Role of Insulin Resistance in Predicting Progression to Type 1 Diabetes

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OBJECTIVE — The purpose of this study was to determine whether insulin resistance is a risk factor for the development of type 1 diabetes in autoantibody-positive first-degree relatives of diabetic family members.

RESEARCH DESIGN AND METHODS — Subjects (n = 186) who had a projected 25–50% risk for diabetes and subjects (n = 170) who had a projected >50% risk for type 1 diabetes in 5 years were followed until clinical diabetes onset or the end of the study as part of the Diabetes Prevention Trial–Type 1. We assessed insulin secretion with the first-phase insulin response (FPIR) and insulin resistance with homeostasis model assessment of insulin resistance (HOMA-IR) from an intravenous glucose tolerance test. The median follow-up was 4.3 years for moderate-risk subjects and 3.7 years for high-risk subjects.

RESULTS — During the follow-up period, 53 subjects in the moderate-risk group and 70 subjects in the high-risk group developed type 1 diabetes. After adjustments for confounders using multivariate analysis, HOMA-IR and the FPIR-to–HOMA-IR ratio were significantly associated with type 1 diabetes in both risk groups. In the moderate-risk population, the hazard ratio (HR) of HOMA-IR was 2.70 (95% CI 1.45–5.06) and the HR of FPIR-to-HOMA-IR was 0.32 (95% CI 0.18–0.57). In the high-risk population, the HR of HOMA-IR was 1.83 (95% CI 1.19–2.82) and the HR of FPIR–to–HOMA-IR was 0.56 (95% CI 0.40–0.78).

CONCLUSIONS — There is clear evidence of the association between insulin resistance and progression to type 1 diabetes. The combination of FPIR and HOMA-IR could be used as a better metabolic indicator for type 1 diabetes risk for prediction and suggests possible intervention strategies for diabetes prevention.

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Type 1 diabetes is directly linked to the dysfunction and death of insulin-secreting pancreatic β-cells (1). Type 1 diabetic patients experience an autoimmune disorder in which proteins associated with islet β-cells are recognized by the immune system as foreign and targeted for an immune response. This response, indicated by autoantibodies, inhibits β-cell production of insulin and progressively destroys β-cells over a period of years. With the early diagnosis of type 1 diabetes, many patients are found to have residual β-cell function, as measured by C-peptide at the time of diagnosis, leading to speculation that the observed hyperglycemia may be the result of functional inhibition of β-cell activity (2,3) or a loss in insulin sensitivity or both.

Genetic associations and autoantibodies (4–7) are thought to mark the immune attack on β-cells, which leads to an inability of insulin secretion to keep up with demand, thus eventually resulting in hyperglycemia. However, it is known that normal glucose homeostasis is a result of the interplay of insulin secretion and insulin sensitivity. It has been suggested recently that clinical disease would be manifested earlier in subjects with both a β-cell lesion and increased demand on those cells from insulin resistance (8). Thus, we wished to determine whether markers of insulin resistance would enhance our ability to predict onset of disease in this population and to determine whether there was an increase in insulin resistance at the time of type 1 diabetes diagnosis.

Two validated methods to evaluate glucose homeostasis in subjects with or at risk for diabetes are homeostasis model assessment of insulin resistance (HOMA-IR) and first-phase insulin response (FPIR), measuring insulin resistance (9–11) and insulin secretion (12), respectively. HOMA-IR has been widely applied as an index of insulin resistance in people with both normal glucose tolerance and impaired glucose tolerance and has been used to document insulin resistance for patients at risk for type 2 diabetes involved in longitudinal studies.

The Melbourne Pre-Diabetes Family Study has shown that islet cell antibody (ICA)-positive relatives who progress most rapidly to diabetes have a subtle disturbance of insulin-glucose homeostasis years before the onset of diabetes, being distinguished by greater insulin resistance for their level of insulin secretion (13). Similar results were reported from the Childhood Diabetes in Finland Study (14). However, the Seattle Family Study showed that insulin resistance did not improve the prediction of clinical disease beyond FPIR alone (15).

