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Prevalence of Prediabetes and Type 2 Diabetes in Children With Nonalcoholic Fatty Liver Disease

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IMPORTANCE Nonalcoholic fatty liver disease (NAFLD) is a major chronic liver disease in children in the United States and is associated with insulin resistance. In adults, NAFLD is also associated with type 2 diabetes. To our knowledge, the prevalence of type 2 diabetes in children with NAFLD is unknown.

OBJECTIVE To determine the prevalence of type 2 diabetes and prediabetes in children with NAFLD and assess type 2 diabetes and prediabetes as risk factors for nonalcoholic steatohepatitis (NASH).

DESIGN, SETTING, AND PARTICIPANTS This was a multicenter, cross-sectional study at 12 pediatric clinical centers across the United States participating in the National Institute of Diabetes and Digestive and Kidney Diseases NASH Clinical Research Network. Children younger than 18 years with biopsy-confirmed NAFLD enrolled in the NASH Clinical Research Network.

MAIN OUTCOMES AND MEASURES The presence of type 2 diabetes and prediabetes as determined by American Diabetes Association screening criteria using clinical history and fasting laboratory values.

RESULTS There were 675 children with NAFLD included in the study with a mean age of 12.6 years and mean body mass index (calculated as weight in kilograms divided by height in meters squared) of 32.5. Most of the children were boys (480 of 675) and Hispanic (445 of 675).The estimated prevalence of prediabetes was 23.4% (95% CI, 20.2%-26.6%), and the estimated prevalence of type 2 diabetes was 6.5% (95% CI, 4.6%-8.4%). Girls with NAFLD had 1.6 (95% CI, 1.04-2.40) times greater odds of having prediabetes and 5.0 (95% CI, 2.49-9.98) times greater odds of having type 2 diabetes than boys with NAFLD. The prevalence of NASH was higher in those with type 2 diabetes (43.2%) compared with prediabetes (34.2%) or normal glucose (22%) ($P < .001$). The odds of having NASH were significantly higher in those with prediabetes (OR, 1.9; 95% CI, 1.21-2.9) or type 2 diabetes (OR, 3.1; 95% CI, 1.5-6.2) compared with those with normal glucose.

CONCLUSIONS AND RELEVANCE In this study, nearly 30% of children with NAFLD also had type 2 diabetes or prediabetes. These children had greater odds of having NASH and thus were at greater long-term risk for adverse hepatic outcomes.

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There are an estimated 7 million children in the United States with nonalcoholic fatty liver disease (NAFLD), and it is now the most common cause of chronic liver disease in the pediatric population.[1] Nonalcoholic fatty liver disease encompasses a broad spectrum of disease severity ranging from isolated steatosis in its mildest form to steatohepatitis with advanced fibrosis and cirrhosis.[2,3] Moreover, NAFLD can lead to liver failure, requiring liver transplantation and hepatocellular carcinoma even in children,[4,5] and has now become the second leading cause of liver transplants in the United States in adults.[6,7] Nonalcoholic fatty liver disease also has serious health consequences outside of the liver and is associated with metabolic impairment and increasing risk for cardiovascular disease, insulin resistance, and subsequent type 2 diabetes.[8,9]

In adults with NAFLD, abnormal glucose metabolism is common. Furthermore, the presence of type 2 diabetes in adults with NAFLD is a clinically relevant risk factor for the more progressive form of NAFLD, nonalcoholic steatohepatitis (NASH), and is a predictor of liver-related mortality.[10,11] The effect of type 2 diabetes in children with NAFLD has been less well defined. Although insulin resistance occurs in most children with biopsy-proven NAFLD, the prevalence of type 2 diabetes and prediabetes is an unaddressed gap in knowledge. To date, sample sizes have been too small to support a stable estimate of the prevalence of type 2 diabetes or prediabetes in the pediatric NAFLD population, and, to our knowledge, targeted analysis of meaningful clinical-histopathologic correlates with type 2 diabetes has not been reported.[12-17]

To further understand the relationship between NAFLD and type 2 diabetes in the pediatric population, we performed a multicenter cohort study with the following study aims: (1) to determine the prevalence of type 2 diabetes and prediabetes in children with well-characterized NAFLD; (2) to determine differences in demographic and key clinical parameters between children with NAFLD who have type 2 diabetes, prediabetes, or normal glucose metabolism; and (3) to assess the relationship between histologic features and severity of NAFLD and the presence of type 2 diabetes and prediabetes in children with NAFLD.

