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A Diagnostic Score for Insulin Resistance in Nondiabetic Patients with Ischemic Stroke or Transient Ischemic Attack

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Abstract

Goal—We sought to develop an instrument to screen for insulin resistance in non-diabetic patients with recent ischemic stroke or transient ischemic attack (TIA).

Materials and methods—Subjects were 7262 nondiabetic patients aged greater than or equal to 40 years with ischemic strokes or TIA within the past 6 months. Features were analyzed in bivariate analysis for association with insulin resistance, measured by the homeostasis model assessment of insulin resistance (HOMA-IR). Features significantly associated with HOMA-IR ($P < .05$) were entered into multivariable analysis. The magnitudes of regression coefficients from the multivariable model were used to assign point values for 2 diagnostic scoring instruments: a basic instrument that did not incorporate laboratory test values and an enhanced instrument that did. The performance of the instruments was tested using receiver operating characteristic (ROC) analysis.

Findings—In the basic model, 5 features were retained in the multivariable regression analysis: male gender, abdominal obesity, body mass index (BMI), elevated waist-to-hip ratio, and systolic blood pressure. In the enhanced model, 4 features were retained in the multivariable regression analysis: BMI, abdominal obesity, fasting glucose greater than or equal to 100 mg/dL, and triglyceride/high-density lipoprotein ratio. In the basic model, the area under the ROC curve (aROC) was .73 in the validation cohort. In the enhanced model, the aROC was .78 in the validation cohort.

Conclusions—Our 2 scoring systems performed well in identifying stroke patients with insulin resistance, but they are probably not sufficiently accurate for high-stake clinical decisions. We suggest strategies for improving the accuracy of future instruments.

Keywords

Stroke; ischemic stroke; transient ischemic attack; insulin resistance; obesity

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Background

Insulin resistance describes a condition in which decreased tissue sensitivity to the metabolic effects of the hormone insulin results in hyperglycemia and compensatory hyperinsulinemia.[1] Insulin resistance, along with insulin deficiency, is one of the fundamental physiologic defects in type 2 diabetes mellitus and has been independently associated with increased risk of development of diabetes, nonalcoholic fatty liver disease, cardiovascular disease, and ischemic stroke.[1–5]

Despite the known public health impact of insulin resistance, identification of nondiabetic patients with the condition remains challenging. Many patients have normal fasting glucose and so require unconventional testing for diagnosis of occult impairment. The gold standard is the hyperinsulinemic–euglycemic clamp. However, this method is expensive, time consuming, and impractical for use in routine clinical practice. Simpler indices for measuring insulin resistance, including the homeostasis model assessment of insulin resistance (HOMA-IR), the quantitative insulin sensitivity check index, and the McAuley index, rely on measures of serum fasting insulin, which are not standardized across laboratory platforms.[6–9] Development of a clinical instrument that identifies patients with higher risk for insulin resistance could help clinicians identify a subset of patients who might benefit from more complex testing.

The value of screening and testing for insulin resistance depends on the availability of effective follow-up treatment. Weight loss, dietary modification, and drugs can each improve insulin sensitivity.[10–13] Only drugs, however, have been tested for efficacy in preventing clinical outcomes. The PROactive trial demonstrated that treatment with pioglitazone reduced major adverse cardiovascular events in patients with type 2 diabetes.[14,15] In addition, the Insulin Resistance Intervention after Stroke (IRIS) study trial recently demonstrated that pioglitazone was effective in preventing stroke and myocardial infarction among non-diabetic patients with a recent ischemic stroke or transient ischemic attack.[16]

In this study, using data obtained during the IRIS trial's enrollment phase, we sought to develop a simple and reliable instrument based on routine clinical assessment and laboratory tests to identify patients at high risk for insulin resistance.

Research Methods

Study Population and Data Collection

The study population comprised subjects screened for eligibility to participate in the IRIS trial. IRIS was a multinational randomized trial that tested the effectiveness of pioglitazone, compared with placebo, for prevention of stroke and myocardial infarction among nondiabetic patients with a recent ischemic stroke or transient ischemic attack (TIA).[16] To be eligible for randomization in IRIS, patients were required to have insulin resistance, defined as a homeostasis model assessment-insulin resistance (HOMA-IR) value (calculated as [fasting insulin, μU/mL × fasting glucose, mmol/L]/22.5) greater than 3.0. At the screening blood test, the subject's age, gender, and modified Rankin Scale grade were

recorded. For the current study, we included only IRIS subjects screened after November 2005 when data collection was broadened to include race, ethnicity, blood pressure, and body habitus measures. All blood tests were processed at a central laboratory (Esoterix, Inc., Austin, TX, or an affiliate laboratory) and included measurements of fasting insulin, glucose, total cholesterol, high-density lipoprotein (HDL), lowdensity lipoprotein, and triglycerides. If HOMA-IR exceeded 3.0, further testing for C-reactive protein and hemoglobin A1c (HgbA1c) was performed on the screening sample. Eligible subjects who were randomized into the IRIS trial underwent a detailed baseline interview and cognitive examination.

