Insulin Resistance and Progression to Type 1 Diabetes in the European Nicotinamide Diabetes Intervention Trial (ENDIT)

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OBJECTIVE — Insulin resistance can modulate progression to type 1 diabetes in individuals with ongoing islet autoimmunity. We wanted to see whether measures of insulin resistance improved risk assessment in islet cell antibody (ICA)-positive relatives when added to other immune and metabolic markers.

RESEARCH DESIGN AND METHODS — The retrospective cohort analysis included 213 family members participating in the European Nicotinamide Diabetes Intervention Trial. All were aged <25 years, with at least one islet antibody in addition to ICA ≥20 Juvenile Diabetes Foundation units. Median length of follow-up was 4.21 years, and 105 individuals developed diabetes. Oral and intravenous glucose tolerance tests were performed at baseline; antibodies to GAD, IA-2, and insulin were determined by radioimmunoassay; and insulin resistance was estimated by homeostasis model assessment. Risk was assessed by Cox regression analysis

RESULTS — The overall cumulative risk of diabetes within 5 years was 54.1% (95% CI 46.0–62.3). Multivariate analysis confirmed that baseline first-phase insulin response (FPIR) quartile ($P < 0.0001$), number of additional antibody markers ($P < 0.0001$), and 120-min glucose in the oral glucose tolerance test ($P < 0.0001$) were independent determinants of risk of progression, whereas addition of homeostasis model assessment of insulin resistance (HOMA2-IR) achieved only borderline significance ($P = 0.06$). HOMA2-IR was an independent determinant in participants with loss of FPIR ($P = 0.025$) but not in those with preserved FPIR ($P = 0.3$).

CONCLUSIONS — These data suggest that insulin resistance accelerates progression to type 1 diabetes in antibody-positive relatives in whom insulin secretion is markedly reduced but does not affect progression when insulin secretion is relatively well preserved.

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The clinical onset of type 1 diabetes appears to be accelerated by situations associated with increased insulin resistance, including puberty, pregnancy, and infection, and insulin resistance may also modulate progression to diabetes in individuals with evidence of islet autoimmunity (1,2).

We investigated the role of insulin resistance in determining risk of progression to diabetes in islet cell antibody (ICA)-positive first-degree relatives of patients with type 1 diabetes recruited to the European Nicotinamide Diabetes Intervention Trial (ENDIT) (3,4). Because 88% of family members who developed diabetes in ENDIT were aged <25 years and had at least one other islet autoantibody in addition to ICA (5), we have focused our analysis on this high-risk subgroup.

RESEARCH DESIGN AND METHODS

— The protocol and outcome of the screening stages of ENDIT and the role of additional immune, genetic, and metabolic markers of risk have been published (3–5). The inclusion criteria were ICA ≥20 Juvenile Diabetes Foundation (JDF) units in at least one sample, as measured in the central laboratory, and ICA ≥5 JDF units in the other sample. Those found to have diabetes on oral glucose tolerance testing were excluded. The protocol was approved by the research ethics committee or equivalent in each participating center and also by the appropriate national drug regulatory authorities. Written informed consent was obtained from all participants. Participants were randomly assigned to receive either oral modified-release nicotinamide or placebo for 5 years and were reviewed at baseline, 1 month, and 6 months after study entry and every 6 months thereafter, with an oral glucose tolerance test (OGTT) every 12 months.

Participants were weighed and measured at study entry, and puberty was staged according to the criteria of Tanner on the basis of breast development in girls and genital development and pubic hair in boys (6). OGTTs and intravenous glucose tolerance tests were performed at study entry according to standardized protocols (3). Baseline samples from all participants were tested for ICA and autoantibodies to GAD, IA-2, and insulin in our laboratories at the University of Bristol, as described previously, and considered positive if ≥97.5th centile of a control population of 2,860 schoolchildren (7). Plasma intact insulin was measured in a single laboratory at the Steno Diabetes Centre (Gentofte, Denmark) using an enzyme-linked two-site immunoassay in which there was no cross-reactivity with proinsulin (8) with use of a correction factor to standardize the measurement to the assay used in the Diabetes

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*A complete listing of the members of the European Nicotinamide Diabetes Intervention Trial Group can be found in the APPENDIX.

