Can Clinical Factors Estimate Insulin Resistance in Type 1 Diabetes?

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An insulin resistance syndrome (IRS) score was developed based on clinical risk factors in adults with childhood-onset type 1 diabetes in the Epidemiology of Diabetes Complications (EDC) Study and was validated using euglycemic-hyperinsulinemic clamp studies. Hypertension, waist-to-hip ratio (WHR), triglyceride and HDL cholesterol levels, family history of type 2 diabetes, and glycemic control were risk factors used to define the score. A score of 1 (lowest likelihood IRS) to 3 (highest likelihood IRS) was assigned for each risk factor. Eligible subjects (n = 24) were recruited from the EDC cohort based on tertile of IRS score. Subjects received an overnight insulin infusion to normalize glucose levels, then underwent a 3-h euglycemic-hyperinsulinemic (60 mU · m^{-2} · min^{-1}) clamp. Glucose disposal rate (GDR) was determined during the last 30 min of the clamp. The GDR differed significantly by IRS group (9.65 ± 2.99, 8.02 ± 1.39, and 5.68 ± 2.16 mg · kg^{-1} · min^{-1}, $P < 0.01$). The GDR was inversely correlated with the IRS score ($r = –0.64$, $P < 0.01$). Using linear regression, the combination of risk factors that yielded the highest adjusted r^2 value (0.57, $P < 0.001$) were WHR, hypertension, and HbA_1. This study found that clinical risk factors can be used to identify subjects with type 1 diabetes who are insulin resistant, and it provides validation of a score based on clinical factors to determine the extent of insulin resistance in type 1 diabetes. This score will be applied to the entire EDC population in future studies to determine the effect of insulin resistance on complications. *Diabetes* 49:626–632, 2000

Coronary artery disease (CAD) is a leading cause of mortality in type 1 diabetes. In nondiabetic subjects, several large prospective studies have suggested that hyperinsulinemia, a marker of insulin resistance, is associated with an increased risk of cardiovascular disease (1–4). Insulin resistance has been documented in type 1 diabetes (5–10) and may contribute to the high risk for cardiovascular disease in this population (5–7). However, the study of the relationship between CAD and insulin resistance in type 1 diabetes is limited by the difficulty encountered with relatively simple determinants of insulin resistance, such as either insulin levels alone or glucose and insulin levels using the homeostasis model assessment (11). Rather, more invasive and costly techniques that are not typically suitable for large-scale population studies, such as the euglycemic-hyperinsulinemic clamp, must be used. It is not known if clinical factors that are more readily obtainable can identify patients with type 1 diabetes who are likely to have insulin resistance.

The insulin resistance syndrome (IRS) is characterized by the clinical characteristics of hypertension, abdominal obesity, high triglycerides, and low HDL levels (1,2). Family history of type 2 diabetes is another clinical factor that may also increase the risk for insulin resistance (12–14). The presence of several clinical factors associated with insulin resistance or the IRS in a given patient may further compound the likelihood of insulin resistance. Identification of clinical components of the IRS that are associated with insulin resistance in type 1 diabetes could have applications both in epidemiological studies, to assess associations between risk factors and outcomes, and in clinical practice, to identify subjects who would benefit from interventions that are known to improve insulin sensitivity. Although several studies to date have examined the pattern and mechanisms of insulin resistance in type 1 diabetes (8,15–17), no studies could be identified that examined the ability of clinical components of the IRS to predict the presence of insulin resistance in this population.

The Pittsburgh Epidemiology of Diabetes Complications (EDC) Study is a prospective study of a representative cohort of subjects with childhood-onset type 1 diabetes, and it offers an opportunity to examine the clinical factors associated with insulin resistance in this population. In a prior study of the EDC population, an elevated waist-to-hip ratio (WHR), a marker of insulin resistance, was positively correlated with triglycerides and systolic and diastolic blood pressure and negatively correlated with HDL cholesterol (18), all of which are characteristics of IRS. In this same population, an elevated WHR was also found to be related to complications of type 1 diabetes (19). In addition, a family history of type 2 diabetes was found to be a risk factor for CAD in the EDC population (20). The purpose of this study was to determine if such clinical data could characterize the likelihood of having insulin resistance as determined by the euglycemic-hyperinsulinemic clamp. Based on the clinical characteristics of hypertension, WHR, triglyceride and HDL cholesterol levels, family history of type 2 diabetes,

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CAD, coronary artery disease; EDC, Epidemiology of Diabetes Complications; GDR, glucose disposal rate; IRS, insulin resistance syndrome; WHR, waist-to-hip ratio.

and glycemic control, an IRS score was developed and validated using the euglycemic-hyperinsulinemic clamp in a subset (n = 24) of the EDC population.