The Diabetes Prevention Trial–Type 1 (DPT-1) was a longitudinal study in North America designed to determine whether type 1 diabetes could be pre-

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Abbreviations: DPT-1, Diabetes Prevention Trial–Type 1; FPIR, first-phase insulin response; HOMA-IR, homeostasis model assessment of insulin resistance; IAA, insulin autoantibody; ICA, islet cell antibody; IVGTT, intravenous glucose tolerance test; OGTT, oral glucose tolerance test.

*A list of the Diabetes Prevention Trial–Type 1 Study Group members can be found in ref. 17.

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

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vented or delayed by a preclinical intervention of insulin supplements. The DPT-1 screened >100,000 individuals at risk for type 1 diabetes who were followed until disease onset or study end. The results from the DPT-1 are consistent with the conclusion that the presence of specific antibodies and specific genotypes are risk markers for type 1 diabetes. The study has also confirmed the results of previous studies showing that a decline in FPIR played a significant role in predicting type 1 diabetes (16). Data from the DPT-1 provide a unique opportunity to evaluate the contribution that insulin resistance makes to the risk of type 1 diabetes in a large population of autoantibody-positive first-degree relatives accessioned and followed in a uniform manner from a large number of collaborating medical centers in the U.S. and Canada.

RESEARCH DESIGN AND METHODS

— The DPT-1 screened 103,390 first- and second-degree nondiabetic relatives of individuals in whom type 1 diabetes had been diagnosed before the age of 45 years. To have been eligible for screening, an individual must have been a first-degree relative of a patient with type 1 diabetes and aged between 3 and 45 years or a second-degree relative aged between 3 and 20 years. Staging of 3,480 relatives who were found to be ICA-positive was performed to quantify the projected 5-year risk of diabetes.

Staging

Staging consisted of ICA confirmation, HLA-DQ typing, determination of insulin antibodies, and glucose tolerance testing (intravenous glucose tolerance test [IVGTT] and oral glucose tolerance test [OGTT]). Relatives with HLA-DQA 1*0102/DQB1*0602 were excluded from the DPT-1. Of 808 subjects, those considered to have a >50% 5-year risk were eligible for entry into the parenteral insulin trial ($n = 339$) if either the FPIR was <1st or 10th percentile (depending on age and relation to the proband) on two occasions and/or there were abnormalities (other than diabetes) on an OGTT. If none of these metabolic abnormalities were present, the FPIR was above threshold (if ≥10 percentile for siblings, offspring, and second-degree relatives or if ≥1st percentile for parents), testing for insulin autoantibody (IAA) was positive, and the 5-year risk was considered to be 25–50%, participants ($n = 372$) were entered into the oral insulin trial. The subjects were randomly assigned to receive antigen intervention or matched placebo/observation. Neither intervention showed a statistically significant difference between the treatment arms in terms of progression to type 1 diabetes. To study the natural history of this disease, we report here the results of 186 subjects from the oral insulin trial (moderate-risk group) and 170 subjects from the parenteral trial (high-risk group) who were randomly assigned to the placebo/observation arms of the studies.

Follow-up

All subjects were seen every 6 months, at which point an OGTT was administered to assess glycemic status. The dose of oral glucose was 1.75 g/kg (maximum, 75 g of carbohydrate). Blood samples were obtained for C-peptide measurements in the fasting state and then 30, 60, 90, and 120 min later. The peak C-peptide was the maximum point of all measurements.

An IVGTT was performed after an overnight fast at baseline, annually thereafter for moderate-risk subjects or biannually thereafter for high-risk subjects, and at study end for all subjects. Samples were obtained through a temporary indwelling intravenous catheter. Measurements of fasting glucose, fasting insulin, FPIR, and HOMA-IR came from the IVGTT sample.

