Familiality of metabolic abnormalities is dependent on age at onset and phenotype of the type 2 diabetic proband


Familiality of metabolic abnormalities is dependent on age at onset and phenotype of the type 2 diabetic proband. Am J Physiol Endocrinol Metab 285: E1297–E1303, 2003. First published September 3, 2003; 10.1152/ajpendo.00113.2003.—To determine the impact of a family history of diabetes on anthropometric and metabolic traits in glucose-tolerant relatives of type 2 diabetic patients, we studied 2,100 first-degree relatives of patients with the common form of type 2 diabetes (FH+) and 388 subjects without a family history of diabetes (FH−). All subjects participated in an oral glucose tolerance test to evaluate measurement of insulin secretion [30-min incremental insulin/glucose (I/G 30)] and insulin sensitivity [homeostasis model assessment (HOMA) of insulin resistance (IR)]. A subset participated in a euglycemic clamp (n = 75) and an intravenous glucose tolerance test (n = 300). To study the effect of a particular phenotype of the proband, insulin secretion and sensitivity were also compared between first-degree relatives of diabetic probands with high and low waist-to-hip ratio (WHR) and probands with early and late onset of diabetes. FH+ subjects were more insulin resistant, as seen from a higher HOMA-IR index (P = 0.006) and a lower rate of insulin-stimulated glucose uptake (P = 0.001) and had more features of the metabolic syndrome (P = 0.02, P = 0.0002) compared with FH− subjects. Insulin secretion adjusted for insulin resistance (disposition index, DI) was also lower in the FH+ vs. FH− subjects (P = 0.04). Relatives of diabetic probands with a high WHR had reduced insulin-mediated glucose uptake compared with relatives of probands with a low WHR (P = 0.04). Relatives of diabetic patients with age at onset <44 yr had higher HOMA IR (P < 0.005) and lower DI (P < 0.005) than relatives of patients with age at onset >56 yr (highest quartile). We conclude that early age at onset of type 2 diabetes and abdominal obesity have a significant influence on the metabolic phenotype in the nondiabetic first-degree relative.

insulin secretion; insulin sensitivity; metabolic syndrome; genetics of type 2 diabetes

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insulin sensitivity and 2) whether the phenotype of the diabetic proband is reflected in the phenotype of the nondiabetic relative.

METHODS

The Botnia study was established in 1990 on the Western coast of Finland and later extended to other parts of Finland and Sweden (9). To date, ~9,000 subjects, patients with type 2 diabetes and their family members, have been studied. The subjects belonged to 1,342 nuclear families, with normoglycemic (FH+) individuals in each family averaging 1.5. For the present study, we excluded all subjects with glutamic acid dehydrogenase (GADA) > 5 relative units and those from families with MODY or both type 1 and type 2 diabetes. All other normoglycemic (plasma glucose concentration < 6.1 mmol/l at fasting and < 7.8 mmol/l 2 h after an oral glucose tolerance test) relatives (n = 2,100) and control subjects without a family history of diabetes (n = 388) were included in the study.

To study the influence of the specific phenotype of the proband on the metabolic phenotype of the relative, diabetic probands (n = 516) were grouped by their WHR and the age of onset of diabetes.

We thereby identified 399 first-degree relatives of diabetic subjects with low WHR (1st quartile, males: < 0.95 and females: < 0.84) and 396 relatives with high WHR (4th quartile, males: > 1.02 and females: > 0.95). Likewise, the numbers of first-degree relatives of diabetic subjects with early (1st quartile, < 44 yr) and late (4th quartile, > 65 yr) age of diabetes onset were 310 and 355, respectively.

Body weight and height were measured with subjects in light clothing without shoes. Fat-free mass (FFM) was measured with infrared spectroscopy from the outer layer of the biceps on the dominant arm with a Futrex-5000 device (Futrex, Gaithersburg, MD). The coefficient of variation (CV) of repeated measurements by the same investigator was < 1%.