Key Points

Question What is the prevalence of type 2 diabetes and prediabetes in children with nonalcoholic fatty liver disease?

Findings In this multicenter study that included 675 children with biopsy-confirmed nonalcoholic fatty liver disease enrolled in the Nonalcoholic Steatohepatitis Clinical Research Network, nearly 30% of children had type 2 diabetes or prediabetes. Among those children with nonalcoholic fatty liver disease, having type 2 diabetes or prediabetes was associated with much greater odds of having nonalcoholic steatohepatitis.

Meaning Children with nonalcoholic fatty liver disease merit evaluation of glucose metabolism and monitoring for progression of liver disease, diabetes, and the consequences of both.

Methods

Study Population

The National Institute of Diabetes and Digestive and Kidney Diseases NASH Clinical Research Network (NASH CRN) includes 12 participating pediatric clinical centers across the United States (see Article Information). Participants in this study were selected from children enrolled in the following NASH CRN studies: longitudinal cohort studies of Database and Database 2 (NCT01061684) and randomized clinical trials of Treatment of Nonalcoholic Fatty Liver Disease in Children (TONIC, NCT00063635) and Cysteamine Bitartrate Delayed-Release for the Treatment of NAFLD in Children (CyNCh, NCT01529268). Nonalcoholic fatty liver disease Database began enrollment in September 2004, TONIC in August 2005, Database 2 in October 2009, and CyNCH in June 2012. These studies were approved by the institutional review boards at University of California San Diego, Texas Children's Hospital, Cincinnati Children's Hospital, Columbia University, Johns Hopkins University, Northwestern University, Indiana University, Emory University, University of California San Francisco, Saint Louis University, University of Buffalo, and Seattle Children's Hospital. Written consent for all participants was obtained from a parent or guardian, and written assent was obtained from all children 8 years or older prior to participation. For this analysis, we included children who were younger than 18 years with biopsy-confirmed NAFLD.

NAFLD Diagnosis

A diagnosis of NAFLD was based on liver histology with at least 5% of hepatocytes containing macrovesicular fat, exclusion of other causes of chronic liver disease by clinical history, exclusion of potentially hepatotoxic medications (eg, long-term corticosteroids, valproic acid, and methotrexate), laboratory studies, and histology.[2] Liver biopsy specimens were stained with hematoxylin-eosin and Masson trichrome stain and centrally reviewed by the pathology committee of the NASH CRN according to the NASH CRN scoring system, which has been validated in the pediatric population.[18] The pathology committee was blinded to all demographic and clinical data. Biopsies were scored for the degree of steatosis present in hepatocytes as follows: grade 0, less than 5% steatosis; grade 1, 5% to 33%; grade 2, 34% to 66%; and grade 3, greater than 66%. Liver biopsies were diagnosed as NASH, borderline NASH, or NAFLD without NASH based on the aggregate presence and degree of the individual features of NAFLD. A typical set of minimum criteria to diagnose NASH would include at least 5% macrovesicular steatosis, lobular inflammation, and hepatocyte injury as manifested by ballooning degeneration. Cases determined to be NAFLD without NASH showed at least 5% steatosis with no or minimal inflammation. This assignment of NASH, borderline NASH, or NAFLD was made as a consensus agreement of the NASH CRN pathology group at the time of central review of cases as per protocol.

