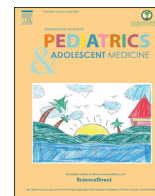


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Treatment of hyperglycemia not associated with NAFLD improvement in children with type 2 diabetes mellitus

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ABSTRACT

Background and objectives: Nonalcoholic fatty liver disease (NAFLD) and type 2 diabetes mellitus (T2DM) have become public health problems in the pediatric population. However, the relationship between these two conditions is not well understood. The primary objective of this study was to assess whether treatment of hyperglycemia in obese, treatment-naïve children with type 2 diabetes (T2DM) was associated with an improvement of surrogate markers of NAFLD.

Materials and methods: This retrospective, longitudinal study included 151 obese children with a diagnosis of T2DM (Age: 14 ± 1 years, 72% female children, BMI: 98.6th percentile, and A1c: $10.3 \pm 0.2\%$). Clinical/demographic information was collected before patients started any diabetes treatment and 1 and 3 years after starting metformin and/or insulin therapy.

Results: Forty-eight patients (32%) had abnormal ALT/AST (i.e., >40 U/L), suggestive of NAFLD. After 1 year of therapy, there were no significant differences in plasma ALT among patients started on insulin, metformin, or combination: 5 ± 4 vs. -10 ± 3 vs. -2 ± 2 IU/L, respectively, $P = .07$. Of note, changes in plasma ALT were small, despite a significant reduction of A1c in patients prescribed insulin (alone or with metformin): $-2.8 \pm 1.0\%$, $P = .01$, and $-2.7 \pm 0.3\%$, $P < .001$, respectively. In line with this, no significant correlations were found between changes in A1c and plasma aminotransferases. In contrast, changes in plasma AST/ALT were more strongly associated with BMI changes ($r = 0.32$, $P < .001$, and $r = 0.19$, $P = .04$, respectively). Similar results were observed after 3 years of follow-up.

Conclusions: Nonalcoholic fatty liver disease is highly prevalent in obese children with T2DM. Treatment of hyperglycemia with metformin and/or insulin did not result in any significant improvement in surrogate markers of NAFLD (i.e., plasma aminotransferases). While changes in ALT and/or AST may not perfectly reflect histological changes in NAFLD, our findings suggest that the treatment of hyperglycemia *per se* may not be associated with NAFLD improvement.

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1. Introduction

Nonalcoholic fatty liver disease (NAFLD) has recently become a serious public health problem worldwide [1]. Driven by the epidemic of obesity, this condition batters all age groups with

similar strength [2]. A recent study that included 408 obese participants aged 9–17 years reported an overall prevalence of NAFLD of 26% in this age group by using magnetic resonance imaging (MRI) [3]. Similar to findings reported in adults, pediatric NAFLD appears to be a progressive disease, with reports describing ~20% of patients with nonalcoholic steatohepatitis (NASH) and ~8% with advanced fibrosis or cirrhosis [4].

In addition to liver-related complications, children with NAFLD are also at risk of undesirable metabolic effects. It is estimated that ~30% of children with NAFLD have prediabetes or type 2 diabetes mellitus (T2DM) [5]. The interaction between NAFLD and T2DM is

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complex and only incompletely understood. There is substantial evidence that in adults with T2DM, liver disease progresses faster [6,7]. This appears to be equally true for children with NAFLD, as recently reported in a small cohort of 38 pediatric patients with NAFLD and T2DM [8]. However, whether this effect is related to hyperglycemia *per se* or the result of other factors (e.g., insulin resistance, subclinical inflammation, etc.) is currently unknown. In addition, it is also unknown whether the treatment of hyperglycemia can directly improve liver disease in these patients.

In this setting, we assessed the relationship between hyperglycemia and liver disease in a large cohort of children at the time of diagnosis of T2DM and the effects of hyperglycemia treatment during their first 3 years of follow-up.

2. Materials and Methods

2.1. Design

This is a retrospective, longitudinal study that included patients with a diagnosis of T2DM followed in the pediatric endocrinology clinic at the Children's Hospital of Alabama, University of Alabama at Birmingham (UAB) between March 2004 and July 2016. Patients were identified using ICD-9-CM diagnosis codes of 250.00 and 250.02. The available information at the diagnosis of T2DM was extracted as well as information at 1 and 3 years of follow-up. The study was approved by the UAB Institutional Review Board. Because of the retrospective nature of the study, written informed consent was not required.