Impaired glucose tolerance

Impaired glucose tolerance by American Diabetes Association criteria (1997) was defined as fasting plasma glucose <126 mg/dl and 2-h plasma glucose between 140 and 199 mg/dl.

Diagnosis of diabetes

Diabetes was diagnosed according to American Diabetes Association criteria: fasting glucose ≥126 mg/dl, 2-h glucose ≥200 mg/dl with confirmation by either an elevated fasting or 2-h glucose level at a follow-up visit, or random plasma glucose ≥200 mg/dl accompanied by symptoms of polyuria, polydipsia, and/or weight loss.

Laboratory measures

Plasma glucose was measured by the glucose oxidize method. Glucose tolerance tests were performed after an overnight fast. FPIR was calculated as the sum of the serum insulin concentrations at 1 and 3 min after intravenous injection of glucose. HOMA-IR was calculated as the fasting insulin (milliunits per liter) × fasting glucose (millimoles per liter)/22.5 from the mean of fasting insulin at 10 and 4 min and fasting glucose at 4 min before each IVGTT performed.

ICA assay

Cytoplasmic ICAs were determined on frozen sections of human pancreas. Samples were considered positive at ≥10 Juvenile Diabetes Foundation units.

IAA assay

IAAs were measured by a competitive liquid-phase radioassay. As noted in the DPT-1 protocol, the initial entry criterion for IAA was a level ≥80 nU/ml, which was subsequently changed to a level ≥39 nU/ml (17).

GAD and ICA512 autoantibody assays

GAD and ICA512 autoantibody levels were measured simultaneously in a combined GAD and ICA512 autoantibody radioassay. The assay was performed in 96-well filtration plates with autoantibody-bound [^{3}H]GAD65 and [^{35}S]ICA512 precipitated with protein A–Sepharose. The cut points were set at indexes of 0.032 (mean ± 2 SD for GAD antibodies) and 0.049 (mean ± 6 SD for ICA512 antibodies), the 99th percentiles of 198 normal control subjects.

HLA-DQ typing

For HLA-DQ typing, DNA was extracted from the buffy coats of peripheral blood leukocytes, and HLA-DQA1 and DQB1 alleles were amplified by PCR with the use of sequence-specific probes. In the analysis of this article, a high-risk HLA genotype was defined as having one of the following haplotype combinations: DQA1*0301-DQB1*0302, DQA1*0501-DQB1*0201, DQA1*04-DQB1*0201, or DQA1*0301-DQB*0201.

Statistical methods

Variables (ICA titers, IAA titers, peak C-peptide, fasting glucose, fasting insulin, FPIR, HOMA-IR, and the FPIR–to–HOMA-IR ratio) that were not normally distributed were log transformed for analysis. For clarity of presentation, the results in Table 1 are expressed as back-transformed mean ± SD or median (interquartile range) values. Categorical variables were compared by Pearson's χ^2 test. The continuous variables were tested by *t* test for the differences in means or by Wilcoxon's rank-sum test for the differ-

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Table 1—*Baseline characteristics of the study subjects*