Outcomes

Children with an existing clinical diagnosis of type 1 diabetes were excluded from the study. As has been done in other large

epidemiologic studies,[19] we assigned our case definitions for prediabetes and type 2 diabetes on a 1-time laboratory measurement based on parameters defined by the American Diabetes Association. Children were considered to have prediabetes if they met at least 1 of the 2 criteria: fasting serum glucose level between 100 mg/dL and 125 mg/dL (to convert to micromoles per liter, multiply by 0.0555) or hemoglobin A_{1c} level between 5.7% and 6.5% (to convert to proportion of total hemoglobin, multiply by 0.01). Children were considered to have type 2 diabetes if they met at least 1 of the 3 criteria: fasting serum glucose level of at least 126 mg/dL; hemoglobin A_{1c} level of 6.5% or greater; or existing clinical diagnosis of type 2 diabetes.[20] Children were considered to have normal glucose metabolism if neither the criteria for prediabetes nor type 2 diabetes were met.

Covariates

A structured interview was used to obtain demographic data on study participants. Weight and height were measured to the nearest 0.1 kg and 0.1 cm respectively. Weight, height, and waist measurements were performed in duplicate while wearing light clothing without shoes. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Body mass index percentile was determined according to age and sex based on data from the Centers for Disease Control and Prevention. To compare BMI among different ages and in both boys and girls, the BMI *z* score was calculated.

Participants fasted overnight for 12 hours before phlebotomy via venipuncture. Each clinical center performed reported laboratory assays on site to include the following tests: glucose, insulin, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, alanine aminotransferase , aspartate aminotransferase, and γ-glutamyltransferase.

Statistical Analysis

Standard descriptive statistics were used to compare children with NAFLD across 3 subgroups based on glucose status (normal glucose metabolism, prediabetes, and type 2 diabetes). The proportion of prediabetes and type 2 diabetes along with its 95% CI were reported. Risk factors for having prediabetes and type 2 diabetes in children with NAFLD were identified using a multinomial logistic regression model with the odds of prediabetes and the odds of type 2 diabetes as the outcomes and the following candidate set of risk factors: age, sex, race/ethnicity, BMI, waist circumference, study, and clinical center. Parallel analyses were done separating children with NAFLD into those with and without NASH. Using glucose status (normal glucose, prediabetes, and type 2 diabetes) as the exposure variable, the odds of having NASH among children with NAFLD were determined using multiple logistic regression with the presence of NASH as the binary outcome and inclusion of the following covariates: age, sex, race/ethnicity, BMI, waist circumference, study, and clinical center. All analyses were 2-sided with a *P* value less than .05 considered to be statistically significant. Analyses were performed using R, version 3.2.2 (R Programming).

Results

Study Population

We included 675 children enrolled in the NASH CRN. There were 2 children with a prior diagnosis of type 1 diabetes who were excluded from the analysis. The demographic and clinical parameters are shown in **Table 1**. The mean (SD) age of the participants was 12.6 (2.7) years. The mean (SD) BMI of participants was 32.5 (6.3) and the mean (SD) BMI *z* score was 2.3 (0.4). The distribution of disease severity was as follows: NAFLD without NASH in 26.7% (180 of 675), borderline NASH in 47.1% (318 of 675), and definite NASH in 26.2% (177 of 675). Most participants were boys (71.1% [480 of 675]). There was no significant difference between boys and girls with respect to age (12.6 years vs 12.5 years, $P = .67$) or race/ethnicity (65.8% Hispanic vs 66.2% Hispanic, $P > .99$). Boys had a significantly higher mean (SD) BMI *z* score than girls (2.3 [0.4] vs 2.2 [0.4]; $P < .001$).