RESEARCH DESIGN AND METHODS

EDC population. The Pittsburgh EDC Study is a 10-year prospective study of a well-defined cohort of childhood-onset (<17 years) type 1 diabetic subjects. Subjects (n = 325 women, 333 men) diagnosed between 1 January 1950 and 30 May 1980 were first seen at the baseline examination (1986–1988) and then biennially for a maximum, in this analysis, of 8 years (maximum of five visits, fifth visit 1994–1996). The design and methods of the study have been previously described (21,22). From this population, subjects (12 men, 12 women) were selected based on their likelihood of manifesting insulin resistance (low, moderate, or high) based on a six-component IRS score determined from clinical factors and described below.

Eligibility criteria. Eligibility criteria for participation in the current study included age >18 years, HbA_1 <11.4% (HbA_{1c} approximately <9.4%) during the most recent EDC visit and the clamp visit, serum creatinine <1.5 mg/dl, and a normal hemoglobin and hematocrit. The cutoff level of 11.4% for HbA_1 was chosen to minimize the likelihood of excessive hepatic production due to poor glycemic control (17). Subjects were also ineligible if they used insulin-sensitizing agents (metformin or troglitazone) within 3 months of examination, had a myocardial infarction within the past 6 months, had a stroke within the past year, or had greater than digital amputations. All women were studied during the follicular phase of their menstrual cycle.

Insulin resistance score. The IRS score was based on variables in five major clinical categories of IRS risk factors: hypertension, WHR, triglyceride and HDL cholesterol levels, and family history of type 2 diabetes. Because poor glycemic control has also been shown to increase insulin resistance in type 1 diabetes (17,23,24), HbA_1 level was also incorporated into the score. Each individual in the EDC population was categorized into age- and sex-tertile distributions for each of the risk factors based on low, moderate, or high likelihood for insulin resistance as described below. Subjects received a score for each risk factor category (1 = low, 2 = moderate, 3 = high). The score for each of the risk factors was summed and then divided by the total number of risk factors for which data were available to determine the IRS score. For example, a subject in the highest age- and sex-specific tertiles for WHR, triglycerides, and HbA_1 level; in the lowest age- and sex-specific tertiles for HDL cholesterol; with a history of hypertension; and with a family history of type 2 diabetes would score a 3.00 for each of these six categories, resulting in a mean score of 3.00.

The categorization of continuous variables for likelihood of the IRS was based on a pooled analysis of all EDC data (baseline through visit 5) as shown in Table 1. The pooled analysis included tertile analysis for sex- and age-specific (third, fourth, and fifth decades) groupings for WHR, triglycerides, HDL cholesterol, and HbA_1. Each individual provided one value for each age-group, representing the mean of that variable for the individual in the applicable cycles. For example, a male in his twenties during the first three examinations provided one data point (for each risk factor) to the pooled distribution based on the mean of three exams. The remaining two cycles were averaged for inclusion into the distribution of males in their thirties. Due to limited numbers of subjects in the extremes of age categories, those aged 18 or 19 were scored according to the 20- to 29-year-old group and those over 50 years of age were scored according to the 40- to 49-year-old group.

For the hypertension component of the score, a two-step process was used. First, subjects were considered to have a high likelihood of demonstrating insulin resistance and placed in the top tertile (score = 3) if their blood pressure was >140 mmHg systolic or >90 mmHg diastolic or if they were receiving antihypertensive medication. Then, of the remaining subjects, those in the lowest tertile for either systolic or diastolic blood pressure in age- and sex-specific groups were considered to have low likelihood for insulin resistance (score = 1); all others were considered to have moderate likelihood (score = 2). Family history information was ascertained on the general medical history questionnaire. A family history of presumed type 2 diabetes (defined as diabetes diagnosed after 30 years of age in a first-degree relative) was further evaluated to validate the diagnosis and type of diabetes as detailed previously (20). Family history of type 2 diabetes in first-degree relatives was scored as a dichotomous variable. Individuals with a positive family history of type 2 diabetes were considered to have the highest likelihood of insulin resistance (score = 3), whereas individuals without a family history were considered at lowest risk (score = 1).