Characteristic	Moderate-risk population			High-risk population		
	Progressor	Nonprogressor	*P* value	Progressor	Nonprogressor	*P* value
n	53 (28)	133 (72)		70 (41)	100 (59)	
Age (years)	9.70 (6.22–11.94)	10.44 (7.34–14.91)	0.035	10.50 (8.41–13.74)	13.69 (9.28–23.06)	0.002
BMI *Z*-score*	−0.67 (−1.56 to 0.53)	−1.10 (−2.61 to 0.33)	0.067	−1.60 (−3.30 to −0.49)	−1.08 (−2.80 to 0.24)	0.094
Genotype			0.252			0.521
High risk	48 (90.57)	111 (84.09)		60 (85.71)	82 (82.00)	
Low risk	5 (9.43)	21 (15.91)		10 (14.29)	18 (18.00)	
Race			0.642			0.345
White	47 (88.68)	116 (89.23)		67 (95.71)	91 (94.79)	
African American	0 (0.00)	2 (1.54)		1 (1.43)	0 (0.00)	
Hispanic	4 (7.55)	10 (7.69)		1 (1.43)	4 (4.17)	
Other	2 (3.77)	2 (1.54)		1 (1.43)	1 (1.04)	
Sex			0.530			0.840
Male	28 (52.83)	77 (57.89)		36 (51.43)	53 (53.00)	
Female	25 (47.17)	56 (42.11)		34 (48.57)	47 (47.00)	
Relationship to patient with diabetes			0.086			0.124
Sibling	36 (67.92)	72 (54.14)		51 (72.86)	61 (61.00)	
Offspring	15 (28.30)	38 (28.57)		13 (32.50)	27 (27.00)	
Parent	1 (1.89)	6 (4.51)		0 (0.00)	5 (5.00)	
Second-degree relative	1 (1.89)	17 (12.78)		6 (8.57)	7 (7.00)	
Immunological factors						
ICA titer (JDF units)	160.00 (80.00–320.00)	80.00 (20.00–160.00)	0.001	160.00 (80.00–320.00)	80.00 (40.00–160.00)	0.002
IAA titer (nU/ml)	385.10 (125.40–672.00)	156.70 (73.70–343.00)	0.001	257.55 (38.40–468.40)	52.50 (22.00–274.55)	0.002
ICA512 autoantibodies			0.010			0.001
Positive	32 (64.00)	50 (42.37)		45 (68.18)	38 (41.30)	
Negative	18 (36.00)	68 (57.63)		21 (31.82)	54 (58.70)	
GAD antibodies			0.674			0.012
Positive	38 (76.00)	86 (72.88)		55 (83.33)	60 (65.22)	
Negative	12 (24.00)	32 (27.12)		11 (16.67)	32 (34.78)	
Metabolic factors						
Fasting insulin (mU/l)	15.00 (11.00–20.00)	13.00 (9.40–17.00)	0.053	10.00 (7.50–14.00)	10.00 (7.00–14.00)	0.811
Fasting glucose (mmol/l)	4.83 (4.50–5.17)	4.83 (4.61–5.11)	0.911	4.97 (4.56–5.33)	4.89 (4.69–5.22)	0.965
Impaired glucose†						0.003
IGT				33 (47.14)	25 (25.00)	
NGT				37 (52.86)	75 (75.00)	
FPIR (μl/ml)	125.00 (101.00–154.00)	140.00 (105.90–187.00)	0.124	56.00 (44.00–80.00)	76.00 (59.00–90.00)	0.004
HOMA-IR	3.20 (2.37–4.24)	2.67 (1.91–3.89)	0.094	2.20 (1.54–3.24)	2.21 (1.50–3.14)	0.861
FPIR–to–HOMA-IR ratio	41.14 (31.25–53.98)	51.90 (40.91–66.06)	0.001	28.54 (17.69–38.96)	32.62 (22.76–45.39)	0.010
Peak C-peptide (nmol/l)	4.60 (3.60–5.60)	5.10 (3.80–6.90)	0.172	3.90 (2.90–5.00)	5.10 (3.95–6.20)	0.001
A1C (%)	5.40 ± 0.32	5.31 ± 0.34	0.072	5.40 ± 0.63	5.36 ± 0.39	0.596

Data are *n* (%), median (interquartile range), or means ± SD. *BMI *Z*-score from the 2000 Centers for Disease Control and Prevention Growth Chart. †All subjects in the moderate-risk group were normal glucose tolerant. IGT, impaired glucose tolerance; JDF, Juvenile Diabetes Foundation; NGT, normal glucose tolerance.