Type 2 Diabetes and Prediabetes in Children With NAFLD

For children with NAFLD, the estimated prevalence of prediabetes was 23.4% (95% CI, 20.3-26.7). The estimated prevalence of type 2 diabetes was 6.5% (95% CI, 4.7%-8.4%). A clinical diagnosis of type 2 diabetes had been established prior to enrollment in the NASH CRN in 33 of the 44 children (75%). As shown in Table 1, the mean age for children with prediabetes and type 2 diabetes was slightly but significantly higher than children with normal glucose metabolism. Girls with NAFLD were significantly more likely to have type 2 diabetes than boys with NAFLD (13.7% vs 3.5%, $P < .001$). Body mass index varied significantly in children with NAFLD by glucose status (normal glucose, 32.0; prediabetes, 33.3; type 2 diabetes, 35.5; $P < .001$); however, the BMI *z* score was not significantly different between groups. Waist circumference also varied significantly across groups (normal glucose, 103 cm; prediabetes, 107 cm; type 2 diabetes, 113 cm; $P < .001$). After controlling for these covariates, girls with NAFLD had 1.6 (95% CI, 1.0-2.4) times greater odds of having prediabetes, and 5.0 (95% CI, 2.5-10.0) times greater odds of having type 2 diabetes than boys with NAFLD (eTable in the Supplement). Mean (SD) serum γ-glutamyltransferase activity was significantly higher across groups by glucose status (normal glucose, 45 [32] U/L [to convert to microkatals per liter, multiply by 0.0167]; prediabetes, 47 [37] U/L; type 2 diabetes, 61 [44] U/L; $P = .02$). There was also a significant difference in mean (SD) serum triglyceride concentration by glucose status (normal glucose, 145 [83] mg/dL; prediabetes, 150 [82] mg/dL; type 2 diabetes, 196 [132] mg/dL; $P = .002$). There was no significant difference in alanine aminotransferase, aspartate aminotransferase, total cholesterol, high-density lipoprotein cholesterol, or low-density lipoprotein cholesterol by glucose status.

NAFLD Histologic Features and Severity

Among children with NAFLD, NASH was present in 21.9% of those with normal glucose metabolism (104 of 473), 34.2% of those with prediabetes (54 of 158), and 43.2% of those with type

Table 1. Demographic and Clinical Variables by Glucose Status

Characteristic	Normal Glucose (n = 473)	Prediabetes (n = 158)[a]	Type 2 Diabetes (n = 44)[b]	Total (n = 675)	*P* Value[c]
Demographics					
Age, mean (SD), y	12.4 (2.7)	13.0 (2.5)	13.8 (2.5)	12.6 (2.7)	<.001
Sex, No. (%)					
Female	116 (24.5)	52 (32.9)	27 (61.4)	195 (28.9)	<.001
Male	357 (75.5)	106 (67.1)	17 (38.6)	480 (71.1)	
Race/ethnicity, No. (%)					
White non-Hispanic	127 (26.8)	47 (29.7)	17 (38.6)	191 (28.3)	.009
Hispanic	327 (69.1)	95 (60.1)	23 (52.3)	445 (65.9)	
Non-Hispanic	19 (4.0)	16 (10.1)	4 (9.1)	39 (5.8)	
Anthropomorphic, mean (SD)					
Height, cm	158.6 (14.1)	161.6 (12.9)	163.2 (11.6)	159.6 (13.7)	.01
Weight, kg	82.3 (25.5)	88.4 (24.7)	96.3 (26.6)	84.6 (25.7)	<.001
BMI	32.0 (6.4)	33.3 (5.9)	35.5 (6.1)	32.5 (6.3)	<.001
BMI *z* score	2.3 (0.4)	2.3 (0.4)	2.4 (0.4)	2.3 (0.4)	.25
Waist circumference, cm, mean (SD)	103.1 (15.5)	106.5 (14.3)	112.9 (16.6)	104.5 (15.5)	<.001
Blood pressure, No. (%)					
Systolic	121 (14)	123 (14)	126 (11)	122 (14)	.03
Diastolic	68 (10)	68 (9)	71 (8)	68 (10)	.11
Liver enzymes, No. (%), U/L					
ALT	106 (84)	114 (91)	114 (136)	108 (90)	.57
AST	63 (48)	68 (54)	72 (65)	65 (51)	.33
GGT	45 (32)	47 (36)	61 (44)	46 (34)	.02
Serum chemistries, No. (%)					
Serum glucose, mg/dL	85 (8)	93 (12)	113 (53)	88 (17)	<.001
HbA_{1C}, mean (SD), %	5.2 (0.3)	5.7 (0.3)	7.8 (3.8)	5.5 (1.2)	<.001
Serum insulin, μIU/mL	32 (42)	40 (47)	43 (41)	35 (44)	.07
Cholesterol, mg/dL					
HDL	39 (9)	39 (9)	38 (11)	39 (9)	.97
LDL	100 (30)	101 (30)	109 (32)	101 (30)	.26
Total	167 (39)	169 (38)	183 (36)	169 (38)	.06
Triglycerides, mg/dL	145 (83)	150 (82)	196 (132)	149 (87)	.002

