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Short Report: Pathophysiology

**Pancreas size and exocrine function is decreased in young children with recent-onset
Type 1 diabetes**

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What's new?

- Pancreatic volume and pancreatic exocrine function are reduced in adults and adolescents with Type 1 diabetes.
- Pancreatic volume is intermediate in adult first-degree relatives, both with and without islet autoimmunity.
- Young children with recent-onset Type 1 diabetes also have reduced pancreatic size and accompanying subclinical exocrine dysfunction.
- The exocrine pancreas is affected in the pathophysiology of Type 1 diabetes presenting in early life.

Abstract

Aims To measure pancreatic area and exocrine function in young children with recent-onset Type 1 diabetes to determine whether the exocrine pancreas is also affected in the pathophysiology of early childhood diabetes.

Methods Thirty-two children (14 boys) aged 5.5 (4.5, 7.3) median (IQR) years presenting with recent-onset Type 1 diabetes and 90 controls (44 boys) of similar age had ultrasound imaging of the pancreas. Children with Type 1 diabetes were receiving insulin and were without ketosis. Transverse and longitudinal areas of the pancreas were measured by digitalized outline. Pancreatic faecal elastase-1 was analysed using an enzyme-linked immunosorbent assay kit in recent-onset Type 1 diabetes and 38 first-degree relative control children.

Results Pancreatic area and exocrine function were reduced in Type 1 diabetes. Mean transverse area (SD) in Type 1 diabetes was 6.82 cm² (1.61) vs. 8.31 cm² (1.74) in controls, adjusted estimate (95% CI) 1.45 (-2.12, -0.79), $P < 0.001$; longitudinal area was 1.28 cm² (0.44) vs. 1.55 cm² (0.43), adjusted estimate (95% CI) -0.27 (-0.45, -0.09), $P = 0.003$. Faecal elastase-1 levels in Type 1 diabetes were 455 (323, 833) ug/g, median (IQR) vs. 1408 μg/g (1031, 1989) in controls, $P < 0.001$.

Conclusion Pancreatic area and accompanying subclinical exocrine function were reduced in very young children with recent-onset Type 1 diabetes. This supports changes in the exocrine pancreas in the pathophysiology of Type 1 diabetes presenting in early life.

<H1>Introduction

Adolescents and adults with Type 1 diabetes have reduced pancreatic volume as measured by organ weight in donors or by volume via magnetic resonance imaging (MRI) (1-4); 98% of the pancreas parenchyma comprises exocrine rather than endocrine tissue. Serum trypsinogen, a marker of exocrine function, is lower in adolescents and adults with Type 1 diabetes, with intermediate levels in islet autoimmune subjects (5). Type 1 diabetes is a heterogeneous disease. Young children who progress more rapidly to Type 1 diabetes before mid-childhood may not necessarily develop these pancreatic changes. Children who present early with Type 1 diabetes have been major contributors to the Type 1 diabetes global epidemic (6). The pancreatic size of very few young children aged < 8 years has been studied (7, 8) as this is an age group in whom a MRI examination often requires a general anaesthetic. Therefore, we aimed to measure pancreatic area by abdominal ultrasound and exocrine function by measurement of human pancreatic faecal elastase-1 (FE-1), the latter as a sensitive, non-invasive measure of exocrine function in young children with recent-onset Type 1 diabetes and in controls.

<H1>Research design and methods

Three groups of a total of 160 children aged 2–8 years were studied from February 2017 until February 2018. The first group, the Type 1 diabetes group, comprised 32 children (14 boys) recruited consecutively from the Women’s and Children’s Hospital (WCH) diabetes clinics.

Inclusion criteria were metabolically stable recent-onset Type 1 diabetes with detectable autoantibodies (to glutamic acid decarboxylase, islet antigen 2 or insulin) and aged 2–8 years.

Median (IQR) duration since diagnosis was 5 (3, 13) days.

Exclusion criteria were ketosis, known gastrointestinal pathology or intercurrent infection. All 36 children aged 2–8 years who were diagnosed at the WCH Children’s Diabetes Centre from February 2017 until February 2018 were approached to enter the study, and 32 of 36 (89%) consented to enter the study. (The centre cares for 88% of children with Type 1 diabetes in South Australia). Thirty-two children had ultrasound assessment of pancreatic area and 30 of 32 had FE-1 measurement.

There were two control groups. Control A comprised 90 (44 boys) unrelated healthy children aged 2–8 years who were referred to the WCH imaging department for an elective abdominal ultrasound. Exclusion criteria were a history of acute or chronic disease, gastrointestinal pathology, any intercurrent illness, or a family history of autoimmune disease, including Type 1 diabetes. All had a normal abdominal ultrasound examination. Control B comprised 38 (21 male) healthy children without islet autoantibodies with a first-degree relative with Type 1 diabetes. They provided a stool sample for FE-1 measurement. Eight of the 38 children had a sibling within the study’s Type 1 diabetes group; 30 of 38 had a sibling or parent with Type 1 diabetes, who were followed in the at-risk pregnancy and early life prospective cohort of the environmental determinants of islet autoimmunity (ENDIA) study (9).

Informed written consent was obtained from participants’ parents/guardians and the study was approved by the WCH Human Research Ethics Committee.