Abbreviations:DPT-1, Diabetes Prevention Trial–type 1; ENDIT, European Nicotinamide Diabetes Intervention Trial; FPIR, first-phase insulin response; HOMA, homeostasis model assessment; HOMA2-IR, homeostasis model assessment of insulin resistance; ICA, islet cell antibody; JDF, Juvenile Diabetes Foundation; OGTT, oral glucose tolerance test; SDS, standard deviation score.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Prevention Trial–type 1 (DPT-1) reference laboratory, University of Washington (Seattle, WA) (3). Plasma glucose was determined in local laboratories.

Statistical analysis

Standard deviation scores (SDSs) for height, weight, and BMI were calculated using cross-sectional stature and weight reference curves for the U.K. (9). First-phase insulin response (FPIR) was calculated as the sum of the insulin levels at +1 and +3 min. Insulin resistance was estimated by homeostasis model assessment of insulin resistance (HOMA2-IR) (10) (www.ocdem.ox.ac.uk). With use of this measure, increasing insulin resistance gives progressively higher scores. Cox proportional hazards models were used to analyze the time-to-event outcome for individual and combined predictive markers, controlling for treatment group. The follow-up period for each individual was calculated from the date of the baseline visit, and the end of follow-up was defined as the date of last contact or date of diagnosis of diabetes. Diabetes was defined according to the World Health Organization criteria (11). The following variables previously shown to be independent determinants of risk in this population were included in the regression model: age at randomization, number of additional autoantibodies, and 120-min plasma glucose in the OGTT and FPIR (5). Additional variables were pubertal stage, height, weight, and BMI SDSs and insulin resistance expressed as HOMA2-IR. The model was built in stages following the general strategy for model selection suggested by Collett (12). Variables with significance $P < 0.1$ in univariate analysis were included in the multivariate model, and the effect of removing each variable from the model was assessed. Variables not significant on univariate analysis were also reconsidered for inclusion in the final multivariate model. Statistical significance was taken as $P < 0.05$. Results are reported as number of participants and events for each risk group and as hazard ratios (HRs) (95% CI) and *P* values from the Cox model analyses. Statistical analysis was performed using SPSS 12.0.1 (SPSS, Chicago, IL).

In view of the interrelation between insulin secretion and insulin sensitivity, analyses were repeated in subgroups defined by FPIR above or below the age-adjusted 10th centile (low and preserved FPIR). The 10th centile is equivalent to 60 mU/l at age <8 years and 100 mU/l at age >8 years, standardized to the Seattle assay (3). In a supplementary analysis, the HOMA2-IR–to–FPIR ratio was substituted for the two separate variables HOMA2-IR and FPIR, as has been reported in other studies (1,2).

Table 1—*Baseline characteristics of trial participants*

	All	Developed diabetes
Placebo/nicotinamide treatment group	102/111	55/50
Sex (male/female)	127/86	68/37
Age at randomization (years)	11.66 (7.99–15.0)	10.20 (7.33–13.6)
Pubertal group		
Prepubertal	104	62
Early puberty (Tanner 2 and 3)	41	18
Late puberty (Tanner 4 and 5)	13	6
Postpubertal	37	12
Islet autoantibodies		
ICA + 1 additional antibody	34	7
ICA + 2 additional antibodies	66	28
ICA + 3 additional antibodies	113	70
FPIR (pmol/l)	337 (181–546)	207 (125–368)
120-min plasma glucose (mmol/l)	5.7 (5.8–6.95)	6.4 (5.1–7.6)
HOMA2-IR	0.59 (0.35–0.87)	0.61 (0.36–0.82)
Weight (SDS)	0.22 (−0.40 to 0.88)	0.32 (−0.40 to 0.98)
Height (SDS)	0.24 (−0.28 to 0.88)	0.24 (−0.46 to 0.88)
BMI (SDS)	0.01 (−0.65 to 0.77)	0.05 (−0.72 to 0.92)

Data are *n* or median (interquartile range).