Statistical Methods

For this study, screened IRIS participants, both those found to be insulin resistant and non-insulin resistant, were divided randomly into a development set (60%) and a validation set (40%).[17] Candidate predictive features were selected for examination in the development set based on associations with insulin resistance described in prior research (i.e., age, sex, race, Hispanic ethnicity, functional status, body mass index [BMI], central obesity, waist-to-hip ratio, blood pressure, fasting glucose, triglyceride/HDL ratio).[18–21] We defined BMI using commonly accepted criteria for normal, overweight, and obese.[22] Abdominal obesity was defined as greater than 88 cm for women and greater than 102 cm for men. Elevated waist-to-hip ratio was defined as greater than .9 in men and greater than .85 in women. Elevated systolic blood pressure (SBP) was defined as greater than or equal to 130 mmHg.[23]

Each candidate feature was analyzed individually in the development set for association with HOMA-IR defined as a continuous variable. Because HOMA-IR values were not distributed normally in the study population, a Spearman rank correlation coefficient was used to measure the strength of associations in bivariate analyses. Multiple linear regression analysis was then performed to examine the relationship between features that were significantly associated with HOMA-IR ($P < .05$) in bivariate analysis. A stepwise algorithm was used with P value for inclusion and retention of .05. Independent features selected in the final regression model were then used to create 2 diagnostic scoring instruments based on the relative magnitude of the regression coefficients: (1) an instrument that incorporates routine clinical variables not requiring blood samples (basic instrument); and (2) an instrument that incorporates routine clinical variables and common laboratory measurements (enhanced instrument).

Defining the presence of insulin resistance as HOMA-IR greater than 3.0, the diagnostic instruments were then tested in the development and validation sets for sensitivity, specificity, and diagnostic accuracy. In addition, we measured the performance of the instruments in both sets using receiver operating characteristic (ROC) analyses.

For randomized IRIS participants, additional patient features were analyzed for their association with HOMA-IR using the same methods as above. Our goal was to identify candidate variables for inclusion in a future improved instrument.

Results

Patients

Among the 7599 patients screened for the IRIS trial, 7262 were screened on or after November 1, 2005, and are included in the present study. The study population was split into a development cohort of 4357 patients and a validation cohort of 2905 patients. No significant differences in demographic or clinical data were observed between the development and validation cohorts (Table 1).

Development of the Basic and Enhanced Instruments

The results of the analyses of the development cohort are shown in Table 2 (bivariate analyses) and Table 3 (multivariate analyses).

In the basic model not requiring data from blood samples, 8 features were found to be significantly associated with HOMA-IR with $P \leq .05$ (Table 2). Of these 8 features, 5 were found to be independent predictors in the multivariable regression analysis (Table 3) and allocated points in the model: male gender (2 points); BMI (25–29 kg/m^2 [2 points]; 30–34 kg/m^2 [4 points]; ≥35 kg/m^2 [8 points]); abdominal obesity (2 points); elevated waist-to-hip ratio (2 points); and SBP (1 point). Points for features in the basic model yield a total score between 0 and 15 (Table 3).

In the enhanced model incorporating data from blood samples, 2 additional features were found to be significantly associated with HOMA-IR with $P \leq .05$ (Table 3). Of these 10 features, 4 were retained in the multivariable regression analysis (Table 3): BMI (25–29 kg/m^2 [1 point]; 30–34 kg/m^2 [2 points]; ≥35 kg/m^2 [4 points]); abdominal obesity (1 point); fasting glucose greater than or equal to 100 mg/dL (4 points); and triglyceride/HDL ratio (1.6–2.3 [1 point]; 2.4–3.5 [2 points]; ≥3.6 [4 points]). Points for features in the enhanced model yield a total score between 0 and 13 (Table 3).

Performance in the Development and Validation Cohorts

Using a HOMA-IR value of greater than 3.0 to define the presence of insulin resistance, the sensitivity, specificity, positive predictive value, and negative predictive value for each point value for both models are displayed in Tables 4 and 5. In the basic instrument, an optimal score of 6 had a sensitivity of 63% and a specificity of 69%, with a positive predictive value of 78%. In the enhanced instrument, an optimal score of 5 had a sensitivity of 68% and a specificity of 73%, with a positive predictive value of 81%. In the basic instrument, the area under the ROC curve (aROC) was .71 in the development cohort and .73 in the validation cohort. In the enhanced instrument, the aROC was .77 in the development cohort and .78 in the validation cohort.