2.2. Patients

Patients with a diagnosis of T2DM [9] were included in the study if they met the following inclusion criteria: age ≤ 18 years, HbA1C $\geq 7.0\%$ at diagnosis, the absence of serum autoimmune markers against islet cell or GAD-65 antigens, BMI > 95 th centile for age and sex, and elevated C-peptide (above the normal fasting level for the laboratory, ≥ 2.2 ng/ml) at diagnosis or follow-up, and the completion of a follow-up visit at 1–1.5 years. Patients were excluded from the study if plasma aminotransferases were not available at the time of T2DM diagnosis or if they were > 160 IU/L ($> 4 \times$ ULN) at the time of diagnosis. Patients with diabetic ketoacidosis (DKA) or severe hyperosmolar hyperglycemic state (HHS) at the time of diagnosis were also excluded from the analysis. Patients with other chronic liver conditions or a diagnosis of type 1 diabetes mellitus (T1DM) were also excluded.

2.3. Information collected

Information including diagnosis codes, demographic information, laboratories, imaging, medications, prescriptions, etc., were collected through University of Alabama at Birmingham's electronic medical record system for each visit. This information was collected at the time of diagnosis of T2DM, including common comorbidities, anthropometric measurements, routine blood and urine biochemistries, use of concomitant medications, and initial T2DM regimen prescribed. The same information, as well as any changes in T2DM, HTN, and dyslipidemia medications, were collected for visits performed at 1 and 3 years after the diagnosis of T2DM. Of note, blood and urine biochemistries were obtained as part of the routine follow-up of these patients.

2.4. Statistical analysis

Data were presented as mean \pm SD for continuous variables (mean (SD) or median (range) in tables) and as percentages for

categorical variables. Between-group comparisons were performed by Student's *t*-test (parametric) or Kruskal-Wallis test (non-parametric) for continuous variables, and with χ^2 and Fisher's Exact test for categorical variables. Before versus after comparisons were performed with paired *t*-test and Wilcoxon matched-pairs signed-rank test. $P < .05$ was considered statistically significant. All statistical analyses were performed with Stata 11.1 (StataCorp LP, College Station, TX). Graphs were performed with Prism 6.0 (GraphPad Software, La Jolla, California, USA).

3. Results

3.1. Baseline characteristics

A total of 151 children with T2DM were included in the study (Table 1). Their ages ranged from 6 to 18 years and 72% were females. We observed a predominance of African-American subjects among this cohort of newly diagnosed patients with T2DM (79% of all patients). A significant percentage of these patients had T2DM-related comorbidities (i.e., hypertension and dyslipidemia). Using 40 IU/L as the upper limit of normal for ALT and AST, we observed that 48 (32%) of these patients had abnormal plasma aminotransferases at the time of T2DM diagnosis, which suggests the presence of NAFLD. When stricter cut-off points were selected (i.e., 19 IU/L for female and 30 IU/L for male subjects as previously described) [10], 66% of the patients showed abnormal plasma aminotransferases.

3.2. Demographic and clinical characteristics of patients with abnormal aminotransferases

In Table 1, we have also provided the baseline clinical characteristics of patients, dividing them based on the presence or absence of elevated plasma aminotransferases. No differences were observed between the two groups with regard to age, sex, BMI, or BMI percentile. There was a trend toward a higher percentage of Caucasian patients among patients with elevated plasma aminotransferases and more African-American patients in the group with normal plasma aminotransferases ($P = .09$). Of note, when plasma ALT and AST were compared between these 2 ethnic groups, patients of African-American origin showed significantly lower levels of ALT (29 ± 16 vs. 50 ± 34 IU/L and $P < .001$) and AST (29 ± 13 vs. 40 ± 25 IU/L and $P = .002$) than Caucasian patients. Interestingly, patients with elevated plasma aminotransferases showed significantly lower plasma glucose levels and hemoglobin A1c than patients with normal plasma aminotransferases (see Table 1). They also had significantly higher plasma C-peptide levels than patients with normal plasma aminotransferases. Despite lower glucose levels, patients with elevated plasma aminotransferases still showed significantly higher plasma triglycerides ($215 [144–324]$ vs. $136 [92–230]$ mg/dl and $P = .009$).