RESULTS — Of 360 ICA$^+$ family members aged <25 years who were randomly assigned in ENDIT, 270 had at least one antibody in addition to ICAs. For technical reasons, including sample hemolysis, baseline glucose, baseline insulin, and/or FPIR, were not available for 57 individuals. This analysis therefore included 213 family members, of whom 105 developed diabetes during follow-up. The median length of follow-up was 4.21 years. The overall cumulative risk of development of diabetes within 5 years was 54.1% (95% CI 46.0–62.3). The baseline characteristics of the study subjects are shown in Table 1. There were no differences in age, sex, and overall frequency of development of diabetes between eligible antibody-positive family members included in the analysis and those for whom data were missing. As expected, BMI SDS, weight SDS, and pubertal status correlated with HOMA2-IR and FPIR (data not shown). The correlation between FPIR and HOMA2-IR is shown in Fig. 1 ($R^2 = 0.17$, $P < 0.001$). HOMA2-IR was higher in those who developed diabetes during follow-up than in those who remained nondiabetic in the subset of 83 individuals with low FPIR

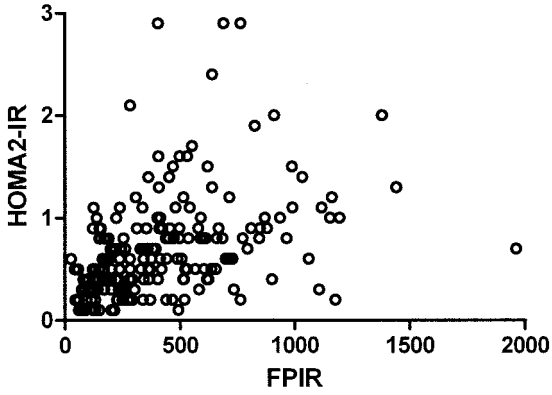

Figure 1—*Relationship between FPIR and HOMA2-IR in 213 family members participating in ENDIT. All were aged <25 years, with at least one islet antibody in addition to ICA ≥20 JDF units.*

Table 2—*Cox proportional hazard models, all participants*

	χ^2	d.f.	*P* value	HR (95% CI)
Univariate models*				
FPIR (pmol/l)†	54.34	1	<0.0001	0.997 (0.996–0.998)
Additional antibodies‡	21.68	1	<0.0001	1.94 (1.43–2.62)
120-min glucose (mmol/l)†	25.00	1	<0.0001	1.37 (1.21–1.54)
Age (years)†	7.87	1	0.006	0.94 (0.90–0.98)
Height SDS†	0.45	1	0.831	1.02 (0.83–1.26)
Weight SDS†	0.63	1	0.428	1.09 (0.88–1.34)
BMI SDS†	0.46	1	0.468	1.07 (0.88–1.30)
Pubertal stage	10.02	3	0.028	
Tanner 5§				1
Tanner 0		1	0.008	2.33 (1.25–4.33)
Tanner 1–2		1	0.370	1.40 (0.67–2.90)
Tanner 3–4		1	0.175	1.97 (0.74–5.28)
HOMA2-IR	0.27	1	0.602	0.90 (0.61–1.33)
Multivariate model*				
FPIR (pmol/l)†	45.86	1	<0.0001	0.998 (0.995–0.998)
Additional antibodies‡	17.64	1	<0.0001	1.85 (1.36–2.52)
120-min glucose (mmol/l)†	14.74	1	<0.0001	1.27 (1.13–1.43)
HOMA2-IR†	3.11	1	0.056	1.43 (0.99–2.06)

*All models controlled for treatment group. †Hazard ratio per incremental unit. ‡Hazard ratio per antibody in addition to ICA. §Reference group.

(below the age-adjusted 10th centile) ($P = 0.006$) but not in the 130 family members with preserved FPIR (above the age-adjusted 10th centile) ($P = 0.08$).