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Table 2—*Univariate Cox proportional hazards model to predict the risk of type 1 diabetes*

Variables	Moderate-risk population			High-risk population		
	Parameter	*P* value	HR	Parameter	*P* value	HR
n	187			170		
Age at randomization	−0.05 ± 0.02	0.035	0.95	−0.07 ± 0.02	<0.001	0.93
BMI *Z*-score at randomization	0.12 ± 0.08	0.14	1.12	−0.06 ± 0.06	0.324	0.94
Race (white vs. nonwhite)	0.07 ± 0.43	0.869	1.07	0.19 ± 0.59	0.742	1.22
Sex	0.15 ± 0.28	0.601	1.16	0.17 ± 0.24	0.467	1.19
Relation to proband (sibling vs. nonsibling)	0.41 ± 0.3	0.172	1.5	0.25 ± 0.27	0.352	1.28
Genotype (high risk vs. low risk)	0.47 ± 0.47	0.319	1.6	0.38 ± 0.34	0.269	1.46
Log (ICA titer)	0.32 ± 0.1	0.001	1.38	0.16 ± 0.08	0.039	1.17
Log (IAA titer)	0.39 ± 0.12	0.002	1.48	0.17 ± 0.08	0.018	1.19
ICA512 (positivity)	0.95 ± 0.3	0.002	2.59	0.79 ± 0.26	0.003	2.2
GAD65 (positivity)	0.06 ± 0.33	0.854	1.06	0.53 ± 0.33	0.106	1.71
Impaired glucose tolerance	NA			1.2 ± 0.25	<0.001	3.32
A1C	0.96 ± 0.4	0.017	2.61	0.97 ± 0.3	0.001	2.64
Log (peak C-peptide)	−0.33 ± 0.35	0.347	0.72	−0.74 ± 0.26	0.005	0.48
Log (fasting insulin)	0.5 ± 0.23	0.034	1.64	0.41 ± 0.22	0.062	1.51
Log (fasting glucose)	0.99 ± 1.24	0.426	2.69	1.22 ± 1.27	0.336	3.38
Log (HOMA-IR)	0.45 ± 0.22	0.038	1.57	0.39 ± 0.21	0.058	1.48
Log (FPIR)	−0.3 ± 0.32	0.352	0.74	−0.37 ± 0.23	0.109	0.69
Log (FPIR–to–HOMA-IR ratio)	−0.96 ± 0.27	<0.001	0.39	−0.53 ± 0.17	0.002	0.59

Data are means ± SE unless otherwise indicated.

ences in order. The association of HOMA-IR and FPIR–to–HOMA-IR ratio with time to type 1 diabetes was adjusted for potential confounders using the multivariate Cox proportional hazards model. The β coefficient parameters indicated the direction of the association between the predictor and response variables, and hazard ratios (HRs) were obtained. A paired *t* test was used to compare the relative change of HOMA-IR and the FPIR–to–HOMA-IR ratio. Correlation coefficients were obtained by Spearman's nonparametric correlation method. Forward selection using a Cox proportional hazards model was applied to select the best risk factors for type 1 diabetes. Tests of significance were two tailed. $P < 0.05$ was considered to be statistically significant. Statistical analyses were performed with SAS (version 9; SAS Institute, Cary, NC). The analysis was performed separately for the subjects in the moderate-risk group and in the high-risk group.

RESULTS

Subjects at baseline

Table 1 shows the clinical and metabolic characteristics of subjects by risk group. By design, subjects in the moderate-risk group who were ICA^+ and IAA^+ with an FPIR above the threshold ($n = 186$) had a projected 25−50% risk for diabetes over 5 years, and subjects in the high-risk group who were ICA^+ and had a below-threshold FPIR or impaired glucose tolerance ($n = 170$) had a projected >50% risk for diabetes over 5 years. In both groups, those who progressed to clinical diabetes were younger than those who did not (moderate-risk group $P = 0.035$; high-risk group $P = 0.002$). Progressors and nonprogressors did not differ in sex, relationship to proband, race, or proportion of subjects with a high-risk HLA. In terms of immunologic factors, the progressors presented higher IAA and ICA titers in both risk groups (moderate-risk group $P = 0.001$; high-risk group $P = 0.002$). Those progressors in the high-risk group had a higher proportion of GAD65 antibodies present than nonprogressors ($P = 0.012$), an observation not found in the moderate-risk group ($P = 0.674$). This finding suggests that the number of antibodies, even among those with loss of FPIR and/or glucose intolerance, is an important predictor of type 1 diabetes.