Waist circumference was measured with a soft tape on standing subjects midway between the lower rib and iliac crest. Hip circumference was measured with the widest part of the gluteal region, and WHR as a measure of central obesity was accordingly calculated. Three blood pressure recordings were obtained from the right arm of each seated person at 5-min intervals after 30 min of rest, and the mean values were calculated. Fasting blood samples were drawn for the measurement of GADA, serum total cholesterol, HDLc and LDLc cholesterol, triglyceride, and free fatty acid (FFA) concentrations.

All subjects participated in an oral glucose tolerance test (OGTT) by ingesting 75 g of glucose in a volume of 300 ml (Glucodyn; Leiras, Turku, Finland) after a 12-h overnight fast. Samples for the measurement of glucose and insulin were drawn at -10, 0, 30, 60, and 120 min. Several indexes of insulin sensitivity and insulin secretion were calculated from the OGTT. The homeostasis model assessment (HOMA) of insulin resistance (IR) index was calculated by using the fasting plasma glucose and insulin concentrations (19).

As measures of insulin secretion we used the incremental 30-min insulin response (I30), as well as the ratio of 30-min insulin and glucose during the OGTT (I/G30) (12). As a surrogate of the disposition index (DI), we considered the product of insulin sensitivity (1/HOMA) and insulin secretion (I/G30) (14, 27).

Insulin action was also measured in a subset of subjects by a hyperinsulinemic euglycemic clamp. Subjects in different subgroups in which euglycemic clamps were performed numbered 54 for FH+ and 21 for FH−. After a priming dose of insulin, an infusion (infusion rate 45 mU/m2) of short-acting human insulin (Actrapid; Novo Nordisk, Bagsvaerd, Denmark) was started and continued until 120 min. Blood samples for the measurement of blood glucose were obtained at 5-min intervals throughout the clamp. A variable glucose infusion of 20% glucose was started to maintain blood glucose concentration unchanged at 5.5 mmol/l, with a CV of 6%. Insulin sensitivity was calculated from the glucose infusion rates during the last 60 min of the euglycemic clamp (M value) and expressed as glucose uptake per lean body mass.

A subset of subjects underwent an intravenous glucose tolerance test (IVGTT; n = 300: FH+ = 278, FH− = 22). Briefly, 0.3 g/kg body weight of a 50% glucose solution was given at time 0. Blood samples for the measurement of insulin and blood glucose were obtained at -10, 0, 2, 4, 6, 8, 10, 20, 40, 50, and 60 min. The first-phase insulin response (FPIR) was calculated as the incremental insulin response during the first 10 min of the study. To quantify the relation between insulin secretion and insulin sensitivity, we measured the DI (3, 15), the product of insulin sensitivity (M value) and insulin secretion (FPIR).

Assays. Plasma glucose during the clamp was measured with a glucose oxidation method by use of a Beckman Glucose Analyzer II (Beckman Instruments, Fullerton, CA). Serum insulin concentrations were measured with a specific radioimmunoassay (Pharmacia, Uppsala, Sweden), with an interassay CV of 5%. Serum C-peptide concentrations were measured with radioimmunoassay (Linco Research, St. Charles, MO) with an interassay CV of 9%. FFA were measured by an enzymatic colorimetric method (Wako Chemicals, Neuss, Germany). Serum total cholesterol, HDL subfractions (after precipitation), and triglyceride concentrations were measured on a Cobas Mira analyzer (Hoffman-La Roche, Basel, Switzerland). GAD65 antibodies were determined by a modified radiobinding assay employing 35S-labeled recombinant human GAD65 (10a). Screening for MODY mutations was carried out as described earlier (15a).

Statistical analysis. All data are expressed as means ± SE. The significance of difference between groups was tested with Student’s t-test and Mann-Whitney’s test when applicable. The average number of individuals from each family was 1.5, with a range from 1 to 6 members in a family. Therefore, the subjects did not completely represent independent observations. To avoid this problem, we reanalyzed the data by using weighted family-specific means from different families for all variables that showed a significant difference in the first analysis. While comparing relatives of diabetic subjects from different phenotypes, we also analyzed the data by limiting...
individuals to one from each family. Measured variables were log transformed when they were not normally distributed. Computation was performed using the NCSS statistical package (Statistical Solutions, Cork, Ireland). Spearman’s correlations were used for univariate correlation between the variables, and least square regression analysis was carried out to test differences in slopes from the regressions.

