Insulin secretion and sensitivity in the prediction of type 1 diabetes in children with advanced β-cell autoimmunity

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Abstract

Objective: Reduced early insulin response has been shown to predict type 1 diabetes (T1D) in first-degree relatives of diabetic patients, while its role, as well as that of insulin resistance, has remained poorly defined in young children representing the general population. The predictive values of these markers and their relation to other risk factors of T1D were assessed in children with advanced β-cell autoimmunity, i.e. persistent positivity for two or more autoantibodies.

Design and methods: Intravenous glucose tolerance tests (IVGTTs) were carried out in 218 children with HLA-DQB1-conferred disease susceptibility and advanced β-cell autoimmunity. Baseline, metabolic and growth data were compared between children progressing to diabetes and those remaining unaffected. Hazard ratios for the disease predictors and the progression rate of T1D were assessed.

Results: Children developing T1D were younger at seroconversion, progressed more rapidly to advanced β-cell autoimmunity and had lower first-phase insulin response (FPIR) and homeostasis model assessment index for insulin resistance (HOMA-IR) than those remaining non-diabetic. The levels of HOMA-IR/FPIR, islet cell antibodies, insulin autoantibodies (IAA) and islet antigen 2 antibodies (IA-2A) were higher in progressors. BMI SDS, FPIR, age at IVGTT and levels of IAA and IA-2A were predictive markers for T1D.

Conclusions: Young age, higher BMI SDS, reduced FPIR and higher levels of IAA and IA-2A predicted T1D in young children with HLA-DQB1-conferred disease susceptibility and advanced β-cell autoimmunity. Disease risk estimates were successfully stratified by the assessment of metabolic status and BMI. The role of insulin resistance as an accelerator of the disease process was minor.

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Introduction

The prediabetic phase of type 1 diabetes (T1D) is characterised by destruction of the pancreatic β-cells leading to reduced insulin release and decreased glucose tolerance. Diabetes-associated autoantibodies can be used as predictive markers of T1D, and the risk assessment may be stratified by studying the insulin secretion and insulin sensitivity among prediabetic first-degree relatives (1, 2, 3, 4). The first-phase insulin response (FPIR) observed during an intravenous glucose tolerance test (IVGTT) provides information on the readily releasable insulin stored in the secretory granules located close to the β-cell membrane (5). A reduced FPIR represents the first marker of impaired insulin secretion, and it may appear at an early stage of prediabetes (6, 7). It has been suggested that insulin resistance can modify the progression rate of preclinical diabetes (8, 9), implicating that increasing obesity in the childhood population might contribute to the rise in the incidence of T1D that has been observed over the last decades (10). We assessed the role of FPIR, homeostasis model assessment index for insulin resistance (HOMA-IR) and insulin release-adjusted insulin resistance (ratio of HOMA-IR to FPIR, i.e. relative insulin resistance) as the predictors of T1D, and their interactions with other risk indicators in young children with signs of advanced β-cell autoimmunity, recruited from the general population on the basis of HLA-DQB1-conferred disease susceptibility.
Metabolic data
Delay (years) from:
Growth data
Baseline data (n %)

Subjects and methods

Table 1 Baseline data and variables related to growth, progression of autoimmunity and metabolic factors in children developing type 1 diabetes (T1D) and remaining unaffected.

All (n=218) Non-diabetic (n=67) T1D (n=151) P value

Gender, male
Family history positive for T1D
Intervention study, participated
HLA-DQB1-associated disease risk
Strongly increased
Moderately increased
Neutral/slightly protective
PTPN22 gene, rs2476601 CC (vs CT/TT)
INS gene, rs689 AA (vs AT/TT)

Growth data (Median (range))
Height-for-age (SDS) at IVGTT
BMI (SDS) at IVGTT
Delay (years) from:
Seroconversion to multipositivity
Multipositivity to persistent multipositivity
Multipositivity to IVGTT
Seroconversion to IVGTT