Recruitment. To recruit an evenly distributed range of subjects with respect to anticipated glucose disposal rate (GDR), an IRS score for all EDC subjects was determined from data collected at the most recent EDC clinic visit. Subjects were categorized as having a low, moderate, or high risk for IRS, according to the score tertiles for the entire population. Eligible subjects were then invited to participate in this study. Based on the IRS score obtained the day of the euglycemic-hyperinsulinemic clamp study, subjects were assigned to a low-, moderate-, or high-risk group for likelihood of insulin resistance. As soon as each group was fully recruited (n = 8 per group), all other subjects with similar IRS scores became ineligible (i.e., quota sampling was used).

The day before the clamp study, subjects completed an informed consent, and a medical history and physical examination was performed. Subjects were admitted to the General Clinical Research Center (GCRC) to stabilize blood glucose levels. Blood pressure, HbA_1, height, weight, and WHR were performed on the evening of admission, and a fasting lipid profile was obtained immediately before the initiation of the clamp study.

Euglycemic-hyperinsulinemic clamp. At approximately 9:00 P.M. the day before the clamp study, two intravenous catheters were inserted. One catheter was placed in a vein in the antecubital region for administration of insulin and glucose, and the second was placed into a vein on the contralateral hand for blood sampling. The blood glucose was monitored hourly, unless otherwise needed, and insulin infusion was regulated according to a standardized protocol to stabilize the blood glucose at 5.6–7.8 mmol/l.

The euglycemic-hyperinsulinemic clamp was started at 8:00 A.M. and was completed at 11:00 A.M., with a continuous infusion of regular insulin at a constant rate of 60 mU · m^{-2} · min^{-1} to obtain plasma free insulin levels of ~700 pmol/l. The hand with the intravenous catheter was placed into a warmer pad to arterialize the venous blood (25). During the clamp, the plasma glucose was maintained at 5.4–5.8 mmol/l by concomitant intravenous infusion of 20% glucose, on the basis of plasma glucose determinations every 5 min at the bedside. Blood was sampled for determination of plasma free insulin every 15 min for the last 60 min of the

TABLE 1
Age- and sex-specific cut points used for the components of the IRS score

	20–29 Years age-group			30–39 Years age-group			40–49 Years age-group		
	Low risk	Moderate risk	High risk	Low risk	Moderate risk	High risk	Low risk	Moderate risk	High risk
Triglycerides (mmol/l)									
Men	<1.78	1.78–2.55	>2.55	<1.97	1.97–3.31	>3.31	<2.35	2.35–3.72	>3.72
Women	<1.71	1.71–2.58	>2.58	<1.64	1.64–2.67	>2.67	<1.73	1.73–2.91	>2.91
HDL cholesterol (mmol/l)									
Men	>1.37	1.37–1.19	<1.19	>1.29	1.29–1.13	<1.13	>1.34	1.34–1.11	<1.11
Women	>1.60	1.60–1.32	<1.32	>1.63	1.63–1.34	<1.34	>1.66	1.66–1.40	<1.40
WHR									
Men	<0.84	0.84–0.87	>0.87	<0.86	0.86–0.89	>0.89	<0.87	0.87–0.92	>0.92
Women	<0.74	0.74–0.79	>0.79	<0.75	0.75–0.80	>0.80	<0.75	0.75–0.80	>0.80
HbA_1 (%)									
Men	<9.8	9.8–11.4	>11.4	<9.6	9.6–11.0	>11.0	<10.0	10–11.1	>11.1
Women	<9.7	9.7–11.11	>11.1	<9.5	9.5–10.9	>10.9	<9.7	9.7–11.1	>11.1