3.3. Predictors of elevated plasma aminotransferases

To assess which factors were associated with higher plasma aminotransferases levels, we performed multiple linear regression analyses. The only factors found to be independently associated with plasma ALT were baseline C-peptide levels ($\beta = 2.88$ and $P = .006$) and African-American ethnicity ($\beta = -19.28$ and $P = .002$). Regarding plasma AST, only C-peptide was independently associated with it ($\beta = 2.66$ and $P = .001$). This occurred even after adjustment for age, sex, BMI, fasting plasma glucose, A1c, triglyceride, and HDL-C levels.

Table 1

Clinical and Demographic Characteristics at the Time of Diagnosis of Type 2 Diabetes Mellitus Based on the Presence or Absence of Elevated Plasma Aminotransferases (using 40 IU/L as cut-off point for AST and ALT).

	All patients (n = 151)	Normal plasma aminotransferases (n = 103)	Elevated plasma aminotransferases (n = 48)	P value
Age, years	14 (2)	14 (2)	14 (3)	.80
Gender, % male	28%	26%	33%	.37
BMI, kg/m ²	36.8 (7.6)	36.8 (8.0)	36.8 (6.8)	.96
BMI Z-score	2.4 (0.4)	2.3 (0.4)	2.4 (0.4)	.69
BMI percentile	98.6 (1.8)	98.5 (1.9)	98.7 (1.4)	.48
Ethnicity				.09
African american, %	79%	83%	69%	
Caucasian, %	18%	15%	25%	
Other, %	3%	2%	6%	
Plasma glucose, mg/dl	250 (145)	269 (153)	205 (113)	.014
Hemoglobin A1c, %	10.3 (2.5)	10.7 (2.6)	9.5 (2.2)	.006
C-peptide, ng/mL	4.2 (2.6)	3.6 (2.5)	5.7 (2.2)	<.001
Plasma ALT, IU/L	34 (24)	23 (8)	58 (28)	<.001
Plasma AST, IU/L	32 (17)	23 (6)	50 (18)	<.001
Total cholesterol, mg/dl	181 (46)	178 (42)	188 (55)	.30
HDL-C, mg/dl	39 (12)	40 (13)	37 (11)	.16
LDL-C, mg/dl	113 (44)	109 (38)	122 (53)	.15
Triglycerides, mg/dl	167 (100–269)	136 (92–230)	215 (144–324)	.009
Non-HDL-C mg/dl	142 (5)	139 (5)	153 (13)	.24
Creatinine, mg/dl	0.7 (0.3)	0.7 (0.3)	0.6 (0.2)	.36
Hypertension, %	48%	47%	53%	.49
SBP, mmHg	126 (16)	126 (16)	126 (16)	.88
DBP, mmHg	71 (11)	71 (11)	71 (12)	.94

3.4. Changes in plasma aminotransferases with hyperglycemia treatment

In Table 2, we have summarized the baseline clinical characteristics of patients based on the initial treatment selected by the providers (i.e., metformin, insulin, or combination of the two). As can be observed in the table, there were no significant differences among the groups with regard to age, sex, ethnicity, BMI, or lipid panel. As expected, both groups prescribed insulin at the time of T2DM diagnosis, had significantly higher fasting plasma glucose, and hemoglobin A1c than the group that received only metformin. The only other variable that was different among the groups was plasma C-peptide, with higher levels in those patients initially

prescribed metformin (5.8 ± 2.6 vs. 2.8 ± 1.7 vs. 3.9 ± 2.4 ng/ml and $P = .003$). In Table 3, we have summarized the changes in anthropometric and biochemical variables after 1 and 3 years of therapy.

In Fig. 1, we have plotted changes in plasma ALT and AST at 1 and 3 years after T2DM medication initiation for those patients who were not lost to follow-up. Of the 42 patients who reached 3 years of follow-up, only 11 patients made changes in their T2DM regimen after 1 year of follow-up: 6 downtitrated their medications (from combination to only metformin or insulin, or from one medication to none) and 5 uptitrated from a single drug to a combination therapy. Patients who changed their medication regimen were switched to the appropriate final group for the purposes of this analysis.