Imaging and measurement were performed unblinded by one ultrasonographer (RG) on one ultrasound machine (Phillips iU22 Ultrasound system, C8-5 tightly curved array transducer,

Bothell, WA, USA). Transverse and longitudinal areas of the pancreas were measured by digitalized outline and standardized against the distance from the aorta and the inferior vena cava. Median coefficient of variation (CV) of three transverse area digitalized measurements in each participant was 3.4% ($n = 32$, Type 1 diabetes) and 4.1% ($n = 90$, Control A). FE-1 was measured by enzyme-linked immunosorbent assay (ScheBo Biotech AG, Giessen, Germany; normal range > 200 ug/g, interassay CV, 10.8% on 36 data points). The dynamic range of the assay was 20–500 ug/g. For initial results > 500 ug/g, dilutions of 1 in 5 and 1 in 25 were performed.

<H2>Statistical analysis

Linear regression models compared pancreatic area between Type 1 diabetes and Control A and FE-1 levels between Type 1 diabetes and Control B. Gender, age and (in the case of pancreatic area) body surface area were prespecified as covariates for adjusted models as potential confounders. Adjusted and unadjusted estimates were similar for all outcomes, indicating that there was no substantial confounding due to these variables. FE-1 levels were log-transformed for analysis, with estimates back-transformed from the log scale, therefore representing ratios of geometric means (approximately ratios of medians).

<H1>Results

Distribution of gender was similar across groups, and also for body surface area between Type 1 diabetes and Control A. Median age (IQR) was Type 1 diabetes 5.5 (4.5, 7.3) years; Control A 6.6 (4.7, 7.8) years; Control B 3.6 (2.7, 4.4) years. Control B was younger than Type 1 diabetes.

Pancreatic area was statistically significantly lower in Type 1 diabetes than in Control A in both transverse and longitudinal planes (Table 1, Fig. 1A).

FE-1 levels were lower in Type 1 diabetes than in Control B (Table 1, Fig. 1B). Children with Type 1 diabetes had median FE-1 levels that were 30% (95% CI 20, 45) of those of Control B. In the majority [25/30 (83%)] of Type 1 diabetes children FE-1 levels, although lower, remained within the normal range. No child had symptoms of pancreatic exocrine deficiency. There was no statistically significant relationship between FE-1 and any of the pancreatic size measures.

Discussion

We report for the first time that young children aged 2–8 years with recent-onset Type 1 diabetes have markedly lower levels of FE-1 in conjunction with smaller pancreatic size. Their reduced exocrine function remained within the normal range in the majority and was subclinical, as shown recently in Finnish children (10). Ultrasound examination of the pancreas and FE-1 measurements were performed early after the initiation of insulin therapy when ketones were cleared and the child was metabolically stable; this early timing is relevant as recent MRI findings show that pancreatic volume reduces over the first 12 months after diagnosis in adolescents with Type 1 diabetes (11).

FE-1 levels increase during the first 10 months of life and are stable thereafter (13). Therefore, the fact that the FE-1 controls were younger than the children with Type 1 diabetes would not be expected to significantly reduce the magnitude of the difference in FE-1, as all participants were older than 2 years of age. While it is also possible that as FE-1 controls had a first-degree relative with Type 1 diabetes they may have lower FE-1 levels than unrelated controls, serum trypsinogen is not reduced in adult first-degree relatives without islet autoimmunity (12). However, recent findings that relative pancreatic volume is smaller in adult first-degree relatives, both with and without islet autoimmunity, suggest that

there may be genetic-environmental influences that modify pancreatic growth in early life in at-risk children (12).

The strengths of our study are the young ages of the children in comparison with other studies, there being one ultrasonographer for all images, and the consistent timing of the investigation of the recent-onset group. Limitations are the need for two separate control groups for pancreatic size and faecal elastase. Further, the ultrasonographer could not be blinded as to whether each child had Type 1 diabetes or not.

Our findings prompt the important question as to when pancreatic size and FE-1 levels decline in young children progressing to Type 1 diabetes? If FE-1 levels fall before or in parallel to the fall in beta cell function they could prove an important biomarker in the progression to Type 1 diabetes. Early life cohorts that follow at-risk children are well positioned to determine whether pancreatic exocrine function falls before, during or after the development of islet autoimmunity.

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Competing interests

The authors declare no conflicts of interest.

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TABLE 1 Pancreatic area and faecal elastase-1 levels in Type 1 diabetes and controls

Outcome measure	Type 1 diabetes	Unrelated controls	Adjusted ^c estimate (95% CI)	Adjusted <i>P</i>	Controls with a first degree relative with Type 1 diabetes	<i>P</i>
n	32	90			38	
Age (years)	5.5 (4.5, 7.3) ^b	6.6 (4.7, 7.8)			3.6 (2.7, 4.4)	
Transverse pancreatic area (cm ²)	6.82 (1.61) ^a	8.31 (1.74)	-1.45 (-2.12, -0.79)	<0.001		
Longitudinal pancreatic area (cm ²)	1.28 (0.44)	1.55 (0.43)	-0.27 (-0.45, -0.09)	0.003		
Faecal elastase-1 (ug/g)	455 (323, 833) ^b				1408 (1031, 1989)	< 0.001

^amean (SD), ^bmedian (interquartile range), ^cadjusted for gender, age and body surface area. Faecal elastase levels were log-transformed for analysis, but estimates (differences in log faecal elastase) were back-transformed to the original scale, yielding ratios of geometric means, which approximate ratios of medians.

FIGURE 1 (A) The dots represent the distribution of transverse and longitudinal pancreatic areas in Type 1 diabetes and 90 (44 boys) unrelated healthy children. (B) The dots represent the distribution of faecal elastase-1 levels in Type 1 diabetes and 38 (21 boys) healthy children with a first degree relative with Type 1 diabetes



