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Magnetic resonance imaging reveals altered distribution of hepatic fat in children with type 1 diabetes compared to controls

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ABSTRACT

Introduction. Children with type 1 diabetes have been identified as a risk group for non-alcoholic fatty liver disease (NAFLD). The aim was to compare total hepatic fat fraction and fat distribution across Couinaud segments in children with type 1 diabetes and controls and the relation of hepatic fat to plasma and anthropometric parameters.

Methods. Hepatic fat fraction and fat distribution across Couinaud segments were measured with magnetic resonance imaging (MRI) in 22 children with type 1 diabetes and 32 controls. Blood tests and anthropometric data were collected.

Results. No children had NAFLD. Children with type 1 diabetes had a slightly lower hepatic fat fraction (median 1.3%) than controls (median 1.8%), and their fat had a different segmental distribution. The fat fraction of segment V was the most representative of the liver as a whole. An incidental finding was that diabetes patients treated with multiple daily injections of insulin (MDI) had a fat distribution more similar to controls than patients with continuous subcutaneous insulin infusion (CSII).

Conclusions. In children with type 1 diabetes, NAFLD may be less common than recent studies have suggested. Children with type 1 diabetes may have a lower fat fraction and a different fat distribution in the liver than controls. Diabetes treatment with MDI or CSII may affect liver fat, but this needs to be confirmed in a larger sample of patients. The heterogeneity of hepatic fat infiltration may affect results when liver biopsy is used for diagnosing fatty liver.

Abbreviations: ANCOVA, analysis of covariance; CSII, continuous subcutaneous insulin infusion; HbA_{1c}, glycated hemoglobin; MDI, multiple daily injections; MRI, magnetic resonance imaging; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PDFF, proton density fat fraction.

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1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver condition in the Western world [1]. Although NAFLD is traditionally associated with obesity and insulin resistance, studies in recent years have identified type 1 diabetes patients as a potential risk group [2,3]. The natural history of pediatric hepatic steatosis is incompletely characterized, but studies suggest that NAFLD in children often has a more rapid and severe course than in adults, with a higher risk of progression to non-alcoholic steatohepatitis (NASH) [4,5].

NAFLD has been found in up to 11.3% of children with type 1 diabetes, compared with 2.6% of children in the general population [6,7]. Adults with type 1 diabetes have also been shown to have a higher prevalence of NAFLD than the general population [8]. However, as previous studies of the prevalence of NAFLD in type 1 diabetes have used ultrasonography, which can only reliably ascertain a fat volume of more than 33%, they may underestimate the prevalence of less severe fatty liver [9]. Conversely, some authors have suggested that ultrasonography may be unable to distinguish NAFLD from glycogenic hepatopathy, leading to possible misdiagnoses and overestimation of the occurrence of NAFLD [10,11].

Magnetic resonance imaging (MRI) overcomes these limitations of liver fat detection and accurately quantifies even mild fatty infiltration of the liver [12,13]. The MRI-determined hepatic fat fraction correlates excellently with the liver fat content measured using liver biopsy, which is considered the reference standard [14]. MRI is non-invasive and does not use ionizing radiation, making it suitable for examining children. A further advantage of MRI over liver biopsy is its capability to quantify the heterogeneity of fat distribution in the liver, which overcomes the possible sampling bias inherent to invasive techniques [15]. Few studies have quantified the variations in amount of fat in different hepatic segments, but it has been found that patients with type 2 diabetes have an uneven fat distribution between the left and rights halves of the liver [16]. Furthermore, subcutaneous insulin administration may result in different macroscopic fat deposition compared to that of physiological, pancreatic insulin secretion because of altered insulin concentrations in the portal vein and hepatic artery [3,17].

In adult type 1 diabetes patients, NAFLD has been correlated to cardiovascular disease, chronic kidney disease, and retinopathy after adjustment for age, sex, smoking history, diabetes duration, HbA_{1c}, low-density lipoprotein, cholesterol, albuminuria, estimated glomerular filtration rate and presence of the metabolic syndrome [8,18,19]. Hepatic fat could therefore potentially be used as a marker of glycemic control and the risk of diabetic complications. Since the liver is a central metabolic organ, it is possible that a disturbed liver function might not just reflect the progression of diabetic complications, but actually contribute to them.

The present study aimed to determine the hepatic fat fraction of children with type 1 diabetes and controls, to determine the distribution of hepatic fat across Couinaud segments of children with type 1 diabetes and controls and to explore correlations between liver fat and HbA_{1c}, plasma lipids and anthropometric parameters.

2. Material and Methods

2.1. Patients and Controls

Type 1 diabetes patients born between 1995 and 2002 who regularly attended the Paediatric and Adolescent Clinic at Skåne University Hospital in Malmö, Sweden, were considered eligible for the study (n = 118). A minimum age of 10 years was chosen to ensure that all patients would be capable of undergoing the MRI examination without difficulty. No patients had any known liver pathology. The patients were asked by mail and telephone to participate in the study, and 22 patients (Table 1) were finally examined with MRI. 12 type 1 diabetes patients were treated with MDI and 10 with CSII (Table 2).

32 control subjects were examined. They were aged 8 to 17 and had no known liver disease. They were recruited by (1) asking the type 1 diabetes patients and their parents whether they knew any other children willing to partake in the study; (2) informing by email the employees in the Clinical Research Centre at the Skåne University Hospital in Malmö about the possibility for their children to participate; and (3) soliciting control subjects participating in the Diabetes Prediction in Skåne (DiPiS) study [20]. All patients, control subjects and legal guardians gave their written informed consent and were free to discontinue their participation in the study at any point.

The MRI scans were performed between May 2012 and November 2013. Information about the patients' blood samples, weight, height and mode and dosage of insulin therapy was taken from the most recent entries in their medical records. Fasting blood samples and body measurements of the control subjects were obtained within 2 months after MRI examination at an additional visit to the hospital. The blood tests in patients and controls were ALAT, C-peptide, cholesterol, HbA_{1c} and triglycerides. Standard deviations from average age-adjusted body mass index (BMI-SD) according to growth charts for Swedish children were used to compare weight in proportion to height [21].

Table 1 – Characteristics of patients and controls. Values are displayed as median (range) where applicable.

	Type 1 diabetes patients	Control subjects	p value
n	22	32	
Sex (girls)	10 (45.5%)	18 (56.3%)	0.531
Age (years)	13.5 (9–17)	12 (8–17)	0.05
BMI-SD	0.6 (−1.0 to 1.8)	0.9 (−1.7 to 2.6)	0.932
Disease duration (years)	5.9 (0.0–13.0)	Not applicable	
HbA_{1c} (mmol/mol)	62.5 (46–98)	33 (29–38)	<0.001
P-ALAT (μkat/l)	0.26 (0.05–0.52)	0 · 27 (0.13–0.78)	0.9
P-cholesterol (mmol/l)	4.3 (3.2–6.3)	3 · 8 (2.9–5.6)	0.112
P-triglycerides (mmol/l)	0.7 (0.4–1.5)	0 · 8 (0.4–2.1)	0.427
Fat fraction of total liver (%)	1.3 (0.4–2.8)	1 · 8 (0.5–3.5)	0.005
Fat volume (cm^3)	15 (5–36)	21 (6–56)	0.168