Table 2

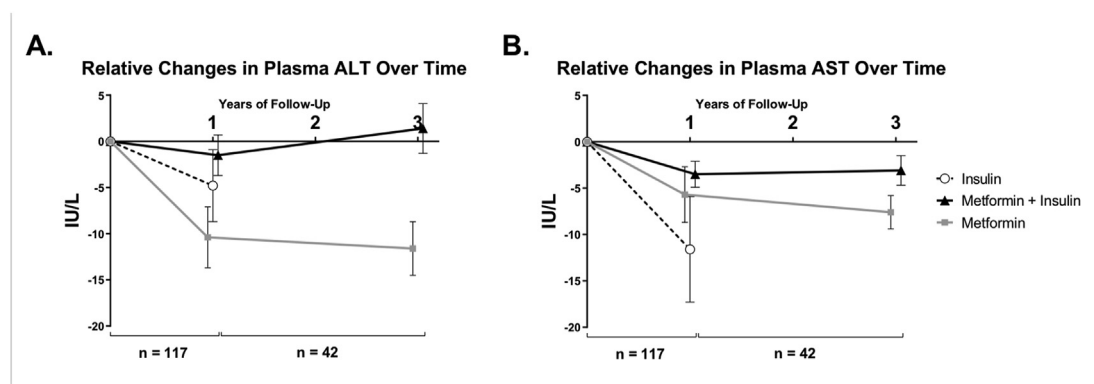
Clinical and demographic characteristics at the time of diagnosis of type 2 diabetes mellitus based on initial diabetes therapy.

	Insulin (n = 16)	Metformin (n = 45)	Metformin + Insulin (n = 90)	P value
Age, years	14 (3)	14 (3)	14 (2)	.97
Gender, % male	29%	26%	33%	.70
BMI, kg/m ²	34.6 (7.1)	37.1 (6.4)	37.0 (8.2)	.52
BMI Z-score	2.2 (0.4)	2.4 (0.3)	2.4 (0.4)	.23
BMI Percentile	97.9 (2.0)	98.8 (1.4)	98.5 (1.9)	.24
Ethnicity				.31
African American, %	81%	76%	80%	
Caucasian, %	13%	20%	18%	
Other, %	6%	4%	2%	
Plasma glucose, mg/dl	315 (183)	159 (62)	283 (147)	<.001
Hemoglobin A1c, %	11.9 (2.5)	8.0 (1.1)	11.2 (2.3)	<.001
C-peptide, ng/mL	2.8 (1.7)	5.8 (2.6)	3.9 (2.4)	.003
Plasma ALT, IU/L	26 (16–34)	30 (22–44)	27 (18–37)	.10
Plasma AST, IU/L	28 (19–34)	31 (23–41)	25 (20–36)	.06
Total cholesterol, mg/dl	176 (15)	183 (49)	181 (47)	.92
HDL-C, mg/dl	37 (9)	44 (12)	37 (12)	.06
LDL-C, mg/dl	112 (26)	109 (46)	114 (44)	.89
Triglycerides, mg/dl	109 (69–146)	172 (78–220)	169 (112–290)	.16
Non HDL-C mg/dl	138 (7)	140 (10)	144 (6)	.91
Creatinine, mg/dl	0.8 (0.3)	0.7 (0.2)	0.7 (0.3)	.36
Hypertension, %	31%	48%	52%	.32
SBP, mmHg	118 (15)	125 (14)	128 (17)	.04
DBP, mmHg	68 (12)	68 (9)	73 (11)	.06
Daily average metformin dose, mg	N/A	1493 (77)	1464 (55)	.76
Daily average basal insulin dose, IU	29 (3)	N/A	33 (2)	.34

Table 3

Changes after 1 and 3 years of therapy in anthropometric and biochemical variables.