The HRs on univariate and multivariate Cox regression analysis are shown in Table 2. Univariate analysis showed that risk varied with number of additional islet autoantibodies, age, pubertal stage, 120-min glucose in the OGTT, and FPIR but not with height SDS, weight SDS, BMI SDS, or HOMA2-IR. Multivariate Cox proportionate hazard modeling showed that risk was associated with FPIR ($P < 0.0001$), number of additional antibodies ($P = < 0.0001$), and 120-min glucose ($P = < 0.0001$). Overall, HOMA2-IR was not an independent determinant of risk (HR 1.27 [95% CI 0.91–2.00], $P = 0.056$). In the subset of individuals with low FPIR, however, HOMA2-IR ($P = 0.025$) was an independent determinant of risk, as well as additional antibodies ($P = 0.002$), FPIR ($P = 0.001$), and 120-min glucose ($P = 0.018$). In contrast, in the individuals with preserved FPIR, additional antibodies ($P = 0.016$), FPIR ($P = 0.019$), and 120-min glucose ($P = 0.001$) were independent determinants of risk but HOMA2-IR was not ($P = 0.295$) (Table 3). Consistent with these findings, alternative models substituting HOMA2-IR/FPIR for the separate variables showed that the ratio was strongly associated with progression to diabetes in the subgroups with low FPIR ($P = 0.001$), with borderline significance in those with preserved FPIR ($P = 0.04$). The HRs associated with HOMA2-IR in groups defined by FPIR tertile are shown in Fig. 2.

CONCLUSIONS — Insulin resistance, as measured by baseline HOMA2-IR, made only a borderline contribution to risk of progression to diabetes in the group as a whole (Table 2), but the impact of insulin resistance varied according to residual insulin secretion. Among participants with a preserved FPIR, neither insulin resistance nor the closely related variable BMI made an independent contribution after correction for other established risk factors such as antibody status and age, but HOMA2-IR emerged as a major determinant of risk in those in whom β-cell function was markedly reduced. (Table 3). This finding suggests that, over the period studied, insulin sensitivity modulates the clinical onset of diabetes only in those with severely compromised β-cell function.

These conclusions are strengthened by the size of this study, the relatively large number of participants who progressed to diabetes, and completeness of follow-up. These factors allowed us to undertake multivariate analyses taking age, antibody status, and other risk factors into consideration (5). All participants were followed using standardized protocols irrespective of baseline insulin secretion or glucose tolerance, and insulin was measured in a single reference laboratory (3). A potential reservation is that nicotinamide was taken by half of the participants and may affect insulin resistance in ICA$^+$ individuals (13), although we found no difference in FPIR between nicotinamide and placebo in ENDIT (4) and have previously found no effect upon insulin secretion in normal subjects (14). We have, however, taken the additional precaution of controlling for treatment group in our analysis, as well as confirming that the findings were consistent in the two groups when analyzed separately (data not shown).

We relied on HOMA to estimate insulin resistance in this population, and some caution is necessary here because the model has not been as extensively validated in children as in adults. Insulin sensitivity determined by homeostasis

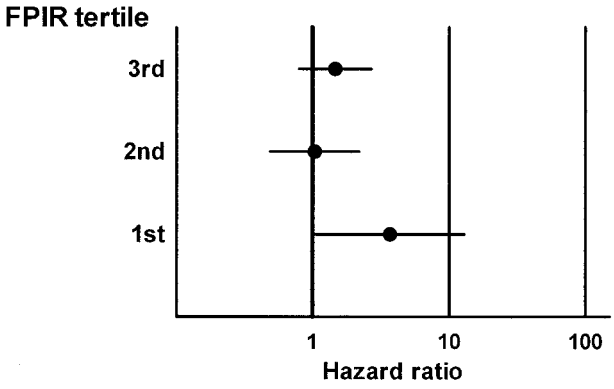

Figure 2—*Multivariate analysis of the relationship between baseline HOMA2-IR and development of diabetes in subgroups of study participants defined by FPIR tertile. The HRs associated with HOMA2-IR in each subgroup were derived from Cox proportionate hazard models that also included 120-min glucose in the 75-g OGTT, FPIR, and the number of antibodies in addition to ICA. FPIR tertiles were equivalent to 225 and 470 pmol/l.*

Table 3—*Multivariate Cox proportional hazard models in subgroups defined by FPIR*