RESULTS

Comparison between subjects with (FH+) and without (FH−) a family history of the common form of type 2 diabetes. Despite similar FFM, FH+ subjects had a higher WHR than the FH− subjects (P = 0.0001; Table 1). The difference remained significant even after adjustment for the difference in body mass index (BMI; P = 0.002). Systolic blood pressure (P = 0.009) and triglyceride concentrations were higher (P = 0.02), and HDL (P = 0.02), particularly the HDL2 (P = 0.0002) concentrations, were lower in the FH+ compared with the FH− subjects. There was no difference in age or BMI between FH+ and FH− subjects who had a euglycemic clamp (n = 75) or the IVGTT (n = 300).

Insulin sensitivity. FH+ subjects were more insulin resistant, as reflected by higher fasting insulin (P = 0.03) and higher HOMA (P = 0.006) values compared with FH− subjects. This was further supported by a reduced rate of glucose uptake (8.11 ± 0.34 vs. 10.3 ± 0.5 mg·FFM kg⁻¹·min⁻¹, P = 0.001) in FH+ compared with FH− subjects. The insulin area under the OGTT curve adjusted for glucose was also higher in the FH+ than in the FH− subjects (P = 0.04), suggesting impaired insulin action.

Insulin secretion. There was no difference in insulin secretion measured as FPIR between FH+ and FH− groups (250 ± 35 vs. 258 ± 10 mU·l⁻¹·10⁻¹·min⁻¹, P = 0.004), suggesting im paired insulin action.

Comparison of clinical and metabolic characteristics between relatives of type 2 diabetic probands with high and low WHR and early and late age of onset of diabetes. The probands were divided into quartiles of WHR and age of onset of diabetes. The relatives of diabetic subjects with high WHR had higher BMI (P < 0.005), and the females had higher WHR compared with relatives of probands with a low WHR (Table 2). The relatives of probands with a high WHR were more insulin resistant, as manifested by a lower rate of insulin-stimulated glucose uptake (8.1 ± 0.6 vs. 10.6 ± 0.7, P = 0.02) and higher lnHOMA IR (0.40 ± 0.02 vs. 0.48 ± 0.02, P = 0.02) compared with relatives of probands from the lowest WHR quartile (Table 2). In addition, they had higher total cholesterol and triglyceride concentrations than relatives of probands with low WHR. The waist circumference in relatives of probands with high (r = 0.526, P < 0.005) and low WHR

Table 1. Clinical characteristics of, and insulin secretion and sensitivity in, all subjects with and without a family history of the common form of type 2 diabetes