Metabolic data
Fasting glucose (mmol/l)
Fasting insulin (mU/l)
Maximal glucose level (mmol/l)
Maximal insulin level (mU/l)
FPIR (mU/l)
HOMA-IR (mmol x mU/l²)
HOMA-IR/FPIR (mU/l)

Summary

Participants were originally recruited to the DIPP Study as newborn infants, based on screening for risk-associated HLA-DQB1 genotypes defined by two risk-associated and two protective alleles. HLA-DR/DQ haplotypes relevant for risk determination were identified by using lanthanide-labelled sequence-specific oligonucleotides (11). As further analyses of DRB1, DQB1 and DQA1 loci revealed later that some of the children actually carried neutral or slightly protective HLA-DQB1 genotypes (Table 1), risk estimates for genotype-associated disease were subsequently categorised into five groups (12). INS (rs689) and PTPN22 (rs2476601) polymorphisms were genotyped by using the Sequenom (San Diego, CA, USA) platform (Genome Centre of Eastern Finland, University of Eastern Finland, Kuopio).

The majority (179; 82.1%) of the children studied participated in a randomised, double-blinded intervention study, participated 179 (82.1%) 54 (80.6) 125 (82.8) 0.698

Table 1

Baseline data (n %)
Gender, male
129 (59.2) 39 (58.2) 90 (59.6) 0.847
Family history positive for T1D
27 (12.4) 6 (9.0) 21 (13.9) 0.306
Intervention study, participated
179 (82.1) 54 (80.6) 125 (82.8) 0.698
HLA-DQB1-associated disease risk
Strongly increased
75 (34.4) 19 (28.4) 56 (37.1) 0.453
Moderately increased
120 (55.0) 40 (59.7) 80 (53.0)
Neutral/slightly protective
23 (10.6) 8 (11.9) 15 (9.9)

Growth data (Median (range))
Height-for-age (SDS) at IVGTT
0.6 (−3.1 to 4.0) 0.6 (−3.1 to 2.4) 0.6 (−1.2 to 4.0) 0.551
BMI (SDS) at IVGTT
0.3 (−2.2 to 5.5) 0.2 (−1.6 to 2.5) 0.4 (−2.2 to 5.5) 0.075
Delay (years) from:
Seroconversion to multipositivity
0.0 (0.0 to 6.6) 0.3 (0.0 to 6.6) 0.0 (0.0 to 6.0) 0.003
Multipositivity to persistent
0.2 (0.2 to 3.3) 0.3 (0.2 to 3.3) 0.3 (0.2 to 3.3) 0.036

Metabolic data
Fasting glucose (mmol/l)
4.7 (2.6 to 6.3) 4.8 (3.7 to 6.0) 4.6 (2.6 to 6.3) 0.061
Fasting insulin (mU/l)
3.8 (0.1 to 13.4) 4.1 (1.1 to 9.9) 3.8 (0.1 to 13.4) 0.084
Maximal glucose level (mmol/l)
19.9 (14.0 to 27.6) 19.8 (14.2 to 26.3) 20.1 (14.0 to 27.6) 0.125
Maximal insulin level (mU/l)
20.2 (3.1 to 157.2) 31.3 (6.5 to 157.2) 17.7 (3.1 to 115.6) <0.001
FPIR (mU/l)
36.0 (5.0 to 273.6) 58.7 (12.1 to 273.6) 30.6 (5.0 to 213.6) <0.001
HOMA-IR (mmol x mU/l²)
0.78 (0.02 to 3.27) 0.81 (0.22 to 2.64) 0.72 (0.02 to 3.27) 0.047
HOMA-IR/FPIR (mU/l)
0.021 (0.003 to 0.139) 0.015 (0.003 to 0.044) 0.024 (0.003 to 0.139) <0.001

IVGTT, intravenous glucose tolerance test; PTPN22, protein tyrosine phosphatase non-receptor type 22; INS, insulin; FPIR, first-phase insulin response; HOMA-IR, homeostasis model assessment index for insulin resistance; HOMA-IR/FPIR, relative insulin resistance.
intervention trial of administration of intranasal insulin vs placebo. The intervention proved to have no effect on the progression to T1D (13). Cases with T1D were diagnosed by the World Health Organization (WHO) criteria (14) and ascertained from the patient records of the University Hospitals of Turku, Oulu, and Tampere, and from the National Diabetes Register (15). Follow-up for T1D continued until the end of October 2012. Local ethics committees had approved the protocol of the DIPP study. Written informed consents were obtained from the guardians of the participants before the commencement of the study procedures.