At baseline, we did not detect a difference in HOMA-IR, but the ratio of FPIR to HOMA-IR was significantly different in both risk groups, comparing progressors to nonprogressors (moderate-risk group $P < 0.001$; high-risk group $P = 0.010$). In the high-risk group, FPIR, peak C-peptide, and proportion of subjects with impaired glucose tolerance were significantly different, comparing progressors with nonprogressors at $P = 0.004$, $P < 0.001$, and $P = 0.003$, respectively.

HOMA-IR and FPIR–to–HOMA-IR ratio for type 1 diabetes risk prediction

Before the end of the study, 53 subjects in the moderate-risk group and 70 subjects in the high-risk group developed type 1 diabetes. The median follow-up was 4.3 years for moderate-risk subjects and 3.7 years for high-risk subjects.

In Table 2, the time to type 1 diabetes was significantly associated with HOMA-IR ($P = 0.038$) and the FPIR–to–HOMA-IR ratio ($P < 0.001$) at baseline in a univariate model in the moderate-risk group. In the high-risk group, there was a significant association between the FPIR–to–HOMA-IR ratio and time to type 1 diabetes ($P = 0.002$) and a marginally significant association between HOMA-IR and time to type 1 diabetes ($P = 0.058$). Time to type 1 diabetes was also shown to be associated with age, ICA titers, IAA titers, ICA512 positivity, A1C, and fasting insulin in the moderate-risk group and with age, ICA titers, IAA titers, ICA512 positivity, impaired glucose tolerance, A1C, and peak C-peptide in the high-risk group.

From the multivariate analysis results (Table 3), progression to type 1 diabetes was strongly associated with HOMA-IR and FPIR in both risk groups (model 1).

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Table 3—*HOMA-IR and the FPIR–to–HOMA-IR ratio are the risk predictors of type 1 diabetes*

	Parameter	*P* value	HR	LCL (HR)	UCL (HR)
Moderate-risk population (*n* = 186)					
Model 1					
Log (IAA titer)	0.34 ± 0.15	0.026	1.41	1.04	1.90
A1C	1.06 ± 0.44	0.015	2.90	1.23	6.84
Log (HOMA-IR)	0.99 ± 0.32	0.002	2.70	1.45	5.06
Log (FPIR)	−1.14 ± 0.41	0.005	0.32	0.14	0.71
Model 2					
Log (IAA titer)	0.42 ± 0.14	0.003	1.53	1.16	2.01
A1C	1.07 ± 0.40	0.008	2.93	1.32	6.47
Log (FPIR–to–HOMA-IR ratio)	−1.14 ± 0.30	<0.001	0.32	0.18	0.57
High-risk population (*n* = 170)					
Model 1					
Age at randomization	−0.07 ± 0.02	<0.001	0.93	0.89	0.97
Impaired glucose tolerance	0.89 ± 0.26	0.001	2.43	1.45	4.07
A1C	0.90 ± 0.29	0.002	2.46	1.39	4.36
Log (HOMA-IR)	0.61 ± 0.22	0.006	1.83	1.19	2.82
Log (FPIR)	−0.56 ± 0.23	0.018	0.57	0.36	0.91
Model 2					
Age at randomization	−0.07 ± 0.02	<0.001	0.93	0.90	0.97
Impaired glucose tolerance	0.89 ± 0.26	0.001	2.44	1.46	4.07
A1C	0.91 ± 0.28	0.001	2.49	1.42	4.34
Log (FPIR–to–HOMA-IR ratio)	−0.58 ± 0.17	0.001	0.56	0.40	0.78

