were made on the fat images from the chemical shift-encoded MRI sequence.

Cardiac assessments included echocardiogram (presence of moderate or worse systolic dysfunction, presence of moderate or worse atrioventricular valve regurgitation), and cardiac catheterization (Fontan pressure and single ventricle end-diastolic pressure). When more than one test was performed, the test closest to the abdominal MRI was used.

### Statistical Analysis

The characteristics of patients with hepatic steatosis and without hepatic steatosis were compared using either the Student $t$ test or Wilcoxon rank-sum test for normally or nonnormally distributed continuous variables, respectively. Fisher's exact test was used to
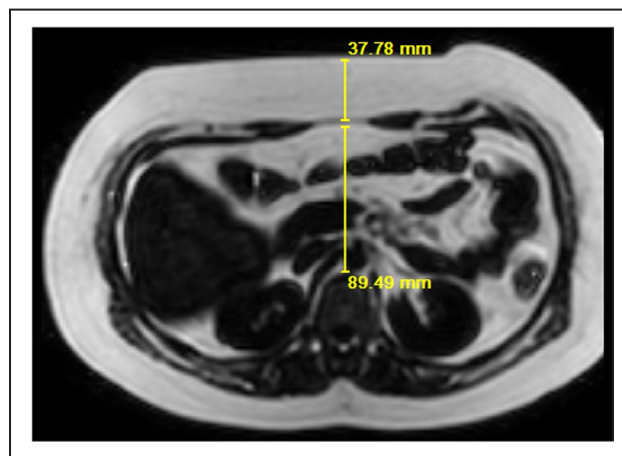


**Figure.** An example of adipose tissue measurements at the L2 vertebral level on magnetic resonance imaging.

compare categorical variables between the groups. A 2-tailed *P* value of ≤0.05 was considered statistically significant. Statistical analyses were performed using JMP (version 12, SAS Institute Inc., Cary, NC).

Chart review was used to assess the outcomes of death, transplant, and escalation of diuretics on follow-up visits after patients had their liver imaging. The average follow-up time of 2.6±2.0 years following liver MRI was based on their most recent office visit notes in our electronic medical record. This was not enough time for evaluation as too few patients had outcomes to provide any appropriate analysis.

# RESULTS

## Demographics and Hepatic Steatosis

The mean age at the time of MRI was 21.5±8.5 years (range of 8.0 to 53.0 years); 35 patients (37%) were younger than 18 years of age. Women comprised 42% (40/95) of the study sample. The mean time since Fontan surgery was 17.0±7.5 years. The most common Fontan type was extracardiac conduit (45%), and 54% of the population had a systemic left ventricle.

Hepatic steatosis, defined as percentage of liver fat ≥5%, was present in 10 of 95 patients (10.5%) by liver MRI. Mean liver fat fraction in the patients with hepatic steatosis was 7.7±4.2%. There were no significant differences between the patients with and without hepatic steatosis in terms of age, sex, time since Fontan surgery, morphology of dominant ventricle, or type of Fontan (Table 1). Of the 10 patients with hepatic steatosis, 9 were 18 years and older, and only 1 patient was below the age of 18 years. Thus, the prevalence of liver steatosis was 1/35 (3%) in children and 9/60 (15%) in adults (*P*=0.086, comparing children with adults).

## Clinical Characteristics and Hepatic Steatosis

Patients with hepatic steatosis had a significantly higher BMI (28.9±4.4 versus 23.9±6.2 kg/m$^2$, *P*=0.006) and were more frequently obese (50% versus 14%, *P*=0.015; Table 2). Although patients with hepatic steatosis were more frequently overweight (80% versus 42%, *P*=0.041; Table 2), this association was lost when just analyzing the adults (18 years and older) as a subgroup. Patients with hepatic steatosis had a significantly greater subcutaneous fat thickness than those without hepatic steatosis (2.6±0.7 versus 1.8±1.0 cm, *P*=0.043; Table 2), though there was no difference in visceral fat thickness (9.4±1.5 versus 8.4±2.2 cm, *P*=0.161). When analyzing the adults as a subgroup, there was no association between hepatic steatosis and subcutaneous fat thickness. On multivariable analysis, none reached statistical significance likely because of the small number of patients with hepatic steatosis. Variables in the multivariable analysis included: BMI, visceral fat thickness, and subcutaneous fat thickness.