**Metabolic and growth data**

The standardised Islet Cell Antibody Register Users Study (ICARUS) protocol was followed while performing the IVGTTs (1). Samples for plasma glucose and serum insulin assays were taken after overnight fasting. The fasting state (pre-infusion) samples were drawn 1 and 5 min before i.v. glucose infusion (20% glucose solution given 0.5 g glucose/kg, maximal dose 35 g; infusion 5 min before i.v. glucose infusion (20% glucose solution fasting state (pre-infusion) samples were drawn 1 and 3 min, while HOMA-IR: FPIR ratio (HOMA-IR:FPIR, FPIR) represented the product of fasting glucose (mmol/l) and serum intact insulin with an enzyme-linked two-site immunoassay (17). The intra-assay coefficient of variation was 12.9% for the insulin concentrations at 1 and 3 min, while HOMA-IR:FPIR ratio (HOMA-IR:FPIR) represented the relative insulin resistance. Children’s height and weight were measured at each follow-up visit. Values obtained (kilogram and centimetre) were adjusted for age and gender (19, 20), and were given as SDS for height-for-age and BMI. Children with a BMI > +2 SDS were identified as overweight and those with a BMI > +3 SDS as obese (20).

**Statistical analyses**

Predictive Analytics Software (PASW Statistic 20.0 release, Armonk, NY, USA) was used for the statistical analyses. As the majority of the continuous variables had skewed distributions, mainly non-parametric tests, e.g. Mann–Whitney U test, Kruskall–Wallis test, Wilcoxon signed-rank test and Spearman correlation analysis, were used. The \( \chi^2 \) test was applied for binary variables and the Kaplan–Meier log-rank test was used for the analyses of the rate of disease progression. Analyses of covariance were performed whenever appropriate. Hazard ratios (HR) for the factors potentially predictive for T1D were assessed in an age-adjusted manner with the Cox regression models. CIs were set at 95% and \( P<0.05 \) (two-tailed) was considered statistically significant. One child with unclear severe hyperinsulinemia was excluded from the analyses.

**Results**

Metabolic data were available for 218 subjects (129 males, 59.2%), 151 (69.2%) of whom developed T1D (progressors) at the median age of 6.4 years (range 1.6–16.8 years; Table 1). The median follow-up time since IVGTT for the 67 subjects remaining non-diabetic (non-progressors) was 8.8 years (range 6.8–15.0 years), and their age at the end of the follow-up was 13.3 years (8.5–17.0 years). Progressors and non-progressors had similar distributions for baseline variables (Table 1), but progressors were younger at seroconversion and at all further time points regarding advanced seropositivity (Supplementary Table 1, see section on supplementary data given at the end of this article). Also, the delays from initial seroconversion to persistent multipositivity and IVGTT were shorter in progressors. As the age at IVGTT correlated significantly with metabolic markers (Spearman correlation coefficient, \( r_S = 0.44 \), \( P<0.001 \) for FPIR; \( r_S = 0.41 \), \( P<0.001 \) for HOMA-IR and \( r_S = -0.14 \), \( P=0.036 \) for HOMA-IR/FPIR), age-adjustment was used in further analyses whenever applicable. Regarding autoantibodies, progressors had both higher numbers of positive autoantibodies and higher levels of ICA, IAA and IA-2A throughout the follow-up, except at the initial

**Figure 2** First-phase insulin response (FPIR; A), homeostasis model assessment index for insulin resistance (HOMA-IR; B), relative insulin resistance (HOMA-IR/FPIR; C) and BMI SDS (D) values (with 95% CIs and medians) in children developing type 1 diabetes (T1D) and remaining unaffected. \( P \) values for Mann–Whitney U tests.
seroconversion. Levels of GADA were comparable between the two groups during the whole follow-up (Supplementary Table 1).