Data are means ± SE unless otherwise indicated. Model 1: moderate-risk population: age, ICA titers, IAA titers, ICA512 positivity, A1C, FPIR, HOMA-IR; high-risk population: age, ICA titers, IAA titers, ICA512 positivity, impaired glucose tolerance, peak C-peptide, A1C, FPIR, and HOMA-IR. Model 2: moderate risk population: age, ICA titers, IAA titers, ICA512 positivity, A1C, FPIR–to–HOMA-IR ratio; high-risk population: age, ICA titers, IAA titers, ICA512 positivity, impaired glucose tolerance, peak C-peptide, A1C, and FPIR–to–HOMA-IR ratio. LCL, lower confidence limit; UCL, upper confidence limit.

In addition, the baseline ratio of FPIR to HOMA-IR was independently associated with progression to type 1 diabetes (model 2). The HRs of HOMA-IR were 2.70 (95% CI 1.45–5.06) in the moderate-risk group and 1.83 (1.19–2.82) in the high-risk group. This indicates that increased insulin resistance increases the risk for type 1 diabetes. The HRs for the FPIR–to–HOMA-IR ratio were 0.32 (0.18–0.57) in the moderate-risk group and 0.56 (0.40–0.78) in the high-risk group. When the ratio of insulin secretion to insulin resistance decreased, the risk of type 1 diabetes increased (online appendix Fig. 1 [available at http://dx.doi.org/10.2337/dc06-2389]).

HOMA-IR and FPIR–to–HOMA-IR ratio relative change

For the progressors, we compared relative changes from the baseline to the last IVGTT test before diabetes onset. In both groups, the average insulin resistance increased during the study course; meanwhile, the ratio of FPIR to HOMA-IR decreased. In the moderate-risk group, the average ± SD HOMA-IR of the progressors was 5.06 ± 4.25 from the last IVGTT test, compared with 3.79 ± 2.69 at baseline ($P = 0.07$), and the FPIR–to–HOMA-IR ratio was 26.35 ± 19.84 versus 44.28 ± 19.20 with $P < 0.001$ using a paired *t* test. In the high-risk group, the HOMA-IR of the progressors was 3.08 ± 1.61 from the last IVGTT test, compared with 2.60 ± 1.34 at baseline ($P < 0.001$), and the FPIR–to–HOMA-IR ratio was 18.37 ± 12.09 versus 28.91 ± 14.59 with $P < 0.001$.

HOMA-IR and fasting insulin were significantly and highly correlated in both risk groups ($r = 0.98$, $P < 0.001$). HOMA-IR was significantly correlated with fasting glucose as might be expected (moderate-risk group $r = 0.51$, $P < 0.001$; high-risk group $r = 0.59$, $P < 0.001$). The correlations between HOMA-IR and FPIR was 0.56 ($P < 0.001$) in the moderate-risk group and 0.37 ($P < 0.001$) in the high-risk group. In the moderate-risk group, the correlations between A1C, peak C-peptide, and HOMA-IR were significant with $r = 0.27$ ($P < 0.001$) and $r = 0.50$ ($P < 0.001$), respectively. In the high-risk group, the correlations between A1C, peak C-peptide, impaired glucose tolerance, and HOMA-IR were significant with $r = 0.32$ ($P < 0.001$), $r = 0.30$ ($P < 0.001$), and $r = 0.28$ ($P = 0.002$), respectively. Because of these correlations, we added fasting insulin and fasting glucose into a multivariate Cox proportional hazards model together with HOMA-IR, FPIR, and the FPIR–to–HOMA-IR ratio to test their independent contribution to type 1 diabetes risk. A forward selection model showed the same risk factors as model 2 (Table 3). Thus, the combination of FPIR and HOMA-IR, measured as the FPIR–to–HOMA-IR ratio, was a better indicator than FPIR and HOMA-IR themselves (or the components, fasting insulin and glucose), suggesting that there was an interaction effect of FPIR and HOMA-IR.