TABLE 2
Characteristics of the study participants by IRS risk category

	IRS risk category		
	Low	Moderate	High
n (M/F)	5/3	3/4	4/5
IRS concurrent score	1.48 ± 0.27	1.93 ± 0.09	2.45 ± 0.27§
Factors in score			
WHR	0.83 ± 0.09	0.84 ± 0.07	0.90 ± 0.09*
Triglycerides (mmol/l)	1.98 ± 0.57	3.38 ± 1.60	3.71 ± 1.55†
HDL cholesterol (mmol/l)	1.27 ± 0.17	1.03 ± 0.17	1.04 ± 0.27*
Hypertension (n)	0	0	5‡
Family history of diabetes (n)	0	0	7§
HbA_1 (%)	8.6 ± 1.1	9.5 ± 1.1	10.3 ± 1.1†
Factors not in score			
Age (years)	36.6 ± 5.1	33.4 ± 10.6	37.2 ± 6.7
Systolic blood pressure (mmHg)	120 ± 12	110 ± 10	126 ± 16*
Diastolic blood pressure (mmHg)	76 ± 8	70 ± 2	77 ± 3
Insulin injections/day	2.8 ± 1.8	3.7 ± 2.4	2.4 ± 0.5
Insulin dose ($U \cdot kg^{-1} \cdot day^{-1}$)	0.57 ± 0.14	0.71 ± 0.27	0.82 ± 0.25*
Activity			
Past year ($kcal \cdot kg^{-1} \cdot week^{-1}$)	63.9 ± 57.3	60.8 ± 34.1	43.3 ± 19.6
Past week ($kcal \cdot kg^{-1} \cdot week^{-1}$)	57.0 ± 59.1	45.0 ± 27.6	34.7 ± 16.0
BMI (kg/m^2)	25.3 ± 3.5	25.3 ± 3.6	29.1 ± 3.5*
Weight (kg)	74.6 ± 13.5	76.2 ± 11.3	81.8 ± 8.8
Waist (cm)	87.1 ± 12.5	88.5 ± 10.5	99.4 ± 12.4*
Cholesterol (mmol/l)	4.12 ± 0.65	4.57 ± 0.72	4.48 ± 0.93
LDL cholesterol (mmol/l)	2.45 ± 0.57	2.86 ± 0.57	2.68 ± 0.85
Serum creatinine (mmol/l)	70 ± 9	80 ± 9	70 ± 9

Data are means ± SD or n. *P < 0.10, †P < 0.05, †P < 0.01, §P < 0.001 by risk groups.

clamp. The GDR, in milligrams per kilogram per minute, was computed over the last 30 min of each clamp.

Clinical and laboratory measures. Details regarding the clinical and metabolic evaluation for the EDC Study have been previously reported (21,22). Weight was measured using a balance-beam scale, and height was measured using a wall-mounted stadiometer with subjects in hospital gowns and without shoes. Blood pressure readings were measured by a random-zero sphygmomanometer according to the Hypertension Detection Follow-up Protocol (26) after a 5-min rest period. Fasting blood samples were obtained for the measurement of lipids, lipoproteins, and HbA_1 as previously reported (21,22). During the clamp study, plasma glucose was determined using the glucose oxidase method on a YSI glucose analyzer (Yellow Springs Instruments, Yellow Springs, OH). Plasma free insulin levels, after immediate precipitation with polyethylene glycol at the bedside, were measured using the method of Nakagawa et al. (27).

Data analysis. Validation of the IRS score was based on analysis of variance (for comparisons of the GDR between groups) and Pearson correlations (to determine the association between GDR and the IRS score across groups). Two methods were used to optimize the IRS score. The first method determined the influence of each component of the IRS score (ranging from 1 to 3) on the GDR. Correlations between the GDR and the IRS score, based on all possible combinations of a range of three to six components of the score, were examined. The second method used the actual clinical parameters (rather than the IRS score per se) to determine an estimated GDR. This approach involved using multiple linear regression using the six principal IRS risk factors as independent variables to estimate GDR. Initially, each individual IRS risk factor, after adjustment for age and sex, was correlated with GDR. The risk factors with the strongest association with GDR were then combined in a forced model, which was considered the estimate of glucose disposal. Variables that were not normally distributed were log-transformed. Data analysis was performed using the Statistical Package for the Social Sciences.

Twenty of the subjects were fully examined in accordance with the protocol. Four subjects (two men and two women) had protocol violations. Two had difficulty with their intravenous catheters, resulting in elevated glucose levels (>7.8 mmol/l) at the initiation of the hyperinsulinemic infusion, and two had HbA_1 levels >11.4% obtained the day before the clamp procedure but had HbA_1 levels <11.4% at their prior EDC examination. Because similar results were obtained when analyses were performed both with and without these four subjects, data are presented for the entire sample (n = 24).

RESULTS

Subjects. The selected sample of subjects had diabetes for 26.4 ± 6.4 years (mean ± SD) and were 35.5 ± 7.5 years of age. No differences in the demographic, anthropometric, or complication characteristics of the clamp participants and the remainder of the EDC cohort were noted. In comparison with the remainder of the EDC cohort, subjects participating in this study had slightly better glycemic control (HbA_1: 9.9 ± 1.8 vs. 10.8 ± 1.8%, P = 0.055), reflecting the inclusion criteria. Men and women did not differ in demographic or diabetes characteristics.