In general, FPIR and HOMA-IR were higher in non-progressors, while relative insulin resistance was higher in progressors (Table 1 and Fig. 2A, B, and C). Regarding HOMA-IR, the difference between the two groups was small and the correlation between HOMA-IR and progression to T1D disappeared after adjustment for age ($r_g = -0.04, P = 0.57$). As expected, HOMA-IR was correlated with BMI SDS ($r_g = 0.17, P = 0.013$). To study the predictive value of metabolic markers and BMI SDS, children were grouped by the quartiles of these variables, and the estimates of the disease progression rates of the different quartiles were compared with the log-rank test in the Kaplan–Meier analyses (Fig. 3A, B, C, and D). For FPIR, progression rate increased by the decreasing insulin secretion capacity, and all but the two middle quartiles differed significantly from each other. Regarding progression rates related to HOMA-IR, HOMA-IR/FPIR and BMI SDS, mainly the highest quartiles differed from the other quartiles. The highest 5-year progression rates were observed for individuals belonging to the lowest FPIR quartile (81.5%; CI 71.1–91.9%) and highest HOMA-IR/FPIR quartile (75.9%; CI 64.5–87.3%) and comparably, the lowest progression rates were recorded for those within the highest FPIR quartile (21.4%; CI 10.6–32.2%) and lowest HOMA-IR/FPIR (37.0%; CI 24.2–49.9%) quartile.

As obesity had been hypothesised to have an accelerating effect on the prediabetic disease process, we assessed whether increased BMI could explain the progression to T1D. In the current study cohort, there were 203 children with their height and weight data recorded both at seroconversion and at IVGTT. At seroconversion, the median BMI for the 65 non-progressors and 138 progressors were 0.2 SDS (range −1.7 to 2.2 SDS) and 0.5 SDS (range −1.8 to 5.5 SDS; $P = 0.004$) respectively. The median decrease in BMI during the follow-up from seroconversion to IVGTT was similar (0.2 SDS; range −0.7 to 1.04 SDS) in both groups and did not correlate with progression to T1D ($r_g = 0.034, P = 0.704$). However, in the Kaplan–Meier analysis, the highest and the lowest BMI SDS quartile groups differed from each other only if the obese children ($n = 6$) were included in the analysis (Fig. 3D). Moreover, even if the BMI SDS was the main independent predictor for T1D in the Cox regression analysis (Table 2; HR 1.354, CI 1.137–1.613) in the whole cohort, this was not the case after excluding the obese children from the analysis. When the subcohort of the non-obese children ($n = 212$) was analysed, age at IVGTT, FPIR and IAA levels remained as significant predictors, while the ICA titre (HR = 1.001, CI 1.000–1.001; $P = 0.006$) replaced the IA-2A level as an independent predictor for T1D.

Discussion

We studied the prognostic value of metabolic data obtained soon after the confirmation of advanced β-cell autoimmunity in young children from the general population, carrying HLA-DQB1-conferred susceptibility to T1D. Our main aims were to test the hypothesis that obesity-related insulin resistance might modify the disease process, to confirm the role of a reduced FPIR as an important risk factor for rapid progression to T1D, and to assess the interactions and significance of the various disease risk factors present at the time of the IVGTT in children from the general population.

Although all children in the current study cohort had fulfilled the criteria of advanced β-cell autoimmunity before IVGTT, their progression rate to T1D was highly variable. In these children, the baseline factors, such as gender, HLA-DQB1 genotypes, insulin and PTPN22 gene polymorphisms, and the family history for T1D, could not identify individuals with rapid disease progression. This may be due to the inclusion criteria used, resulting in a relatively homogeneous study population, but may also reflect the idea that factors contributing to the initiation of the disease process might be different from those driving
the process towards overt disease. However, as previously shown (2, 3, 6, 21, 22), several of the factors associated with the initiation of \( \beta \)-cell autoimmunity do contribute to the phenomena associated with the progression rate, such as age at initial seroconversion, the pace of progression towards persistent multipositivity and autoantibody levels. The current study confirmed the prior observations that progression to T1D is related to young age at seroconversion, early progression to multipositivity, higher numbers of detectable autoantibodies and to higher levels of ICA, IAA and IA-2A (1, 2, 3).