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); GGT, γ-glutamyltranspeptidase; HbA_{1c}, hemoglobin A_{1C}; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

SI conversion factors: To convert ALT to microkatals per liter, multiply by 0.0167; AST to microkatals per liter, multiply by 0.0167; GGT to microkatals per liter, multiply by 0.0167; hemoglobin A_{1C} to proportion of total hemoglobin, multiply by 0.01; HDL cholesterol to micromoles per liter, multiply by 0.0259; LDL cholesterol to micromoles per liter, multiply by 0.0259; triglycerides to micromoles per liter, multiply by 0.0113.

[a] Prediabetes defined as (1) fasting serum glucose level between 100 mg/dL and 125 mg/dL or (2) hemoglobin A_{1c} level between 5.7% and 6.5%.

[b] Type 2 diabetes defined as (1) fasting serum glucose level at least 126 mg/dL; (2) hemoglobin A_{1C} level at least 6.5%; or (3) existing clinical diagnosis of type 2 diabetes.

[c] *P* values are calculated based on *F* test for continuous variables and a χ^2 test for categorical variables.

2 diabetes (19 of 44) (*P* < .001) (**Table 2**). After controlling for age, sex, race/ethnicity, BMI, and waist circumference among children with NAFLD, the odds of NASH were significantly higher in those with prediabetes (OR, 1.9; 95% CI, 1.21-2.86) or type 2 diabetes (OR, 3.1; 95% CI, 1.51-6.22) compared with those with normal glucose metabolism (**Table 3**). There was no difference in steatosis grade or inflammation among groups; however, the ballooning degeneration was significantly different among children with normal glucose, prediabetes, and type 2 diabetes (Table 2). Children with normal glucose had less ballooning degeneration than those with prediabetes or type 2 diabetes (Table 2). Among children with NAFLD, those with NASH had significantly higher mean (SD) fasting glucose levels (93 [25] mg/dL vs 87 [13] mg/dL; *P* = .001) and insulin concentrations (46 [69] μIU/mL vs 30 [28] μIU/mL [to convert to picomoles per liter, multiply by 6.945]; *P* = .003) than children without NASH.

Discussion

We studied the prevalence of type 2 diabetes and prediabetes in a large, multicenter cohort of children with NAFLD from pediatric centers across the United States. Nearly 30% of children with NAFLD had abnormal glucose metabolism, with 6.5% satisfying our criteria for type 2 diabetes. Notably, independent of age and BMI, girls with NAFLD were more likely to have type 2 diabetes than boys with NAFLD. Finally, among children with NAFLD, children with type 2 diabetes had more than 3 times the odds of having nonalcoholic steatohepatitis (NASH), which is the more progressive form of NAFLD.

Among our cohort, the prevalence of children with type 2 diabetes was much higher than would be expected based on contributions from obesity alone. The best available epidemiologic study of diabetes, the SEARCH study, estimated US