## Laboratory Testing and Hepatic Steatosis

Laboratory data were available for 91 of the 95 patients. On average, laboratory testing was performed 0.4±0.8 years from the liver MRI. High-density lipoprotein cholesterol was lower in patients with hepatic steatosis (35±9 versus 43±14 mg/dL, *P*=0.050). There was no difference in aspartate aminotransferase, alanine aminotransferase, triglycerides, albumin, total bilirubin, gamma-glutamyl transferase, platelets, splenomegaly, radiologic portal hypertension, or magnetic resonance elastography assessment of liver stiffness between patients with and without steatosis (Table 3).

**Table 1.  Demographics of Patients With and Without Hepatic Steatosis**

| | All Patients (n=95) | Hepatic Steatosis | | P Value |
| --- | --- | --- | --- | --- |
| | | Yes (n=10) | No (n=85) | |
| Age at time of liver magnetic resonance imaging, y | 21.5±8.5 | 24.0±6.9 | 21.3±8.7 | 0.267 |
| Time since Fontan, y | 17.1±7.5 (n=94) | 19.9±6.6 (n=9) | 16.8±7.6 | 0.213 |
| Sex (female) | 40 (42%) | 5 (50%) | 35 (41%) | 0.738 |
| Type of Fontan | AP=14 (15%) | AP=2 (20%) | AP=12 (14%) | 1.000* |
| | LT=37 (39%) | LT=5 (50%) | LT=32 (38%) | 0.489† |
| | ECC=44 (46%) | ECC=3 (30%) | ECC=41 (48%) | 0.585‡ |
| Dominant ventricle (LV) | 51 (54%) | 6 (60%) | 45 (53%) | 0.501 |

*P* values reflect comparisons between groups with and without hepatic steatosis. Statistical analyses include Student *t* test and Fisher's exact test. AP indicates atriopulmonary; ECC, extracardiac conduit; LT, lateral tunnel; and LV, left ventricle.

*Comparison between AP and LT.

†Comparison between LT and ECC.

‡Comparison between AP and ECC.

**Table 2.  Clinical Characteristics of Patients With and Without Hepatic Steatosis**

| | | Hepatic Steatosis | | |
|---|---|---|---|---|
| | All Patients (n=95) | Yes (n=10) | No (n=85) | P Value |
| BMI, kg/m$^2$ | 24.4±6.2 | 28.9±4.4 | 23.9±6.2 | 0.006* |
| Overweight | 44 (46%) | 8 (80%) | 36 (42%) | 0.041* |
| Obese | 17 (18%) | 5 (50%) | 12 (14%) | 0.015* |
| Subcutaneous fat, cm | 1.9±1.0 (n=55) | 2.6±0.7 (n=7) | 1.8±1.0 (n=48) | 0.043* |
| Visceral fat, cm | 8.5±2.2 (n=55) | 9.4±1.5 (n=7) | 8.4±2.2 (n=48) | 0.161 |

Overweight=adults with BMI ≥25 kg/m$^2$ or children with BMI ≥85th percentile; obese=adults with BMI ≥30 kg/m$^2$ or children with BMI ≥95th percentile. P values reflect comparisons between groups with and without hepatic steatosis. There were 55 patients with imaging adequate to measure subcutaneous and visceral fat. Statistical analyses include Student t test and Fisher's exact test. BMI indicates body mass index.

*Significant associations.

## Cardiovascular Status and Hepatic Steatosis

Post-Fontan surgery catheterization data were available for 67 patients. The average time between catheterization and liver MRI was 1.6±1.9 years. There was no significant association between the presence of hepatic steatosis and Fontan pressure, nor single ventricle end-diastolic pressure. Ninety-three patients had echocardiographic data available. The mean time interval between echocardiogram and liver MRI was 1.0±1.9 years. There was no significant association between the presence of hepatic steatosis and the degree of either systolic ventricular dysfunction or atrioventricular valve regurgitation (Table 4).

## DISCUSSION

This study examined the prevalence of hepatic steatosis in patients with a Fontan circulation seen at a single center and the factors associated with hepatic steatosis. The prevalence of hepatic steatosis in this cohort of young adults was 10.5% (3% in those younger than 18 years old and 15% in those 18 years and older). Hepatic steatosis was associated with being overweight or obese, dyslipidemia (low high-density lipoprotein cholesterol level), and subcutaneous fat thickness. There was no association between hepatic steatosis and any metric of hemodynamics or cardiac function. There was also no association between hepatic steatosis and either liver transaminases or radiologic portal hypertension.