	Changes from baseline after 1 year of therapy				Changes after 3 years of therapy as compared to year 1		
	Insulin (n = 13)	Metformin (n = 36)	Metformin + Insulin (n = 68)	P value	Metformin (n = 10)	Metformin + Insulin (n = 32)	P value
BMI, kg/m ²	−0.1 (1.0)	−0.8 (0.3)	0.6 (0.4)	.04	1.3 (0.7)	0.8 (0.5)	.58
BMI Z-score	−0.13 (0.11)	−0.18 (0.03)	−0.03 (0.03)	.006	−0.02 (0.03)	−0.09 (0.03)	.23
BMI Percentile	−2.4 (2.1)	−1.0 (0.3)	−0.3 (0.3)	.06	−0.1 (0.1)	−0.7 (0.4)	.37
Hemoglobin A1c, %	−2.8 (1.0)	−0.1 (0.4)	−2.7 (0.3)	<.001	1.2 (0.5)	0.6 (0.5)	.51
Plasma ALT, IU/L	−5 (4)	−10 (3)	−2 (2)	.07	−1 (3)	3 (3)	.43
Plasma AST, IU/L	−12 (6)	−6 (3)	−3 (1)	.19	−2 (2)	0 (2)	.44
Total cholesterol, mg/dl	−7 (16)	−14 (12)	−14 (5)	.93	3 (7)	2 (6)	.92
HDL-C, mg/dl	2 (4)	0 (2)	4 (1)	.30	−2 (2)	1 (2)	.38
LDL-C, mg/dl	−2 (22)	−7 (8)	−12 (5)	.80	4 (7)	−5 (7)	.49
Triglycerides, mg/dl	47 (−12 – 136)	−24 (−37 – 4)	−39 (−122 – 1)	.049	12 (−8 – 58)	3 (−65 – 59)	.46
Non HDL-C mg/dl	−9 (17)	−14 (11)	−18 (5)	.84	5 (7)	1 (6)	.73
Creatinine, mg/dl	−0.1 (0.1)	0.0 (0.0)	0.0 (0.0)	.052	0.0 (0.1)	0.0 (0.0)	.61
SBP, mmHg	1 (6)	−1 (2)	−4 (2)	.47	2 (3)	2 (2)	.92
DBP, mmHg	3 (3)	−1 (2)	−4 (2)	.12	1 (2)	0 (1)	.84

**Fig. 1.** Relative Changes in Plasma ALT and AST Over Time After Diagnosis of Type 2 Diabetes Mellitus.

After 1 year of therapy, there were no significant differences in changes in plasma ALT among the three groups (Insulin: 5 ± 4 vs. Metformin: 10 ± 3 vs. Combination: 2 ± 2 IU/L and $P = .07$). Within group comparison of changes in plasma ALT (i.e., pre vs. post) showed significant changes only after 1 year in the metformin group (38 ± 4 vs. 28 ± 2 IU/L and $P = .003$). Changes in plasma AST were of similar magnitude, but numerically higher for patients prescribed insulin than for those receiving metformin or combination therapy (-12 ± 6 vs. -6 ± 3 vs. -3 ± 1 IU/L, respectively, and $P = .19$). Of note, in contrast with these relatively small changes in plasma ALT and AST, patients prescribed insulin (alone or combined with metformin) had significant changes in hemoglobin A1c: $-2.8 \pm 1.0\%$, $P = .01$ and $-2.7 \pm 0.3\%$, $P < .001$, respectively (Fig. 2). No significant changes in A1c were observed after 1 year of metformin initiation (-0.1 ± 0.4 , $P = .69$). In line with these findings, no significant correlations were found between changes in hemoglobin A1c and plasma AST or ALT. This lack of relationship between changes in A1c and changes in AST/ALT remained unchanged regardless of baseline A1c (i.e., no association was observed for patients with A1c $>10.0\%$, those with A1c between 8.0% and 10.0% or those with A1c $<8.0\%$ at baseline). Changes in plasma AST and ALT were more closely associated with changes in BMI ($r = 0.32$, $P < .001$, and $r = 0.19$, $P = .04$, respectively) during the first year of follow-up.

To assess whether long-term changes in A1c were associated with changes in plasma ALT and AST, we further analyzed changes after 3 years of follow-up in those 42 patients reaching this mark with complete data. Overall, we observed no significant association between changes in A1c and changes in plasma ALT or AST after 3

years of follow-up.

3.5. Sensitivity analyses

Because of the well-known impact of ethnicity in the prevalence and progression of NAFLD, analyses regarding the relationship between A1c and AST/ALT were repeated adjusting for ethnicity. When analyses were restricted to African-American patients, we still observed no association between changes in A1c and changes in ALT and AST. Despite the relatively small Caucasian cohort ($n = 27$), similar results were observed in this ethnic group. To further assess the role of ethnicity, we also performed multiple regression analysis to examine the relationship between changes in A1c and changes in ALT and AST, using ethnicity as a covariate. The relationship between A1c and ALT/AST was again similar in both ethnic groups.