Validation of the IRS score. Subject characteristics based on the IRS score are shown in Table 2. Each of the risk groups differed in factors included in the IRS score. No sex differences in the factors included in the IRS score were observed, in concordance with the selection criteria used to balance sex characteristics between the three groups. Among the characteristics not directly accounted for in the score, differences of borderline significance (P < 0.10) across groups in systolic blood pressure, insulin dose, and BMI were noted. Although systolic blood pressure is not directly accounted for in the score, it was used in defining hypertension.

The three risk groups attained comparable steady-state free insulin levels during the clamp study (low: 618 ± 132, moderate: 624 ± 139, high: 624 ± 154 pmol/l, P = 0.99). Serum glucose concentrations at baseline and during the clamp were comparable between the three groups (Fig. 1). The GDR ranged from 3.8 through 13.4 $mg \cdot kg^{-1} \cdot min^{-1}$. The mean GDR determined from the clamp study differed significantly by IRS risk group (P < 0.01, Fig. 2). Similar results were obtained when the GDR was calculated using body surface

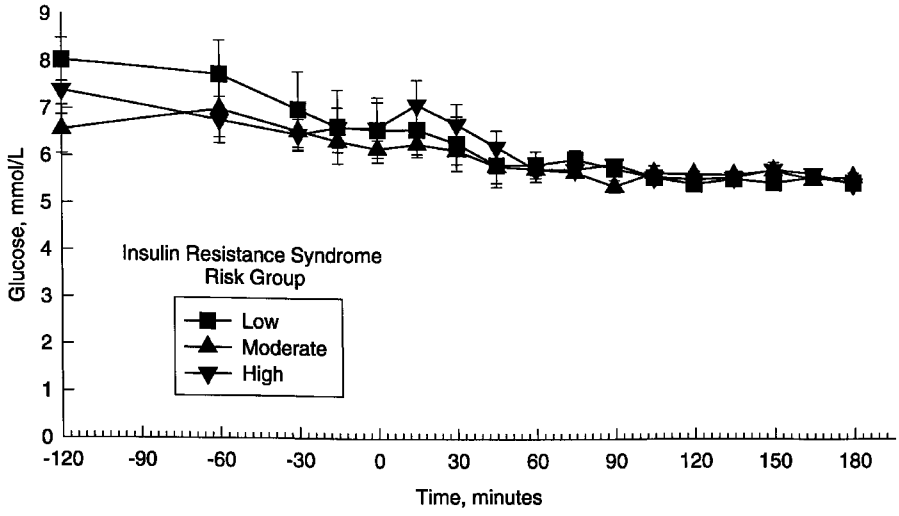

FIG. 1. Glucose levels during euglycemic-hyperinsulinemic clamp plotted by IRS risk group.

area. Adjustment for glycemic control (HbA_1) did not influence the mean GDR by sex or risk groups.

The IRS score had a significant inverse correlation with the GDR (r = –0.64, P < 0.01, Fig. 3). The strongest individual correlates of the GDR were inverse and comprised HbA_1 (r = –0.57, P < 0.01), WHR (r = –0.57, P < 0.05), waist circumference (r = –0.50, P < 0.05), and triglycerides (r = –0.51, P < 0.01). The association between HDL cholesterol and GDR did not reach statistical significance (r = 0.13). Strong correlations were also observed for GDR and both BMI (r = –0.48, P < 0.05) and insulin dose ($U \cdot kg^{-1} \cdot day^{-1}$, r = –0.48, P < 0.05). Controlling for BMI attenuated the association between the GDR and both WHR (r = –0.26, P = 0.23) and waist circumference (r = –0.27, P = 0.22).

Optimization of the IRS score. Subsequent analyses were performed to refine the IRS score to determine if a particular combination of risk factors more optimally defined the score. To determine the relationship between GDR and the six individual components of the IRS score, correlations for multiple combinations of the score components were analyzed. Initially, one component was removed in each of the combinations. Only the removal of triglycerides (r = –0.67, P < 0.01) and HDL cholesterol (r = –0.71, P < 0.0l) resulted in improved correlations. Additional combinations were analyzed, using four and then three components per score. The two best combinations of the score components incorporated history of hypertension, family history of type 2 diabetes, and WHR, with or without HbA_1 level (r = –0.74, P < 0.01 both with and without inclusion of HbA_1 level). These combinations were then examined using linear regression analysis (Table 3). As in the correlation analysis, the most explanatory set of predictors comprised history of hypertension, family history of type 2 diabetes, WHR, and HbA_1 level (r^2 = 0.56, P < 0.001) and was considered the optimized IRS score. Using the Fischer's Z test for comparing two correlation coefficients, correlations between GDR and the five- and six-component scores (r = –0.74 and –0.64, respectively) were not significantly

