Screening for liver disease in children and adolescents with type 1 diabetes mellitus: a cross-sectional analysis

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Summary and conclusions:

We present the first representative cohort of children and adolescents with type 1 diabetes mellitus (DM) from a Western country that was comprehensively screened for liver disease. In contrast to literature from adult patients with type 1 DM, our results do not indicate an increased prevalence of liver pathology in this cohort compared to known prevalence data from the general population. These data advocate against the systematic screening for liver disease for all pediatric patients with type 1 DM, and to limit screening for liver disease to those with a specific risk profile (obesity, poor glycemic control, etc.).

Background

The liver is one of the most important organs in glucose metabolism and closely related to diabetes pathophysiology. **Non-alcoholic fatty liver disease (NAFLD) is well known in type 2 diabetes mellitus (DM), but also adult patients with type 1 DM are at increased risk for NAFLD**.

Methods and description of patient cohort:

We used **laboratory investigation (alanine aminotransferase [ALT], conventional ultrasound, and ultrasound-based liver stiffness measurement (Fibroscan® [FS] and Acoustic radiation force imaging [ARFI]) as noninvasive screening methods for liver disease** in a cross-sectional analysis of n=93 children and adolescents with type 1 DM in Germany.

To exclude selection bias, basic clinical characteristics of the study cohort were compared and did not show significant differences to those of the 223 other patients that were seen in our paediatric diabetes outpatient clinic and did not participate in the study.

Table 1: Basic clinical characteristics of study cohort:

Results given as mean ± standard deviation (minimum-maximum), *one-way ANOVA. Discrete variables given as frequency, **Pearson chi-square	Study cohort (n=93)	Remaining patients at our institution (n=223)	P
Age (years)	11.9 ± 4.0 (3-18)	12.4 ± 4.1 (2-19)	0.36*
Diabetes duration (days)	1671 ± 1268 (275-5601)	1703 ± 1370 (0-6198)	0.85*
BMI-SDS	0.48 ± 0.92 (-2,0-3.38)	0.59 ± 0.87 (-1.7-3.52)	0.33*
Mean HbA1c (mmol/mol) (%)	60 ± 9 (39-101) 7.6 ± 0.8 (5.7-11.4)	63 ± 12 (52-99) 7.9 ± 1.1 (6.9-11.2)	0.21*
Insulin dose (U)/kg /day	0.81 ± 0.36 (0.3 – 3.25)	0.81 ± 0.34 (0.16-2.76)	0.96*
Patients with CSII therapy (%)	33%	35%	0.78**

Results and conclusions:

1. **82/93 patients (88.1%) had completely normal results**.
2. Seven patients (7.5%) showed only one single mildly pathologic aspect of the examined items, in summary probably not indicating significant hepatic pathology (Table 2).
3. **Only four patients (4.3%) had conclusively evidence for potential NAFLD** (Table 2: increased liver stiffness, elevated liver transaminases, three were overweight/obese and all four had suboptimal glycemic control with HbA1c >58mmol/mol [>7.5%]).
4. Variables indicating hepatic abnormalities (Fibroscan, ARFI and ALT) did not show any correlation with HbA1c, body mass index, or diabetes duration (data not shown).

These results **do not show an increased prevalence of liver disease in children and adolescents with type 1 diabetes compared to established prevalence data form non-diabetic individuals** (Abnormal laboratory markers of liver disease in 8-11% of children and adolescents from the US [4] or Germany [5], fatty liver in 17.3% of histologic analyses of children in the U.S. that died unnaturally [6]).

In contrast, **conclusively pathologic results were limited to four patients with a specific risk profile (obesity, poor glycemic control, etc.).**

Acknowledgements and references

Written and informed consent was obtained from all parents or respective guardians before inclusion in the study, additionally from participants if they were ≥ 8 years of age. The study protocol was approved by the Ethics Committee of the Medical Faculty of the Heinrich-Heine-University Duesseldorf (Study number 3755, February 2012) and was in accordance with the ethical guidelines of the 1975 Declaration of Helsinki, as revised in 1983.
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Table 2: Summary of all patients with at least one pathologic result in ultrasound, ALT, Fibroscan or ARFI.

		Basic clinical characteristics						Abnormality detected? (+ yes, + no)			
	ID	sex	Age (years)	Diabetes duration (years)	Body Mass Index--SDS	Mean HbA1c in % (mmol/mol)	Insulin dose (U/kg/day)	Fibroscan® (Median) Reference <7.65 kPa	ARFI (Median) Reference <1.31 m/s	Ultrasound (2 or more of 6 criteria abnormal?)	ALT (reference range: male <25, female <22 U/l)
7/93 had only one mildly pathologic result without additional risk factor, in summary probably not indicating significant hepatic pathology	18	m	8.5	5	-0.6	53 (7.0)	0.73	+ (8 kPa)	- (1.3 m/s)	-	- (13 U/l)
	19	m	8.9	5.2	1.1	57 (7.4)	0.59	- (6.5 kPa)	- (1.22 m/s)	-	+ (28 U/l)
	24	m	10.0	6.5	0.18	58 (7.5)	0.55	+ (9.8 kPa)	- (1.25 m/s)	-	- (13 U/l)
	40	f	13.7	1	1.15	51 (6.8)	0.35	+ (7.7 kPa)	- (1.21 m/s)	-	- (8 U/l)
	63	f	17.1	6.3	-0.09	50 (6.7)	0.97	+ (8.2 kPa)	- (1.16 m/s)	-	- (16 U/l)
	88	m	17.7	6.1	0.42	51 (6.8)	0.89	- (4.8 kPa)	- (1.13 m/s)	+ mildly enlarged: MCL 17,8cm (reference range <15,5cm), and AAL 16,9cm (reference range <16,2cm), mild parenchymal hyperechogenicity	- (21 U/l)
	91	m	10.9	1.1	0.09	51 (6.8)	0.65	- (3.3 kPa)	+ (1.36 m/s)	-	- (15 U/l)
4/93 had conclusively evidence for potential NAFLD , all of them had suboptimal HbA1c, 3 of 4 were markedly obese	25	f	10.0	1	2.05	69 (8.5)	0.66	- (3.3 kPa)	- (1.02 m/s)	-	+ (51 U/l)
	38	m	13.4	4.5	1.97	74 (8.9)	1.29	- (4.8 kPa)	- (1.11 m/s)	-	+ (28 U/l)
	62	f	16.9	3.9	3.38	78 (9.3)	1.01	No reproducible measurement possible due to obesity	+ (2.02 m/s)	-	- (22 U/l)
	90	f	8.0	2.7	0.15	69 (8.5)	0.98	+ (10.1 kPa)	+ (1.33 m/s)	-	- (19 U/l)

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