	χ^2	d.f.	Significance	HR (95% CI)
Low FPIR (below age-adjusted 10th centile)				
FPIR (pmmol/l)*	10.08	1	0.001	0.994 (0.990–0.998)
Additional antibodies†	9.24	1	0.002	1.82 (1.20–2.76)
120-min glucose (mmol/l)*	5.64	1	0.004	1.20 (1.03–1.39)
HOMA2-IR*	5.05	1	0.025	3.67 (1.12–11.10)
Preserved FPIR (above age-adjusted 10th centile)				
120-min glucose (mmol/l)*	9.63	1	0.001	1.39 (1.14–1.70)
FPIR (pmol/l)*	7.07	1	0.019	0.998 (0.996–1.000)
Additional antibodies†	6.57	1	0.016	1.80 (1.12–2.89)
HOMA2-IR*	0.98	1	0.295	1.27 (0.91–2.00)

All models controlled for treatment group. *Hazard ratio per incremental unit. †Hazard ratio per antibody in addition to ICAs.

model assessment (HOMA) has been shown to correlate poorly with the insulin sensitivity index based on the minimal model in peripubertal children (15), and, although a study in children has shown excellent overall correlation between insulin sensitivity assessed using the gold standard of a euglycemic-hyperinsulinemic glucose clamp and by HOMA, the correlation was lowest in white nonobese prepubertal children (16), who constituted the majority of the participants in ENDIT (17). The impact of this potential limitation is, however, minimized, as we have used the model to compare groups of similar age and size rather than to derive an absolute measure of insulin sensitivity (10). A further caveat is that the fasting insulin levels were generally low in this group, and, although the HOMA-2 model used is valid down to insulin levels of 1 pmol/l (lower than that of any of the participants in this study), it may become less discriminating in insulin deficiency (10). An additional caution, which we were unable to address because repeat assessments of insulin sensitivity were not available, is that insulin sensitivity may have varied over the follow-up period. For example, our analysis used baseline pubertal status and did not allow for the fact that some children became much more insulin resistant during the course of the study as they entered puberty.

A final limitation is the possibility that our study may have lacked the power to detect an independent association between HOMA-2IR and future diabetes in the group with preserved FPIR in whom the overall risk of diabetes was lowest. Follow-up in this study is limited to 5 years, and participants with higher FPIR at baseline may develop diabetes at a later date. Confirmation of our findings in a larger cohort of high-risk individuals with preserved FPIR, followed for a longer time, would therefore be useful.

Other studies have examined the role of insulin resistance in determining risk of progression to type 1 diabetes and reached various conclusions. The two studies that showed insulin resistance to be important were smaller than ENDIT and included some family members at lower risk, selected on the basis of positivity for a single antibody (1,2). These investigators have also based their conclusions on the HOMA-(IR)–to–FPIR ratio, a measure that is strongly influenced by FPIR and in our view potentially misleading. Findings similar to our own have, however, been reported for two larger studies, the DPT-1 and SEARCH for Diabetes in Youth. In DPT-1, in which participants had at least two antibodies, ICA and insulin autoantibodies, HOMA-IR quartile was not associated with risk of progression to diabetes in univariate analysis and, in Cox proportional hazards analysis, was an independent determinant of risk only in those with low FPIR (18). Similarly, SEARCH, studying islet autoantibody-positive children and young people at the time of diagnosis, found that high BMI was associated with early age of onset of type 1 diabetes only in the context of low fasting C-peptide levels (19,20).

Smaller studies (1,2) have suggested that modification of insulin sensitivity by agents such as metformin or thiazolidinediones offers the potential to delay or prevent the clinical onset of type 1 diabetes. Such benefit might be mediated by optimizing the metabolic effects of residual insulin secretion or by rendering the remaining β-cells less active and therefore less immunogenic. We found that insulin resistance played a minor role in modulating progression to diabetes within this high-risk cohort as a whole but played a major role in the subgroup with impaired insulin secretion. It should be noted, however, that the term "insulin resistance" is potentially misleading in this context because individuals who are able to maintain glucose homeostasis despite a low FPIR are, by the same token, relatively sensitive to insulin (Fig. 1). Our findings imply that relative resistance to insulin has a limited role in determining the rate of β-cell destruction in the group of nonobese individuals studied. Interventions designed to increase insulin sensitivity might be expected to produce short-term delay in clinical onset in individuals with severe impairment of insulin secretion but are unlikely to have an impact on progression to diabetes in the remainder over a 5-year treatment period.

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APPENDIX

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