<table>
<thead>
<tr>
<th>Variable</th>
<th>FH+</th>
<th>FH−</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n, M/F%</td>
<td>2100</td>
<td>388</td>
<td>0.0001</td>
</tr>
<tr>
<td>Age, yr</td>
<td>46.0 ± 0.3</td>
<td>45.9 ± 0.6</td>
<td>0.01</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.6 ± 0.08</td>
<td>25.1 ± 0.2</td>
<td>0.002</td>
</tr>
<tr>
<td>FFM, kg</td>
<td>54.1 ± 0.3</td>
<td>53.3 ± 0.6</td>
<td>0.002</td>
</tr>
<tr>
<td>WHR</td>
<td>0.88 ± 0.002</td>
<td>0.86 ± 0.004</td>
<td>0.0002</td>
</tr>
<tr>
<td>BP, mmHg</td>
<td>128 ± 0.4</td>
<td>125 ± 0.8</td>
<td>0.009</td>
</tr>
<tr>
<td>Plasma glucose, mmol/l</td>
<td>78.3 ± 0.2</td>
<td>77.4 ± 0.5</td>
<td>0.0002</td>
</tr>
<tr>
<td>Fasting</td>
<td>5.3 ± 0.6</td>
<td>5.3 ± 0.2</td>
<td>0.0001</td>
</tr>
<tr>
<td>Fasting C-peptide, nmol/l</td>
<td>0.47 ± 0.009 (938)</td>
<td>0.43 ± 0.002 (130)</td>
<td>0.001</td>
</tr>
<tr>
<td>Insulin area, uM·l⁻¹·120 min</td>
<td>4,623 ± 67</td>
<td>4,337 ± 126</td>
<td>0.04</td>
</tr>
<tr>
<td>Glucose uptake, mg·FFM kg⁻¹·min⁻¹</td>
<td>8.1 ± 0.34 (54)</td>
<td>10.3 ± 0.5 (21)</td>
<td>0.001</td>
</tr>
<tr>
<td>lnHOMA IR</td>
<td>0.19 ± 0.004</td>
<td>0.16 ± 0.004</td>
<td>0.006</td>
</tr>
<tr>
<td>I/G30, mU·mmol</td>
<td>21.6 ± 1.1</td>
<td>22.2 ± 3.8</td>
<td>0.04</td>
</tr>
<tr>
<td>ln(I/G30)/HOMA</td>
<td>0.99 ± 0.007</td>
<td>1.04 ± 0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>FPIR</td>
<td>258 ± 10.2 (278)</td>
<td>250 ± 34.9 (22)</td>
<td>0.04</td>
</tr>
<tr>
<td>DI</td>
<td>1,805 ± 155 (34)</td>
<td>2,715 ± 422 (14)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, nos. of subjects, with nos. in parentheses representing individuals with available data. FH+ and FH−, subjects with and without a family history of diabetes; BMI, body mass index; WHR, waist-to-hip ratio; BP, blood pressure; FFA, free fatty acids; FFM, fat-free mass; I30, incremental insulin response during 30 min of an oral glucose tolerance test (OGTT); I/G30, ratio of insulin and glucose during OGTT; HOMA, homeostasis model assessment; IR, insulin resistance; FPIR, first-phase insulin response; DI, disposition index. *Data corrected for sex and BMI; †data corrected for glucose area.
The present study adds several pieces of new information regarding familiarity of insulin secretion and insulin sensitivity. Insulin resistance was a predominant feature of FH+ subjects, particularly if the proband had abdominal obesity or early onset of diabetes. The presence of insulin resistance was further supported by the occurrence of features of the metabolic syndrome, including high WWH, blood pressure, and

DISCUSSION

The present study adds several pieces of new information regarding familiarity of insulin secretion and insulin sensitivity. Insulin resistance was a predominant feature of FH+ subjects, particularly if the proband had abdominal obesity or early onset of diabetes. The presence of insulin resistance was further supported by the occurrence of features of the metabolic syndrome, including high WWH, blood pressure, and

DISCUSSION

The present study adds several pieces of new information regarding familiarity of insulin secretion and insulin sensitivity. Insulin resistance was a predominant feature of FH+ subjects, particularly if the proband had abdominal obesity or early onset of diabetes. The presence of insulin resistance was further supported by the occurrence of features of the metabolic syndrome, including high WWH, blood pressure, and

Fig. 1. Relationship between waist circumference (waist; x-axis) and insulin resistance (IR) described by the homeostasis model assessment (HOMA) in relatives of diabetic subjects with a high waist-to-hip ratio (WHR; solid line) and relatives of diabetic subjects with a low WHR. Note difference between the 2 regression lines: unbroken line, relatives of probands with high WHR; broken line, relatives of probands with low WHR. $P = 0.0002$.
triglycerides and low HDL cholesterol concentrations in FH+ subjects.