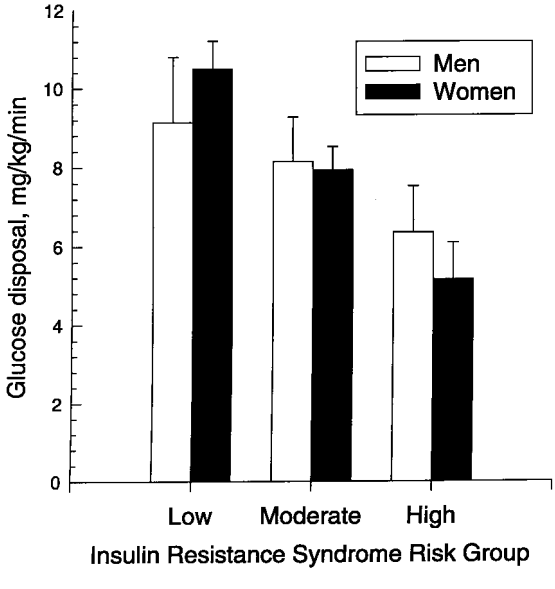

FIG. 2. Glucose disposal by IRS risk group. The mean glucose disposal differed significantly by IRS risk group (P < 0.01).

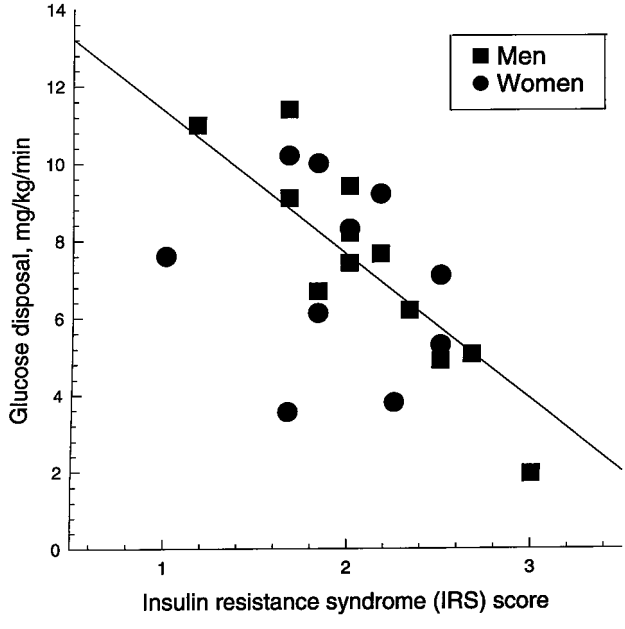

FIG. 3. Scatterplot of IRS score and glucose disposal (r = –0.64; P < 0.01).

TABLE 3
Linear regression analysis for the optimization of the IRS score

Model	R^2	Adjusted R^2	P
IRS concurrent score (6 factors)	0.43	0.34	0.009
Score 2: WHR, FH, HTN, HDL, TG	0.38	0.29	0.020
Score 3: A_1, FH, HTN, HDL, TG	0.38	0.29	0.020
Score 4: A_1, WHR, HTN, HDL, TG	0.36	0.27	0.027
Score 5: A_1, WHR, FH, HDL, TG	0.33	0.23	0.044
Score 6: A_1, WHR, FH, HTN, TG	0.51	0.43	0.002
Score 7: A_1, WHR, FH, HTN, HDL	0.47	0.39	0.005
Score 12: A_1, WHR, FH, HTN	0.56	0.49	<0.001
Score 22: WHR, FH, HTN	0.55	0.49	<0.001

The six-factor score includes HbA_1 (A_1) level, WHR, family history of type 2 diabetes (FH), hypertension (HTN), HDL cholesterol level, and triglycerides (TG). Score number represents the sequence in which the scores were analyzed, initially using five of the six risk factors (scores 2–7), then four of the six risk factors (scores 8–21), then three of the six risk factors (scores 22–30).

different, suggesting that the inclusion or exclusion of HDL levels and triglycerides added little to the overall IRS score as it related to GDR.