Additionally, we examined the relationship between changes in A1c with changes in ALT or AST, stratifying patients based on the presence or absence of normal plasma aminotransferases at baseline (i.e., using a cut-off point of 40 IU/L). Average A1c was slightly higher in patients with normal AST and ALT than in patients with abnormal plasma aminotransferases ($10.7 \pm 0.3\%$ vs. $9.5 \pm 0.3\%$ and $P = .006$). However, we observed no significant association between changes in A1c and changes in AST/ALT regardless of the baseline AST and ALT levels. Of note, no significant differences were found when the definition of normal aminotransferases was changed to <19 IU/L for female and <30 IU/L for male subjects, or when we analyzed changes after 3 years.

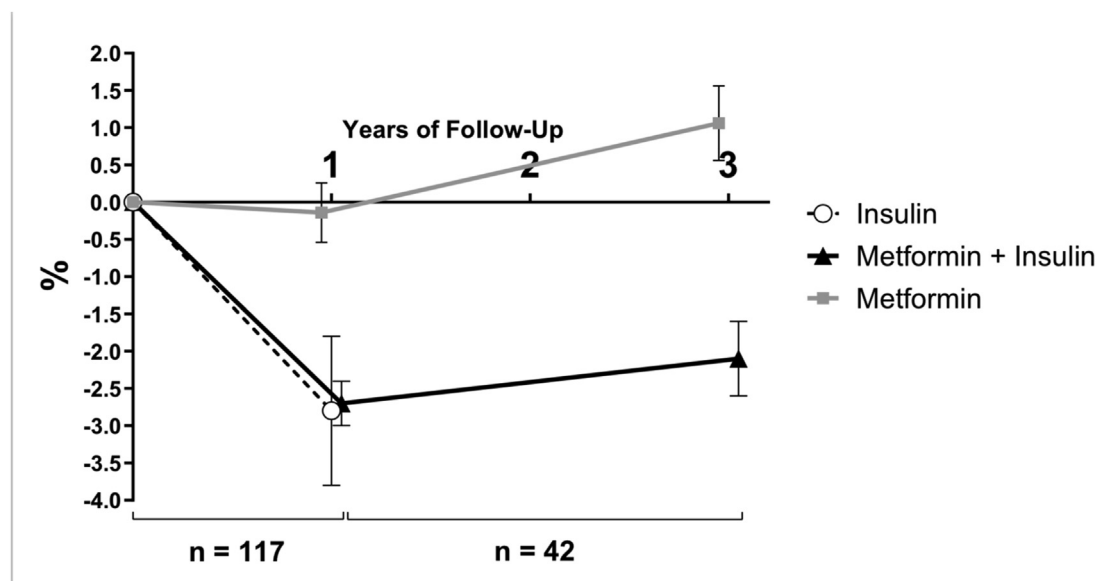


Fig. 2. Changes in A1c After the Diagnosis of Type 2 Diabetes Mellitus Based on Treatment Prescribed.

4. Discussion

In the current work, we have shown that the prevalence of NAFLD based on abnormal plasma aminotransferases is high in children with T2DM. However, plasma ALT and AST levels were not associated with the degree of hyperglycemia or A1c levels at the time of T2DM diagnosis. Moreover, glucose-lowering treatment with metformin, insulin, or combination of the two was not associated with improvements in plasma aminotransferase levels despite significant reductions in A1c after 1 and 3 years of follow-up. Taken together, these findings might suggest that treating hyperglycemia *per se* may not result in improvement of NAFLD in patients with T2DM. If confirmed in larger studies using liver biopsies to assess severity of liver disease, these results may imply that other factors (other than hyperglycemia) may contribute to the higher prevalence and faster progression of NAFLD in patients with T2DM.