Impairment in insulin action has been reported in nondiabetic relatives of patients with diabetes (6, 11, 13, 34). On the other hand, there have been conflicting reports regarding the impact of a family history of diabetes on insulin secretion (1, 18, 21, 24). Compared with these earlier studies, the present study is unique in several aspects. First, we have a truly homogeneous population of a large number of individuals without confounding factors affecting pancreatic β-cell function, like the presence of GAD antibodies or known MODY mutations. Second, we have included only subjects with normal glucose tolerance. Third, insulin secretion has been adjusted for the degree of glycemia and insulin sensitivity. Fourth, we have also taken into account the possible heterogeneity in the phenotype of the diabetic probands.

Insulin sensitivity was clearly impaired in FH+ subjects, reflected by lower insulin-stimulated glucose uptake and higher HOMA IR. Also, insulin secretion (FPIR) adjusted for insulin sensitivity (M value) was reduced, suggesting that the FH+ subjects were not able to compensate for their degree of insulin resistance. This measure (DI) is an important test of the degree of metabolic derangement, because subjects with low DI have been shown to have an increased risk of developing future diabetes (36).

A key finding was also that relatives of diabetic probands with abdominal obesity were more insulin resistant and showed more features of the metabolic syndrome than relatives of nonobese probands. Interestingly, in siblings of probands with high WHR, a small increase in abdominal obesity had a greater impact on insulin resistance than in siblings of probands with low WHR. Several studies have shown that measures of abdominal obesity show strong heritabil-

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**Table 3. Clinical characteristics of, and measures of insulin secretion and sensitivity in, normoglycemic first-degree relatives of probands with early and late onset of diabetes**

<table>
<thead>
<tr>
<th>Status of Relative</th>
<th>Status of Proband Age of Onset of Diabetes</th>
<th>Early (&lt;44 yr)</th>
<th>Late (&gt;65 yr)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n, (M/F)</td>
<td>Early (&lt;44 yr)</td>
<td>310 (131/179)</td>
<td>353 (120/233)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Age, yr</td>
<td>Early (&lt;44 yr)</td>
<td>42.9 ± 0.8</td>
<td>48.3 ± 0.7</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>Early (&lt;44 yr)</td>
<td>25.4 ± 0.2</td>
<td>25.4 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>LBM, kg</td>
<td>Early (&lt;44 yr)</td>
<td>55.1 ± 0.8</td>
<td>54.5 ± 0.6</td>
<td></td>
</tr>
<tr>
<td>WHR</td>
<td>Male</td>
<td>0.88 ± 0.009</td>
<td>0.89 ± 0.008</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>0.88 ± 0.006</td>
<td>0.87 ± 0.005</td>
<td></td>
</tr>
<tr>
<td>BP, mmHg</td>
<td>Systolic</td>
<td>128 ± 1.0</td>
<td>130 ± 0.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diastolic</td>
<td>78 ± 0.6</td>
<td>80 ± 0.5</td>
<td></td>
</tr>
<tr>
<td>Plasma glucose, mmol/l</td>
<td>Fasting</td>
<td>5.31 ± 0.02</td>
<td>5.37 ± 0.02</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 h</td>
<td>5.74 ± 0.06</td>
<td>5.76 ± 0.06</td>
<td></td>
</tr>
<tr>
<td>FFA, μmol/l</td>
<td>Early (&lt;44 yr)</td>
<td>652 ± 38 (34)</td>
<td>647 ± 25 (65)</td>
<td></td>
</tr>
<tr>
<td>Triglycerides, mmol/l</td>
<td>Early (&lt;44 yr)</td>
<td>1.21 ± 0.002</td>
<td>1.21 ± 0.009</td>
<td></td>
</tr>
<tr>
<td>Cholesterol, mmol/l</td>
<td>Early (&lt;44 yr)</td>
<td>5.26 ± 0.06</td>
<td>5.41 ± 0.07</td>
<td></td>
</tr>
<tr>
<td>Cholesterol, mmol/l</td>
<td>Early (&lt;44 yr)</td>
<td>5.26 ± 0.06</td>
<td>5.41 ± 0.07</td>
<td></td>
</tr>
<tr>
<td>HDL</td>
<td>Early (&lt;44 yr)</td>
<td>1.33 ± 0.001</td>
<td>1.42 ± 0.001</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>HDL₄</td>
<td>Early (&lt;44 yr)</td>
<td>0.47 ± 0.001</td>
<td>0.52 ± 0.001</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>HDL₃</td>
<td>Early (&lt;44 yr)</td>
<td>0.84 ± 0.001</td>
<td>0.90 ± 0.001</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Fasting insulin, mU/l</td>
<td>Early (&lt;44 yr)</td>
<td>7.8 ± 0.2</td>
<td>6.6 ± 0.2</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Insulin area, mU·l⁻¹·min⁻¹</td>
<td>Early (&lt;44 yr)</td>
<td>4,367 ± 176</td>
<td>4,758 ± 157</td>
<td></td>
</tr>
<tr>
<td>Glucose uptake, mg·kcal⁻¹·min⁻¹</td>
<td>Early (&lt;44 yr)</td>
<td>9.3 ± 1.2 (13)</td>
<td>9.6 ± 0.7 (25)</td>
<td></td>
</tr>
<tr>
<td>lnHOMA IR*</td>
<td>Early (&lt;44 yr)</td>
<td>0.48 ± 0.02</td>
<td>0.37 ± 0.02</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>ln(G30/mmol)</td>
<td>Early (&lt;44 yr)</td>
<td>1.15 ± 0.02</td>
<td>1.24 ± 0.02</td>
<td>0.001</td>
</tr>
<tr>
<td>ln(ln(G30/HOMA)*)</td>
<td>Early (&lt;44 yr)</td>
<td>0.94 ± 0.01</td>
<td>1.08 ± 0.01</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>FPIR</td>
<td>Early (&lt;44 yr)</td>
<td>301 ± 24 (21)</td>
<td>315 ± 23.1 (74)</td>
<td></td>
</tr>
<tr>
<td>DI</td>
<td>Early (&lt;44 yr)</td>
<td>2,572 ± 420 (12)</td>
<td>2,343 ± 433 (14)</td>
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</tr>
</tbody>
</table>

