Reduced Pancreatic Volume in Hepatocyte Nuclear Factor 1A-Maturity-Onset Diabetes of the Young

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Context: There are interplays between the endocrine and exocrine pancreas. We recently reported an increased frequency of exocrine dysfunction in HNF1A-maturity-onset diabetes of the young (MODY3) patients, compared with controls. Reduced pancreatic volume is seen in HNF1B-MODY (MODY5) and diabetes types 1 and 2.

Objective: The aim of this study was to investigate whether HNF1A mutation carriers have reduced pancreatic volume or abnormal pancreatic structure and whether any changes are associated with exocrine dysfunction.

Methods: Fifteen HNF1A mutation carriers recruited from the Norwegian MODY Registry, 31 subjects with type 1 diabetes, 10 subjects with type 2 diabetes, and 11 controls underwent computed tomography of the pancreas. We measured pancreatic volume and X-ray attenuation. Pancreatic volume index was defined as pancreatic volume divided by body surface area.

Results: Pancreatic volume index was reduced in subjects with HNF1A-MODY (34.5 ml/m$^2$; $P = 0.02$) and type 1 diabetes (21.4 ml/m$^2$; $P < 0.001$) as compared with nondiabetic controls (45.7 ml/m$^2$), and was reduced in subjects with diabetes in combination with fecal elastase deficiency ($P = 0.03$). Subjects with type 1 diabetes had smaller pancreatic volume index, compared with HNF1A mutation carriers ($P < 0.001$). Reduced pancreatic volume index was associated with increasing duration of diabetes. Pancreatic X-ray attenuation in HNF1A mutation carriers was not significantly different from that of nondiabetic controls.

Conclusions: HNF1A mutation carriers have reduced pancreatic volume but less reduced than in patients with type 1 diabetes. Insulinopenia could explain both the pancreatic volume reduction and the associated pancreatic dysfunction. (J Clin Endocrinol Metab 93: 3505–3509, 2008)

Abbreviations: BMI, Body mass index; CEL, carboxyl-ester lipase gene; CT, computed tomography; HU, Hounsfield Units; MODY, maturity-onset diabetes of the young.
ilar to those reported for HNF1B-MODY might be suspected. We therefore aimed to study pancreatic structure and its relation to exocrine function in HNF1A-MODY and to make a comparison with type 1 and type 2 diabetes subjects as well as normal controls.

Subjects and Methods

Subjects

We invited all adult HNF1A mutation carriers in the Norwegian MODY Registry and subjects with types 1 and 2 diabetes recruited consecutively from an outpatient diabetes clinic to test for pancreatic exocrine dysfunction. The clinical characteristics of the study subjects are described in Table 1. Subjects diagnosed with exocrine dysfunction, were compared with subjects of the same diabetes subtype but with normal exocrine function. There was no significant difference in age, at examination, body mass index (BMI) or body surface area between the groups. All subjects were investigated with computed tomography (CT) of the pancreas by a standardized protocol. From a CT archive, we included controls without known diabetes or pancreatic disease that were matched for age, sex, and body surface area.

The study was approved by the Regional Committee for Research Ethics and the Norwegian Data Inspectorate and performed according to the Helsinki Declaration. We obtained written informed consent from all participants.

Measurement of pancreatic volume and x-ray attenuation

For the radiological study, helical CT (Light Speed Ultra; GE, Milwaukee, WI) of the pancreas (5 mm collimation, 5 mm reconstruction increment) was performed with and without contrast. Some examinations performed at local hospitals had slightly modified scan parameters. A radiologist (I.S.H.) traced the contour of the pancreas on contrast series on every slice to estimate the pancreatic volume as previously described (4). Pancreatic attenuation on contrast series in the encircled areas were used to calculate average x-ray attenuation measured in Hounsfield Units (HU) values equalling −1000 in air, −100 in fat, 0 in water, and +1000 in bone. To control the volume of influence on the pancreas, the pancreatic volume index was calculated by dividing pancreatic volume by body surface area (6) as calculated by the formula of DuBois (13).

Definition of pancreatic exocrine dysfunction

Fecal elastase-1 was determined by ELISA using a kit specific for human elastase-1 (ScheBo-Tech GmbH, Wettenberg-Giessen, Germany). Pancreatic exocrine dysfunction was defined as fecal elastase deficiency, i.e. fecal elastase levels less than 200 μg/g in two consecutive tests. Seventy-two hour stool samples were collected as previously described (12), and fecal fat was quantified according to van de Kamer et al. (14), considering 7 g or less of fat per 24 h normal.

Statistics

Results for continuous variables are given as mean (SD). We used one-way ANOVA for global assessment and two-tailed, unpaired Student’s t tests in the subgroup analyses for comparison of clinical characteristics and for comparison of pancreatic volume index and x-ray attenuation between HNF1A mutation carriers and each control group. We chose a significance level of 5% but 1% in the case of multiple testing. Associations between pancreatic volume index and attenuation, respectively, with age, BMI, duration of diabetes, fecal elastase level (continuous), and fecal elastase deficiency status (defined as a discrete variable: fecal elastase more or less than 200 μg/g), respectively, were computed by univariate or multivariate linear regression (supplementary data, published as supplemental data on The Endocrine Society’s Journals Online site at http://jcem.endojournals.org). In the multiple regression analyses, age and the significant variables from the univariate analyses were included. All data were analyzed using Stata 8.0 (Stata Statistical Software, Stata Corp., College Station, TX).