The prevalence of NAFLD in patients without Fontan palliation in the United States is 33% to 46% in adults and 8% to 10% in children.[3–6] The prevalence of hepatic steatosis in our cohort of patients with a Fontan circulation was 10.5%. All of the patients with a Fontan circulation at our institution are screened with a liver MRI, so there is little selection bias, and our prevalence can be considered representative of a larger population. When separating our cohort into pediatric (younger than 18 years of age=3% prevalence) and adult (18 years and older=15% prevalence) populations, both groups had less prevalence

**Table 3.  Liver Laboratory and Imaging Results of Patients With and Without Hepatic Steatosis**

| | All Patients (n=95) | Hepatic Steatosis | | |
|---|---|---|---|---|
| | | Yes (n=10) | No (n=85) | P Value |
| Liver stiffness by magnetic resonance elastography, kPa | 4.5±1.0 | 4.3±1.2 | 4.5±1.0 | 0.766 |
| Splenomegaly | 29 (32%) | 4 (40%) | 25 (31%) | 0.720 |
| Portal hypertension (radiologic) | 32 (34%) | 4 (40%) | 28 (33%) | 0.728 |
| Alanine aminotransferase, U/L | 40±26 (n=91) | 64±62 (n=9) | 37±17 (n=82) | 0.239 |
| Aspartate aminotransferase, U/L | 27±11 (n=91) | 36±25 (n=9) | 26±9 (n=82) | 0.281 |
| Alkaline phosphatase, U/L | 135±76 (n=85) | 131±111 (n=9) | 136±72 (n=81) | 0.895 |
| Total bilirubin, mg/dL | 1.0±0.7 (n=90) | 0.8±0.3 (n=9) | 1.0±0.7 (n=81) | 0.144 |
| Gamma-glutamyl transferase, U/L | 88±75 (n=85) | 101±76 (n=9) | 87±75 (n=76) | 0.609 |
| Albumin, g/dL | 4.2±0.5 (n=92) | 4.2±0.3 (n=9) | 4.2±0.6 (n=83) | 0.819 |
| Triglycerides, mg/dL | 103±65 (n=55) | 181±136 (n=7) | 91±33 (n=48) | 0.130 |
| High-density lipoprotein cholesterol, mg/dL | 42±14 (n=54) | 35±9 (n=7) | 43±14 (n=47) | 0.050* |

P values reflect comparisons between groups with and without hepatic steatosis. Portal hypertension is defined as the presence of at least 2 of the following: splenomegaly, ascites, or varices. Statistical analyses include Student t test and Fisher's exact test.

*Significant associations.

**Table 4.    Key Cardiovascular Testing Variables of Patients With and Without Hepatic Steatosis**

|  | All Patients (n=95) | Hepatic Steatosis | | P Value |
|---|---|---|---|---|
|  |  | Yes (n=10) | No (n=85) |  |
| At least moderate ventricular dysfunction | 9 (1%) (n=92) | 0 (n=9) | 9 (11%) (n=83) | 0.591 |
| At least moderate atrioventricular valve regurgitation | 14 (15%) (n=91) | 2 (14%) (n=9) | 12 (15%) (n=82) | 0.624 |
| Fontan pressure, mm Hg | 13±4 (n=66) | 14±5 (n=4) | 13±4 (n=62) | 0.861 |
| Ventricular end-diastolic pressure, mm Hg | 10±4 (n=67) | 13±7 (n=5) | 10±3 (n=62) | 0.441 |

*P* values reflect comparisons between groups with and without hepatic steatosis. Statistical analyses include Student *t* test and Fisher's exact test.

compared with their respective general US populations. The average age of our pediatric group was 14 years, whereas the average age of our adult group was 26 years. NAFLD is most commonly diagnosed in the fifth and sixth decades of life, and with the average age of our entire study cohort being 22 years, it is not surprising that the prevalence of hepatic steatosis in our patients was closer to what is seen in the general US pediatric population.[14]