Regarding IVGTT and metabolic data, the young and relatively variable age of the participants complicated the analyses. First of all, for HOMA-IR or HOMA-IR/FPIR scarcely any comparable age-adjusted data from a healthy, non-obese reference population was available, and second, as FPIR, HOMA-IR and HOMA-IR/FPIR correlated strongly with the age at IVGTT, age adjustments were required in the analyses. However, we confirmed that a low FPIR \(< 24\) mU/l identifies the future cases of T1D with high accuracy (5-year progression rate \(> 80\%\)), while children with reasonably high insulin secretion (FPIR \(> 59\) mU/l) remain unaffected for several years (5-year progression rate 21\%), although they already have signs of advanced \( \beta \)-cell autoimmunity.

The observation that HOMA-IR was remarkably low in the current cohort, and especially that it was slightly higher in non-progressors, implicates that the role of insulin resistance may be modest in the prediabetic process in young, mainly non-obese children. However, there were indications that both obesity-related insulin resistance and insulin resistance occurring in parallel with a reduced insulin secretion may modify the disease risk. These include the findings that HOMA-IR/FPIR was higher in progressors, it correlated positively with BMI SDS and the fact that in the Kaplan–Meier analyses assessing the rates of disease progression, the difference

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**Table 2** Factors potentially predictive for type 1 diabetes (T1D) in the Cox univariate and multivariate analyses.

<table>
<thead>
<tr>
<th>Variables in the univariate analyses</th>
<th>Hazard ratio with CI</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Background data</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender male vs female*</td>
<td>0.965 (0.696–1.337)</td>
<td>0.829</td>
</tr>
<tr>
<td>Family history for T1D positive vs negative*</td>
<td>0.793 (0.465–1.174)</td>
<td>0.200</td>
</tr>
<tr>
<td>HLA-DQB1 genotype by decreasing disease risk class (see Table 2)*</td>
<td>0.876 (0.671–1.143)</td>
<td>0.330</td>
</tr>
<tr>
<td>( INS ) genotype rs689 AA vs AT/TT*</td>
<td>0.806 (0.538–1.207)</td>
<td>0.296</td>
</tr>
<tr>
<td>( PTPN22 ) genotype rs2476601 CC vs CT/TT*</td>
<td>0.719 (0.516–1.001)</td>
<td>0.051</td>
</tr>
<tr>
<td>Intervention study, participated vs refused</td>
<td>0.928 (0.608–1.416)</td>
<td>0.728</td>
</tr>
<tr>
<td><strong>Time-related variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at seroconversion (years)</td>
<td>0.837 (0.748–0.936)</td>
<td>0.001</td>
</tr>
<tr>
<td>Age at persistent multipositivity (years)</td>
<td>0.795 (0.716–0.884)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age at IVGTT (years)*</td>
<td>0.778 (0.701–0.862)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Delay from seroconversion to IVGTT (years)*</td>
<td>0.747 (0.621–0.897)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Data on autoantibodies</strong></td>
<td></td>
<td></td>
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<tr>
<td>Autoantibody levels at IVGTT</td>
<td></td>
<td></td>
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<tr>
<td>ICA (JDFU)*</td>
<td>1.000 (1.000–1.001)</td>
<td>0.001</td>
</tr>
<tr>
<td>IAA (RU)*</td>
<td>1.012 (1.008–1.016)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GADA (RU)*</td>
<td>1.000 (0.997–1.003)</td>
<td>0.732</td>
</tr>
<tr>
<td>IA-2A (RU)*</td>
<td>1.007 (1.004–1.010)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number of positive autoantibodies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At seroconversion</td>
<td>1.383 (1.127–1.696)</td>
<td>0.001</td>
</tr>
<tr>
<td>At seroconversion for multiple autoantibodies</td>
<td>1.622 (1.306–2.014)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>At persistent multipositivity</td>
<td>1.669 (1.328–2.098)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>At IVGTT*</td>
<td>1.643 (1.343–2.011)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Metabolic and growth related data</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FPIR (mU/l)*</td>
<td>0.978 (0.970–0.985)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HOMA-IR (mmol × mU/l^2)*</td>
<td>0.719 (0.484–1.069)</td>
<td>0.103</td>
</tr>
<tr>
<td>HOMA-IR/FPIR (μmol/l)*</td>
<td>1.019 (1.013–1.028)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Height-for-age (SDS)</td>
<td>1.124 (0.967–1.307)</td>
<td>0.124</td>
</tr>
<tr>
<td>BMI (SDS)*</td>
<td>1.280 (1.092–1.501)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Independent predictors of T1D (multivariate model)</strong></td>
<td></td>
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</tr>
<tr>
<td>BMI (SDS)</td>
<td>1.354 (1.137–1.613)</td>
<td>0.001</td>
</tr>
<tr>
<td>Age at IVGTT (years)</td>
<td>0.872 (0.780–0.974)</td>
<td>0.015</td>
</tr>
<tr>
<td>FPIR (mU/l)</td>
<td>0.985 (0.978–0.993)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IAA at IVGTT (RU)</td>
<td>1.010 (1.005–1.014)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IA-2A at IVGTT (RU)</td>
<td>1.005 (1.002–1.009)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