Results

By CT, none of the patients with exocrine dysfunction displayed dilatation of the pancreatic duct, calcifications, or pseudocysts, which are frequently identified in chronic pancreatitis. Clinical characteristics are given in Table 1.

Pancreatic volume

The global assessment by ANOVA showed significant variance for the pancreatic volume index (P = 0.00001; F = 18.98, 3 df). Mean pancreatic volume index was reduced in HNF1A mutation carriers (34.3 ml/m² ± 9.9) as well as type 1 diabetes patients (21.4 ml/m² ± 7.4), compared with nondiabetic controls (45.7 ml/m² ± 11.8; P = 0.007 and <0.001, respectively), whereas for type 2 diabetes patients, no significant reduction in pancreatic volume index was seen (36.9 ml/m² ± 13.2; Fig. 1A). Type 1 diabetes subjects had smaller pancreatic volume index, compared with HNF1A mutation carriers (P < 0.001). Further-

### Table 1. Characteristics of the study subjects

<table>
<thead>
<tr>
<th></th>
<th>MODY3</th>
<th>Nondiabetic controls</th>
<th>P&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Type 1 diabetes</th>
<th>P&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Type 2 diabetes</th>
<th>P&lt;sup&gt;b&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>n</td>
<td>15</td>
<td>11</td>
<td></td>
<td>31</td>
<td></td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Ages, n (%)</td>
<td>7 (47)</td>
<td>7 (64)</td>
<td>ns</td>
<td>24 (77)</td>
<td>ns</td>
<td>8 (80)</td>
<td></td>
</tr>
<tr>
<td>Age at examination (yr)</td>
<td>51 ± 13</td>
<td>51 ± 10</td>
<td>ns</td>
<td>52 ± 12</td>
<td>ns</td>
<td>60 ± 11</td>
<td>ns</td>
</tr>
<tr>
<td>Age at onset of diabetes (yr)</td>
<td>24 ± 9</td>
<td>NA</td>
<td>ns</td>
<td>22 ± 13</td>
<td>ns</td>
<td>48 ± 10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of diabetes (yr)</td>
<td>28 ± 13</td>
<td>NA</td>
<td>ns</td>
<td>31 ± 15</td>
<td>ns</td>
<td>12 ± 6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25 ± 3</td>
<td>26 ± 4</td>
<td>ns</td>
<td>26 ± 3</td>
<td>ns</td>
<td>27 ± 2</td>
<td>ns</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.9 ± 0.1</td>
<td>1.9 ± 0.3</td>
<td>ns</td>
<td>2.0 ± 0.2</td>
<td>ns</td>
<td>2.0 ± 0.1</td>
<td>ns</td>
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<tr>
<td>Fecal elastase deficiency, n (%)</td>
<td>5 (33)</td>
<td>NI</td>
<td>15 (48)</td>
<td>5 (50)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Fecal fat excretion (g/d) (&lt; 7)</td>
<td>14 ± 7</td>
<td>NI</td>
<td>12 ± 5</td>
<td>9 ± 6</td>
<td>ns</td>
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<td></td>
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<td>Fecal fat excretion greater than 7 g/d, n</td>
<td>6 of 6</td>
<td>NI</td>
<td>14 of 17</td>
<td>1 of 3</td>
<td>ns</td>
<td></td>
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</tr>
</tbody>
</table>

Data are means ± sd. The P values represent two-sample Student’s t tests comparing MODY3 and P<sup>a</sup> (nondiabetic controls), P<sup>b</sup> (type 1 diabetes subjects), and P<sup>b</sup> (type 2 diabetes subjects), respectively. NA, Not applicable; NI, not investigated; ns, not significant.

<sup>a</sup> Fecal fat excretion was measured in six MODY3, 17 type 1 diabetes, and three type 2 diabetes subjects.
more, diabetes duration was inversely associated with pancreatic volume index in all diabetes patients \(P = 0.001, \beta = -0.37 \) \((-0.58, -0.17), R^2 = 0.2\), and this was also found in a subgroup analysis of \(HNF1A\) mutation carriers \(P = 0.004, \beta = -0.53 \) \((-0.86, -0.20), R^2 = 0.48\), whereas there was no association between pancreatic volume index and current age or BMI. Pancreatic volume index was associated with fecal elastase deficiency in subjects with diabetes of any type \(P = 0.03; \beta = -6.86 \) \((-13.0, -0.72), R^2 = 0.09\); however, no such association was observed within any diabetes subgroup. In the multivariate analysis, pancreatic volume index was significantly higher in \(HNF1A\) mutation carriers than in type 1 diabetes subjects after adjusting for age, diabetes duration, and fecal elastase deficiency \(P < 0.001, \beta = -11.86 \) \((-16.91, -6.81), R^2 = 0.49\).