Table 2. Liver Histology Distribution by Glucose Status

Liver Histology	No. (%) Normal Glucose (n = 473)	Prediabetes (n = 158)[a]	Type 2 Diabetes (n = 44)[b]	Total (n = 675)	*P* Value[c]
Steatosis grade, %					
<33	125 (26.4)	39 (24.7)	10 (22.7)	174 (25.8)	.55
34-66	155 (32.8)	43 (27.2)	14 (31.8)	212 (31.4)	
>66	193 (40.8)	76 (48.1)	20 (45.5)	289 (42.8)	
Lobular inflammation					
<2 under 20×	271 (57.3)	75 (47.5)	23 (52.3)	369 (54.7)	.18
2-4 under 20×	174 (36.8)	71 (44.9)	16 (36.4)	261 (38.7)	
>4 under 20×	28 (5.9)	12 (7.6)	5 (11.4)	45 (6.7)	
Ballooning					
None	282 (59.6)	77 (48.7)	13 (29.5)	372 (55.1)	<.001
Few	128 (27.1)	49 (31.0)	19 (43.2)	196 (29.0)	
Many	63 (13.3)	32 (20.3)	12 (27.3)	107 (15.9)	
Diagnosis					
NAFLD, not NASH	134 (28.3)	39 (24.7)	7 (15.9)	180 (26.7)	<.001
Borderline NASH					
Zone 3 pattern	81 (17.1)	23 (14.6)	13 (29.5)	117 (17.3)	
Zone 1, periportal pattern	154 (32.6)	42 (26.6)	5 (11.4)	201 (29.8)	
Definite NASH	104 (22.0)	54 (34.2)	19 (43.2)	177 (26.2)	
Fibrosis stage					
No.	471	157	43	671	.04
0: None	146 (31.0)	48 (30.6)	10 (23.3)	204 (30.4)	
1a: Mild, zone 3 perisinusoidal	33 (7.0)	7 (4.5)	7 (16.3)	47 (7.0)	
1b: Moderate, zone 3 perisinusoidal	20 (4.2)	8 (5.1)	5 (11.6)	33 (4.9)	
1c: Portal/periportal only	137 (29.1)	41 (26.1)	9 (20.9)	187 (27.9)	
2: Zone 3 and periportal	59 (12.5)	33 (21.0)	8 (18.6)	100 (14.9)	
3: Bridging	67 (14.2)	19 (12.1)	3 (7.0)	89 (13.3)	
4: Cirrhosis	9 (1.9)	1 (0.6)	1 (2.3)	11 (1.6	

Abbreviations: NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

[a] Prediabetes defined as (1) fasting serum glucose level between 100 mg/dL and 125 mg/dL or (2) hemoglobin A_{1c} level between 5.7% and 6.5%.

[b] Type 2 diabetes defined as (1) fasting serum glucose level at least 126 mg/dL; (2) hemoglobin A_{1C} level at least 6.5%; or (3) existing clinical diagnosis of type 2 diabetes.

[c] *P* values are calculated based on F-test for continuous variables and a χ^2 test for categorical variables.

population prevalence for type 2 diabetes for 10- to 19-year-olds at 0.42 per 1000 (95% CI, 0.29-0.45).[21] Because type 2 diabetes occurs predominantly among the 20% of youths with obesity, an estimated diabetes rate among obese youth of 0.42 per 200 remains less than 1%, much less than the 6.5% prevalence observed in our cohort of children with NAFLD. Although the NASH CRN enrollment does not aim to represent the population, the findings suggest that youths with NAFLD have substantially higher risk of type 2 diabetes than obese youths in general.[22,23] It is possible we overdiagnosed type 2 diabetes based on using single measurements of fasting glucose and hemoglobin A_{1c} to classify glucose status in this study. That said, most youths who met criteria of type 2 diabetes were given this diagnosis by clinicians: the minority were assigned a diagnosis of type 2 based on single laboratory measurements.

Although systemic insulin resistance is believed be important in the pathogenesis of both pediatric NAFLD and type 2 diabetes, to our knowledge, there are no longitudinal studies that evaluate the cause-effect relationship between these 2 associated conditions. Several studies in children have shown that higher intrahepatic fat content is associated with greater degrees of insulin resistance and impaired glucose regulation prior to the onset of overt diabetes.[24,25] Moreover, children diagnosed as having NAFLD have been shown to have significantly higher rates of impaired fasting glucose compared with overweight and obese matched control individuals.[8] In our cross-sectional analysis, more than 6% of children with NAFLD had diabetes. However, among pediatric populations with type 2 diabetes, 50% to 60% had suspected NAFLD based on elevated alanine aminotransferase.[26,27] As such, our study contributes to the collective body of evidence supporting the contention that NAFLD may be a precursor to type 2 diabetes development.