Those with hepatic steatosis are known to have 1 or more components of metabolic syndrome, which includes obesity and dyslipidemia.[15] The only significant associations with hepatic steatosis in our cohort of patients with a Fontan circulation were obesity (higher BMI, being overweight, being obese) and dyslipidemia (low high-density lipoprotein). This correlates with the fact that people with a Fontan circulation have a similar prevalence of being overweight and obese compared with adults without congenital heart disease.[8,16–18] Having a Fontan circulation may not put patients at increased risk of hepatic steatosis, but it does put patients at risk of FALD. To avoid a possible second insult to their livers, patients with a Fontan circulation should avoid developing hepatic steatosis by avoiding their main risk factors: obesity and metabolic syndrome. Adults with a Fontan circulation are 3 times more likely to be overweight/obese if their BMI was ≥85th percentile in childhood.[19] Thus, preventing obesity with diet and exercise should be started during childhood years, as it would be best to avoid developing hepatic steatosis when older and vulnerable to FALD. There is currently no consensus on which patients with FALD may require a combined heart-liver transplantation versus isolated heart transplantation, but hepatic steatosis may represent another factor to take into consideration while making this complex decision.

Subcutaneous fat thickness was associated with hepatic steatosis in our study, but in the general population, both subcutaneous fat thickness and intra-abdominal visceral fat thickness have been associated with an increased risk of hepatic steatosis.[20–23] Visceral fat thickness has been shown to increase with worse hemodynamics in patients with a Fontan circulation.[24] In our cohort, hepatic steatosis was not associated with worse hemodynamics, which may explain why hepatic steatosis was also not associated with visceral fat thickness.

In the general population, increased visceral adipose tissue is associated with increased cardiovascular risk, metabolic syndrome, and NAFLD.[22,24] One potential explanation for the lack of association with visceral adipose tissue in our study is that patients with a Fontan circulation have baseline elevated visceral adipose tissue. In a previous study, obese adolescents (average age of 16.7 years) without a Fontan circulation had an average visceral fat thickness of 5.2 cm measured by ultrasound.[25] Although this is a slightly younger cohort than ours (average age 21.5±8.5), the visceral fat thickness in these obese adolescents (5.2 cm) is markedly less than in our Fontan circulation patients without hepatic steatosis (8.4±2.2 cm). We speculate that unlike in the general population, subcutaneous adipose tissue poses a greater risk than visceral adipose tissue to developing hepatic steatosis in patients with a Fontan circulation, as their visceral adipose tissue is already elevated above baseline.

Patients with Fontan and hepatic steatosis had minimal and not statistically significant increases in liver function tests compared to those without hepatic steatosis in our cohort. Liver enzymes are commonly within 2 to 5 times the upper limit of normal in patients with NAFLD; however, the degree of transaminitis is not predictive of liver disease severity, and normal levels are not exclusionary for NAFLD.[26,27] Hepatic steatosis was not associated with increased magnetic resonance elastography derived liver stiffness, a known marker of failing Fontan physiology in relation to liver disease.[11] This may suggest that steatosis in this young population may not increase the severity of FALD at a young age, although the risk may increase as this population becomes older; this was not investigated in this study.

## Limitations

Appropriate interpretation of these results should take into account the retrospective single-center study design, which may introduce selection and information biases and may limit external validity. The small overall sample size and the low number of patients with liver steatosis limits the statistical power to identify associations

with other uncommon clinical diagnoses and outcomes. Null results may reflect the true lack of an association or inadequate statistical power. The relatively young age of our cohort and mean follow-up time (<3 years) are also limiting factors, as the prevalence of NAFLD increases with age, including higher rates of more advanced fibrosis in adults in their 40s to 50s compared with children and young adults. NAFLD is a diagnosis of exclusion, and although our patients had radiographic evidence of hepatic steatosis, there were no liver biopsy data to rule in or rule out other causes. Time-to-event analysis was not performed as many patients had an escalation of diuretics before or at the time of the liver magnetic resonance elastography and only 1 patient with hepatic steatosis had an outcome of death, transplant, or escalation of diuretics. Lastly, missing data affected some analyses because testing was performed for clinical indication.

## CONCLUSIONS

The population of patients with a Fontan circulation is aging, and the presence of FALD is increasing. There does not appear to be an increase in the prevalence of hepatic steatosis compared with historical population-based cohorts of children and adults. Patients with a Fontan circulation appear to share the same risk factors for hepatic steatosis (obesity, elevated BMI, and dyslipidemia) as the general population. There was no association of Fontan pressure or ventricular dysfunction with hepatic steatosis. This suggests that hepatic steatosis is not related to failing Fontan hemodynamics and is more related to the traditional risk factors, including obesity and dyslipidemia.

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