### Pancreatic x-ray attenuation

The global assessment by ANOVA showed significant variance for the mean pancreatic x-ray attenuation \(P = 0.007; F = 4.37, 3 df\). The mean pancreatic x-ray attenuation in \(HNF1A\) mutation carriers \((81.1 \pm 19.4 \text{ HU})\) was not statistically different from nondiabetic controls \((66.0 \pm 23.6 \text{ HU}, P = 0.09; \text{Fig. } 1, \text{ B and C})\). Interestingly, the attenuation was significantly increased in type 1 diabetes patients \((84.4 \pm 21.9 \text{ HU})\), compared with nondiabetic controls \((P = 0.02)\), whereas subjects with type 2 diabetes had attenuation similar to nondiabetic controls \((60.1 \pm 21.4 \text{ HU})\). Fecal elastase deficiency was not associated with pancreatic attenuation. Pancreatic attenuation was significantly and inversely associated with age \(P = 0.04, \beta = -0.50 \) \((-0.97, 0.03), R^2 = 0.06\) and BMI \(P < 0.001, \beta = -3.27 \) \((-5.20, -1.19), R^2 = 0.20\) in the uni-
Discussion

To our knowledge, this is the first study on pancreatic size and structure in HNF1A-MODY. We found that HNF1A as well as type 1 diabetes patients had significantly reduced pancreatic volume index, compared with nondiabetic controls. Our results for types 1 and 2 diabetes are consistent with previous reports (6, 15, 16). Subjects with type 1 diabetes had smaller pancreatic volume index than HNF1A mutation carriers, and this reduction remained significant after adjusting for age, diabetes duration, and fecal elastase deficiency. Reduced pancreatic volume index was associated with diabetes duration in agreement with some (8) but not all (6, 7) previous studies. Reduced insulinotropic effects on the acinar cells is a possible mechanism for the reduction in pancreatic volume (10, 11), and reports show association of small pancreatic volume with insulin use (8) or reduced insulin secretion (7). This is in line with our data because type 1 diabetes patients generally have the most pronounced endogenous insulinopenia.

Subjects with fecal elastase deficiency had a significant reduction in pancreatic volume index, in accordance with a recent report showing an association between pancreatic volume index and the exocrine pancreatic function marker serum immunoreactive trypsin (6). Both the reduced pancreatic volume and reduced pancreatic exocrine function observed in our patients may be due to local paracrine effects of insulinopenia (10). The more severe insulin deficiency observed in type 1 diabetes probably explains the greater pancreatic volume reduction compared with HNF1A-MODY. We cannot, however, rule out the possibility that primary exocrine disease is involved in the pancreatic volume reduction.

A recent study reported higher pancreatic fat content in type 2 diabetic compared with nondiabetic men and a negative correlation of pancreatic fat with β-cell function (17), whereas others found no increase in pancreatic fat in type 2 diabetes (16). Interestingly, we experienced that pancreatic x-ray attenuation adjusted for age and BMI was significantly increased in subjects with type 1 diabetes and observed the same tendency in HNF1A mutation carriers. In contrast, type 2 diabetes patients had pancreatic x-ray attenuation similar to controls. We further found that pancreatic x-ray attenuation decreased with increasing BMI, confirming previous findings of strong correlation within BMI and fat content in the pancreas (16, 18). The observed differences between diabetes subtypes may be due to differences in insulin secretion, which has been reported to be directly associated with pancreatic fat content (18).

Pancreatic lipomatosis is an early structural marker of pancreatic exocrine disease in CEL mutation carriers preceding development of diabetes (5). Fatty replacement of the pancreas has also been observed in cystic fibrosis and Johansson-Blizzard syndrome, two monogenic conditions with primary affection of the exocrine pancreas and frequent development of secondary diabetes (19, 20). We did not find any association of pancreatic x-ray attenuation with fecal elastase in HNF1A mutation carriers. This suggests a different pathophysiological mechanism for the development of pancreatic changes in HNF1A-MODY.

In conclusion, the pancreatic volume index was reduced in HNF1A-MODY, compared with nondiabetic controls, but less than in type 1 diabetes. A striking pancreatic atrophy such as in HNF1B MODY was not observed. Although HNF1A and HNF1B are closely related and interact in the transcriptional network, HNF1A clearly has less pronounced effect on pancreas volume and structure than HNF1B (1, 2, 21). Our data support the notion that insulinopenia is the main factor determining the reduction in pancreatic volume in HNF1A-MODY as well as in type 1 diabetes, whereas in HNF1B-MODY a developmental effect is likely to be involved. Insulinopenia probably also explains the pancreatic exocrine dysfunction associated with pancreatic volume reduction, but further studies, particularly of nondiabetic HNF1A mutation carriers, would be helpful to evaluate a possible primary role of the exocrine pancreas.

Acknowledgments

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References