Prior studies have suggested that the presence of T2DM is associated with a high prevalence of NAFLD, and that these patients progress faster to NASH and advanced fibrosis [11]. While the mechanisms responsible for this particular behavior of NAFLD in patients with T2DM are unclear, hyperglycemia has always been considered a potential culprit [12]. However, patients with T1DM, who characteristically have hyperglycemia and increased free fatty acids as patients with T2DM, appear not to develop NAFLD more frequently than the general population [13,14]. While the absolute lack of insulin may act as a “protective” mechanism against NAFLD in patients with T1DM, hyperglycemia in the setting of hyperinsulinemia (as seen in patients with T2DM), may be a detrimental combination for the liver. It is also possible that a minimal “permissive” amount of insulin is required for hyperglycemia to exert its damage on the liver. However, even in our cohort of T2DM, our results do not support hyperglycemia *per se* as a key determinant of the severity of NAFLD based on AST and ALT levels. Moreover, a surprising finding in our work was that C-peptide concentration was the stronger predictor of ALT and AST levels. This finding supports the notion that hyperinsulinemia and/or insulin resistance are the key promoters of NAFLD in patients with T2DM, and that hyperglycemia plays only a minor (if any) role in the progression of liver disease. Unfortunately, it is impossible to

analyze whether the association between C-peptide and plasma aminotransferases is due to higher insulin resistance in patients with elevated plasma aminotransferases or more severely impaired insulin secretion in patients without plasma aminotransferase elevations.

Type 2 diabetes mellitus occurs because of an imbalance between increased insulin resistance and relative insulin deficiency (i.e., impaired insulin secretion), which is unable to compensate for the insulin resistance. But each patient with T2DM may be at different point in this continuum: while some patients may have extremely elevated insulin resistance, others may be characterized by severely impaired insulin secretion with relatively minor insulin resistance. Patients of African-American ethnicity have higher prevalence of T2DM, but lower prevalence of NAFLD than BMI-matched Caucasians [15]. Therefore, it is likely that the relationship between insulin sensitivity, insulin secretion, and liver steatosis is unique in this ethnic group. Because our cohort was composed of 79% of African-American patients, it is possible that our results cannot be extrapolated to other ethnic groups. In addition, as we only included patients with at least 1 year of follow-up, it is possible that those patients lost to follow-up could have been systematically different than the cohort included in the study, further decreasing the external validity of the study. Other potential limitations of the current study include its retrospective nature, single-center study, low sensitivity of plasma ALT and AST for the diagnosis of NAFLD [16,17], and the fact that information on follow-ups was only collected at 1 and 3 years, and therefore, we lack potentially important information about medication changes and diabetes control that could have occurred between these visits.

Nevertheless, this cohort of patients provided an excellent opportunity to assess the relationship between hyperglycemia and plasma AST and ALT concentrations for several reasons. First, all these patients were included in the study at the time of their T2DM diagnosis, and therefore, anti-hyperglycemic medication use was avoided as a potential confounding factor. In addition, studies in adult populations are usually affected by significant number of drugs used, including sulfonylureas, GLP-1 agonists, SGLT-2 inhibitors, statins, etc. Second, because of the limited pharmacological options to treat pediatric patients with T2DM, our cohort of patients consisted mainly of patients treated with metformin and/

or insulin, medications known to have little (if any) effects on liver steatosis and histology [18–20]. Therefore, it is likely that most of the effects observed in these patients are secondary to their anti-hyperglycemic effect. Third, while children are at a significant risk of NAFLD and NASH, there is a relative lack of information in this population as they have had only a minor participation in clinical studies on NAFLD.

Our results suggest that hyperglycemia is not a key determinant of liver damage in NAFLD as assessed by AST and ALT levels. Moreover, in our cohort, anti-hyperglycemic treatment does not *per se* improve AST and ALT levels. If confirmed in larger longitudinal studies, these results would suggest that other factors such as insulin resistance may play a bigger role in the development and progression of NAFLD. The most straightforward clinical implications of these results is that in the setting of T2DM and NAFLD, therapies targeted at improving insulin sensitivity and/or reducing weight (i.e., lifestyle intervention, thiazolidinediones, GLP-1 agonists, and bariatric surgery) may help in providing supplemental benefit. Unfortunately, many pharmacological therapies have not been assessed in children and remain in the research domain.

Authors contribution

Giovanna Beauchamp: Writing – original draft and data interpretation, Mary M. Barr: data collection, Ariana Vergara: data collection, Ambika Ashraf: Conceptualization, data collection, and revision of final manuscript, Fernando Bril: Conceptualization, Writing – original draft, Formal analysis, data interpretation, and revising final manuscript.

Visual abstract

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijpam.2021.02.007>.

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