A major finding in this study was that children with NAFLD who had type 2 diabetes had 3.1 times the odds for NASH. Although prognostic implications of NASH in childhood are not fully known, in adulthood, the NASH phenotype conveys substantially greater risk for cirrhosis.[10] Furthermore, the risk of a more pronounced hepatic injury is compounded by the presence of type 2 diabetes. Younossi et al[11] demonstrated that in 132 adult participants with histologically confirmed NAFLD, 25% of those with type 2 diabetes had cirrhosis compared with only 10% of those without diabetes.[11] Type 2 diabetes has also been shown to be independent risk factor for hepatocellular carcinoma development in adults with NAFLD.[28] Finally, adults

Table 3. Risk Factors for NASH

Characteristic	NASH, OR (95% CI)
Glucose status	
Normal glucose	1 [Reference]
Prediabetes	1.9 (1.2-2.9)
Type 2 diabetes	3.1 (1.5-6.2)
Age, y	1.1 (1.0-1.2)
Sex	
Male	1 [Reference]
Female	1.4 (0.9-2.1)
Race/ethnicity	
White non-Hispanic	1 [Reference]
Hispanic	0.7 (0.5-1.1)
Other	0.7 (0.3-1.6)
BMI	1.01 (1.0-1.1)
Waist circumference, cm	1.01 (0.98-1.03)
(Intercept)	NA

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); NA, not applicable; NASH, nonalcoholic steatohepatitis; OR, odds ratio.

with type 2 diabetes have nearly 3 times the risk of dying from chronic liver disease.[29] Our study advances the literature by showing that as early as childhood, prediabetes and type 2 diabetes emerge as clear risk factors for NASH with potential downstream implications for future morbidity and mortality.

There was a striking influence of sex on type 2 diabetes risk in children with NAFLD in this study. Epidemiologic data to date have consistently demonstrated that NAFLD in children affects predominantly boys.[30-32] However, we showed that among the subpopulation of children with abnormal glucose metabolism, there was a notable predominance in girls, with more than 60% of those with type 2 diabetes being girls compared with only 25% with NAFLD alone. This female predominance is consistent with what has been previously described in large epidemiologic studies of children with type 2 diabetes.[33,34] The reason for this sex difference is not explained by other demographic or clinical factors and thus remains unclear. From this information, it seems that although girls are less likely to have NAFLD overall, they are more likely to have associated comorbidities that increase their risk for many negative health consequences.[9] As such, understanding these sex differences is a major unmet research need.

To our knowledge, this is the first study to examine the prevalence of abnormal glucose metabolism in a large, multicenter cohort of children with biopsy-proven NAFLD. This study was performed by the NASH CRN, which has diverse geographic representation of children with accurate and rigorously characterized NAFLD. There were limitations in this study in that there was only a single time measure of glucose metabolism. In the clinical world, diagnosis of prediabetes and diabetes is more complex and based on multiple measurements, assessment of symptoms, and islet cell antibody status. In addition, study participants did not undergo oral glucose tolerance testing. Therefore, the true prevalence of abnormal glucose metabolism may be overestimated or underestimated. Moreover, there have been acknowledged challenges in using hemoglobin A_{1c} levels in childhood to characterize abnormal glucose metabolism because the ideal cut point to capture those at greatest risk for prediabetes, diabetes, and diabetic sequelae is controversial.[35,36] In addition, hemoglobin A_{1c} has had a heterogeneous diagnostic performance among different racial/ethnic populations[37] and can be inaccurate when nonglycemic test factors, such as hemoglobinopathies, iron-deficient anemia, or impaired renal function, are present.[38,39] Despite this, hemoglobin A_{1c} parameters chosen in this study were consistent with the 2014 American Diabetes Association recommendations for screening[20] and are regarded as effective in screening for prediabetes and diabetes in overweight and obese populations.[40]

Conclusions

In children with NAFLD, both type 2 diabetes and prediabetes are common. As many as 1 in 3 children with NAFLD will have abnormal glucose metabolism. The presence of type 2 diabetes in children with NAFLD identifies the highest risk population for NASH. Although children with NAFLD overall were typically boys, girls with NAFLD in our study were more likely to have diabetes. Special attention should be given to children with the combination of type 2 diabetes and NASH because they are at particularly high risk for premature morbidity and mortality. Children with NAFLD merit a detailed clinical evaluation of abnormal glucose metabolism along with long-term monitoring for progression of liver disease, diabetes, and the consequences of both.

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