Estimation of GDR. Although the IRS score has an inverse relationship with insulin sensitivity, an estimate of GDR using the score may have more clinical relevance and thus may be easier to interpret. Using multivariate linear regression analysis, the individual and multiple determinants of GDR were examined. Table 4 shows multivariate regression analysis for the estimate of GDR. Model 1 is the best forward stepwise regression of the dependent variable, GDR, allowing any of the components of the insulin resistance syndrome to enter the model, i.e., triglycerides, HDL, hypertension, family history of type 2 diabetes, WHR, HbA_1, sex, and age. As shown, Model 1 includes only WHR and hypertension, where increasing WHR and presence of hypertension result in decreased glucose disposal. The adjusted R^2 for this model is 0.54.

To determine which individual factors were associated with glucose disposal, separate models were examined. Age and sex made no contribution to any of the models shown in Table 4. Where one of the IRS risk factors was forced into the model, for example, only HDL cholesterol did not have even a borderline association with GDR. This is consistent with the data presented in the validation of the IRS score. Using the remaining factors in a forced entry (model 8) combined for an r^2 value of 0.63 ($P < 0.001$). This particular model will be used as the estimate of glucose disposal in future analysis. Based on this model, the estimated GDR, in $mg \cdot kg^{-1} \cdot min^{-1}$, can be calculated as follows:

$$24.31 - 12.22(WHR) - 3.29(HTN) - 0.57(HbA_1)$$

where WHR is waist-to-hip ratio, HTN represents history of hypertension (0 = no, 1 = yes), and HbA_1 level is in %. When waist circumference was used in place of WHR, a similar pattern of results was obtained.

TABLE 4
Linear regression analysis for the estimation of glucose disposal

	β	R^2	R^2 adjusted	R^2 change	P
Model 1 (forward stepwise)					
Hypertension	–3.961			0.375	0.006
WHR	–14.661			0.203	0.001
Constant	21.174	0.578	0.535		<0.001
Model 2					
Hypertension	–4.078				0.002
Constant	8.536	0.368	0.339		<0.001
Model 3					
Family history of type 2 diabetes	–3.150				0.009
Constant	8.605	0.275	0.242		<0.001
Model 4					
WHR	–15.246				0.019
Constant	–20.760	0.226	0.191		0.001
Model 5					
HbA_1	–1.244				0.004
Constant	19.482	0.326	0.294		<0.001
Model 6					
Triglycerides	–0.0248				0.010
Constant	10.604	0.263	0.230		<0.001
Model 7					
HDL cholesterol	0.0349				0.599
Constant	6.175	0.013	–0.032		0.044
Model 8 (forced entry)					
Hypertension	–3.289			0.375	0.005
WHR	–12.223			0.203	0.020
HbA_1	–0.568			0.051	0.120
Constant	24.312	0.629	0.571		<0.001

Age, sex, triglycerides, HDL cholesterol, hypertension, family history of type 2 diabetes, and WHR were available for model 1.

DISCUSSION

Several clinical components have been used to define the IRS, which can manifest clinically as hyperinsulinemia, glucose intolerance, increased triglycerides, decreased HDL cholesterol, increased blood pressure, increased WHR, increased small, dense LDL cholesterol, and increased plasminogen activator inhibitor-1 activity (1–4). These factors, alone or in combination, can also increase the risk for coronary heart disease (1–4). Insulin resistance has long been recognized in type 1 diabetes (5–10), but few studies have examined the association between the components of IRS and insulin resistance in this population. To our knowledge, this is the first study to show that cardiovascular risk factors associated with IRS are strongly associated with insulin resistance in type 1 diabetes. The best clinical predictors of insulin resistance in type 1 diabetes were an elevated WHR, the presence of hypertension, a family medical history of type 2 diabetes, and HbA_1 level.

In this study, WHR was the component of the IRS score that was the strongest predictor of insulin resistance. Because prior studies have shown WHR to be a stronger predictor than overall adiposity of hyperinsulinemia and CAD (28–30), as well as cardiovascular risk factors and complications in type 1 diabetes (18,19), WHR was chosen as a component of the IRS score for this study. BMI and waist circumference had comparable associations with insulin resistance, confirming the relationship between greater and overall adiposity and insulin resistance. These findings support the adverse effects of obesity in type 1 diabetes (31) and raise the possibility that therapies to reduce overall and regional adiposity, such as weight loss and exercise, may be beneficial.