Values are means ± SE. Nos. in parentheses, nos. of individuals with available data. *Data corrected for age.

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Fig. 2. Insulin sensitivity (lnHOMA IR) and disposition index (U/G30/HOMA IR) in relatives of probands with early (solid bars) and late onset (open bars) of diabetes mellitus.
phenotype characterized by abdominal obesity, as this study further emphasizes the value of stratifying for a bands with early- but not of late-onset diabetes. The selected for genetic studies, because the metabolic phe-
portance of age at diabetes onset when patients are 
tained, this is not due to admixture of patients with 
greater degree of familiality than in relatives of type 2 
evations in the Pima Indians, where the offspring of 
onset diabetes. Our results agree with similar obser-
ing data suggest not only that the probands with 
duced/H9252 
evance, whereas genetic factors are more 
greater recurrence risk of diabetes in relatives of nonobese than obese type 2 diabetic patients 
ed 
CREASED insulin concentrations in nondiabetic 
related abnormalities. 
Relatives of diabetic probands with early-onset dis-
ese were more insulin resistant and had lower insulin 
scretion compared with relatives of subjects with late-
onset diabetes. Our results agree with similar observa-
itons that a trait is inherited; twin studies have shown that both genetic and environmental factors contribute 
to insulin resistance, whereas genetic factors are more 
lkely to determine insulin secretion (16). These find-
ings may seem at variance with studies suggesting 
brates of nonobese than obese type 2 diabetic patients 
to the Botnia Research Group for excellent technical assistance and 
In conclusion, this study clearly reinforces the im-
portance of age at diabetes onset when patients are 
lected for genetic studies, because the metabolic phe-
type of the proband is shared by relatives of prob-
ands with early- but not of late-onset diabetes. The study further emphasizes the value of stratifying for a 
phenotype characterized by abdominal obesity, as this characteristic also shows a high degree of familiality.

We express our sincere gratitude to the participating subjects and 
to the Botnia Research Group for excellent technical assistance and 
for recruiting and clinically studying the patients.

DISCLOSURES

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