CONCLUSIONS — Differing degrees of insulin sensitivity can be accommodated by altering insulin secretion to maintain normal blood glucose concentrations for those who have normal β-cell function (18). Defects in insulin secretion resulting from β-cell death and dysfunction characterize type 1 diabetes. However, the state of glucose tolerance is determined by the physiological relationship between insulin secretion and insulin resistance, which can also influence the progression to clinical disease. The regulatory mechanism governing hepatic glucose output and insulin secretion suggests that increasing insulin resistance generally results in increased insulin se-

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cretion (19,20). A 1996 study showed that normoglycemic ICA$^+$ first-degree relatives of type 1 diabetic patients became more insulin resistant and had a decrease in intravenous glucose tolerance after 2 weeks of nicotinamide treatment and that these effects were associated with the expected increase in insulin secretion (21). It is postulated that the increased incidence of clinical type 1 diabetes during puberty and the anecdotal reports of a precedent illness could be attributed to the influence of relative insulin resistance during these time periods. Insulin resistance during the development of type 1 diabetes may be related to counter-regulatory hormones such as those associated with puberty (22,23).

Three longitudinal studies have been conducted to evaluate the risk of insulin resistance downregulating insulin action and leading to glucose abnormalities in the progression of subclinical type 1 diabetes. In the Melbourne Pre-Diabetes Family Study, insulin resistance measured by HOMA-IR in relation to secretion assessed by FPIR in IAA$^+$ individuals accounted for increased risk for progression to clinical diabetes. Similar results were observed in the Childhood Diabetes in Finland Study. In contrast, using estimates of insulin resistance derived from a modification of the Bergman minimal model from the frequently sampled IVGTT, the Seattle Family Study showed that such measurements of insulin resistance did not improve the prediction of clinical disease. In the DPT-1, we followed two different populations with a 25–50% or >50% projected risk of developing type 1 diabetes within 5 years. In this study, we found a significant association between HOMA-IR, the ratio of FPIR to HOMA-IR, and the onset of diabetes in both risk groups after adjustments for other risk factors. In addition, the subjects who developed type 1 diabetes in both groups showed an increased HOMA-IR and decreased FPIR–to–HOMA-IR ratio at the time of diagnosis, relative to their baseline values. These findings confirmed earlier studies (13,14) using nearly the same methodology for measuring insulin resistance in a larger well-defined multi-institutional cohort accessioned across the U.S. and Canada. The one study that did not show the same association between insulin resistance and progression to type 1 diabetes used a different methodology, which might suggest an explanation for its findings.

We note, however, that Wallace et al. (24) suggested that insulin resistance measured by HOMA-IR, as was done in this study, may underestimate actual insulin resistance values. Despite this possible underestimation of actual resistance, HOMA-IR and the ratio of FPIR–to–HOMA-IR are shown to be useful in predicting the risk of type 1 diabetes in this longitudinal study. They confirm the importance of the ratio of insulin secretion after an IVGTT to the product of the fasting insulin and glucose levels. The findings also support the prognostic significance of the baseline A1C values in both risk groups.

In summary, using a multivariate Cox proportional hazards model in our studies, we have found clear evidence of an association between insulin resistance and progression to type 1 diabetes. The FPIR–to–HOMA-IR ratio, which is a measure of the combination of insulin resistance and insulin secretion, has also been found to be a better risk predictor than either measure used separately. With a better understanding of the metabolic mechanism of glucose production and uptake for this disease, effective intervention therapies may be developed based on targeting both insulin secretion and insulin sensitivity in the preclinical period of type 1 diabetes.

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