Hypertension has long been recognized as a component of IRS. While essential hypertension is a known risk factor for heart disease, the presence of elevated blood pressure in type 1 diabetes is frequently evidence of underlying nephropathy (32). Although inclusion of all hypertensive subjects poses the problem of identifying subjects at increased risk for insulin resistance for two separate reasons (nephropathy and/or essential hypertension), either condition could increase the risk for insulin resistance, because insulin resistance has been observed in nephropathy in type 1 diabetes (9). In this study, absolute blood pressure levels did not differ dramatically between IRS risk groups, and four of the five subjects with hypertension were identified based on their use of antihypertensive medications. In all cases, the antihypertensive medication was an ACE inhibitor, which may have attenuated the association between hypertension and insulin resistance via the potential of these medications to reduce insulin resistance (33,34).

Several prior studies have identified a family history of type 2 diabetes as a risk factor for insulin resistance (12–14). This is one of the first studies to our knowledge to identify family history of type 2 diabetes as a risk factor for insulin resistance in type 1 diabetes. In type 1 diabetes, a family history of type 2 diabetes has also been shown to increase the risk for cardiovascular complications (20), raising the possibility that this increase in complications may be mediated via insulin resistance. Future studies will explore the relationship between insulin resistance in type 1 diabetes and cardiovascular complications.

Several factors have been shown to contribute to insulin resistance in type 1 diabetes, including reduced skeletal muscle glucose transport (15), reduced skeletal muscle blood flow (16), and excessive hepatic glucose production (8,17). Poor glycemic control also contributes to insulin resistance in type 1 diabetes via impaired suppression of hepatic glucose production (17), and improvement in glycemic control can improve insulin resistance (24). When other IRS risk factors were considered in this study, HbA_1 level had a minor effect on the level of insulin resistance. However, subjects with poor glycemic control (HbA_1 >11.4%) were excluded from this study and would probably be even more insulin resistant. Thus, the importance of HbA_1 in the score may tend to be underestimated. In light of the known impact of improved glycemic control on the microvascular complications of type 1 diabetes, optimizing glycemic control remains a key clinical priority.

Interestingly, HDL cholesterol and triglyceride levels, which are core components of IRS in subjects without type 1 diabetes, did not significantly contribute to the level of insulin resistance in this study. The implications of these findings may be that in the absence of hyperinsulinemia per se, these components are not related to insulin resistance. Another possibility is that compared to the other components used in the score (WHR, history of hypertension, family history of type 2 diabetes), these variables are more dynamic and susceptible to variability in measurement. Total daily insulin dose correlated with insulin resistance but was not included in the IRS score because of the differences in types of insulin used, administration patterns, and clinical practice patterns. The dose of insulin is also likely to be a confounding factor for glycemic control, as insulin dose ($U \cdot kg^{-1} \cdot day^{-1}$) was positively correlated with HbA_1 level (r = 0.51, $P < 0.05$).

Although this study has shown an association between clinical factors and insulin resistance in type 1 diabetes, because the clamp is a costly and invasive procedure, sample size was limited. Therefore, the results from the regression analysis should be carefully interpreted. However, the results from the IRS score and estimated GDR are remarkably consistent. Alternatively, the frequently sampled intravenous glucose tolerance test could have been used to assess insulin resistance (35). In type 1 diabetes, this testing would have also required an overnight hospital admission for discontinuation of long-acting insulin and stabilization of glucose levels, a practice that could also limit sample size.

An advantage of the IRS score is that it allows identification of a subgroup of subjects at risk for insulin resistance. Identification of these subjects would allow assessment of the effects of the composite score on outcomes and help to target a group that may benefit from therapies to improve insulin sensitivity. Limitations of this index, if used to predict clinical outcomes, are that the effects of insulin resistance independent of the risk factors used to define the score cannot be discerned and that the components of the score could possibly be caused by factors other than insulin resistance.

In summary, this study showed that clinical factors are strongly associated with insulin resistance in type 1 diabetes. Although the association between these clinical factors and insulin resistance has been well documented in normoglycemic subjects, the finding that these risk factors are also associated with insulin resistance in type 1 diabetes is relatively novel. The clinical implications of these findings are that subjects may be identified by these factors, and interven-

tions such as exercise, weight loss, improved glycemic control, and potentially insulin-sensitizing medications can be considered to improve insulin resistance. Future studies will assess the ability of the IRS score to determine micro- and macrovascular complications in the EDC population.

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