\( INS \), insulin; \( PTPN22 \), protein tyrosine phosphatase non-receptor type 22; \( IVGTT \), intravenous glucose tolerance test; \( ICA \), islet cell antibodies; \( JDFU \), Juvenile Diabetes Research Foundation Unit; \( IAA \), insulin autoantibodies; \( RU \), relative unit; \( GADA \), autoantibodies to GAD; \( IA-2A \), autoantibodies to islet antigen 2; \( FPIR \), first-phase insulin response; \( HOMA-IR \), homeostasis model assessment index for insulin resistance; \( HOMA-IR/FPIR \), relative insulin resistance. * indicates variables in multivariate analysis.
between the two highest BMI quartiles disappeared after excluding the obese children from the analysis, as did the significance of BMI as an independent predictor of T1D in the Cox regression analysis.

Our current findings are in line with the results of the British study on identical twins (23) and the data from the European Nicotinamide Diabetes Intervention Trial (ENDIT; (24)). In both studies, HOMA-IR was an independent predictor of T1D only in subjects with reduced FPIR, not in the whole study cohorts. The observation that both in the Diabetes Prevention Trial-Type 1 (DPT1) Study and in the Childhood Diabetes in Finland Study (DiMe) HOMA-IR and FPIR/HOMA-IR were predictive indicators for T1D (2, 4) might be explained by the older age of the study participants. In all, it seems that even if a low-grade insulin resistance is unable to shift glucose metabolism towards diabetes in individuals with normal FPIR, it might do so in individuals with reduced insulin release.

To conclude, the role of insulin resistance as an accelerator of the prediabetic disease process of T1D seems to be minor. However, the assessment of the metabolic status provides important information regarding the stratification of the disease risk in prediabetic children. This information can be applied in intervention trials aimed at preventing T1D: for the identification of the optimal trial participants, for the assessment of the metabolic changes during and after the treatment and as guidance in the interpretation of the study results.

Supplementary data
This is linked to the online version of the paper at http://dx.doi.org/10.1530/EJE-13-0206.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement
H T Siljander analysed the data, wrote the first version of the manuscript and edited the manuscript. R Hermann was involved in the genetic analyses. H T Siljander, A Hekkalá, J Lähde, I Tanner, P Keskinen and R Veijola were involved in the clinical follow-up of the study participants. J Ilonen, O Simell and M Knip are the Principal Investigators of the DIPP study. J Ilonen was responsible for the genetic analyses and M Knip and R Veijola for the autoantibody analyses. M Knip planned the study and contributed to the discussion. All authors reviewed and approved the manuscript. M Knip is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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