Additional Variables in the Randomized Cohort

Four additional variables were found to be significantly associated with HOMA-IR among randomized IRIS participants: (1) hypertension history; (2) current cigarette smoking; (3) increasing C-reactive protein; and (4) increasing HgbA1c. However, because these associations were found in the randomized cohort, which comprises only subjects with

HOMA-IR greater than 3.0, these variables could not be included in the final prediction instrument.

Discussion

Our goal was to develop a simple screening instrument for insulin resistance that was adequately sensitive and specific for use in selecting patients with a recent ischemic stroke or TIA for more advanced testing. An optimal instrument would identify almost all patients with insulin resistance with adequate specificity to avoid unnecessary advanced testing in persons without insulin resistance. Unfortunately, neither our basic nor enhanced instrument demonstrated performance characteristics required for clinical care. At an optimal score of 5, the better of the two instruments (i.e., the enhanced model) had a sensitivity of 68% and a specificity of 73%. Lower scores achieved better sensitivity, as expected, but were associated with specificity values that are probably unacceptable for a clinical test of this purpose and considering the complexity of more definitive testing.

Several other groups have developed clinical instruments for the diagnosis of insulin resistance based on routine clinical data and demographics, although not in patients with established cerebrovascular disease. Forst et al. proposed the IRIS II score (unrelated to the IRIS trial upon which this study is based) to diagnose insulin resistance, defined by the authors as HOMA-IR greater than 2, in patients with diabetes mellitus.[24] The score assigns point values to categorical levels of BMI, fasting blood glucose, fasting triglycerides, and fasting HDL. The authors found a significant correlation between their scoring system and HOMA-IR ($r = .42$, $P < .0001$) with a positive predictive value of .95, a specificity value of .95, and a sensitivity value of .34 at a score above 70. However, unlike our prediction instrument, which was developed in nondiabetic patients, the IRIS II score was developed to predict insulin resistance in patients with known diabetes mellitus who have a very high pretest probability of having the condition.

We are aware of 1 instrument, which, like ours, uses exclusively clinical information, not including fasting insulin level, to identify nondiabetic patients with insulin resistance. Stern et al. used regression tree analysis to create 3 rule-based models to identify diabetic and nondiabetic patients with insulin resistance, defined as less than 28 μmol/min*kg lean body mass by euglycemic insulin clamp.[25] Stern's first model included HOMA score as a component variable and therefore was not comparable to ours. Stern's second model used nonlaboratory clinical variables and, therefore, was comparable in construction to our basic model. In this model, a patient is identified as insulin resistant if BMI is greater than 28.7 kg/m^2 or greater than 27 kg/m^2 and there is family history of diabetes. This rule had a sensitivity of 78.7% and a specificity of 76%. Stern's third model included clinical variables but also incorporated lipid values other than fasting insulin, similar to our enhanced model. In this model, a patient was identified as insulin resistant based on the following: (1) BMI is greater than 28.7 kg/m^2; (2) BMI is greater than 27.0 kg/m^2 and family history of diabetes is positive; or (3) family history of diabetes is negative, but triglycerides are greater than 2.44 mmol/L. This rule had a sensitivity of 81.3% and a specificity of 76.3%.

Although our instrument selected similar features as Stern's models, we have several theories about why our instrument did not perform as well. First, Stern's models defined insulin resistance by the euglycemic insulin clamp, the gold standard for the measurement of insulin resistance. Our instrument, on the other hand, used HOMA-IR as the definition of insulin resistance, which may not be an accurate enough measure of insulin resistance. Although the results of the HOMA-IR correlate with the results obtained from the euglycemic clamp and other advanced tests, correlations are not perfect and range from .53 to .66.[26,27] In addition, there is no standardized reference range for HOMA-IR. Our criterion of HOMA-IR greater than 3.0 was based on limited epidemiologic data.[6,24] Furthermore, Stern's second and third models include family history of diabetes, probably a highly predictive feature for insulin resistance, which likely contributes to the models' performance. Information about family history was not available in our database. Lastly, comparison between the performance of our instruments and Stern's is difficult given the different populations in which the instruments were developed. Stern's study population comprised 2321 subjects from 3 major sources: (1) the European Group for the Study of Insulin Resistance consisting of Caucasian subjects from multiple European countries with normal fasting glucose and normal glucose tolerance test; (2) the Pima Indian Study consisting of Pima Indian adults aged 18–35 years; and (3) studies performed in San Antonio, TX, in a mostly Mexican-American population.[28–30] The demographic information of Stern's population is not described in detail, but includes heterogeneous groups of subjects that included many adults with insulin resistance, particularly from the native American and Latino populations, known to be at significantly increased risk for this condition, and, ultimately, for type 2 diabetes.

We recognize several other limitations to our study. First, our predictive instrument was validated using a split sample technique.[17] However, by selecting development and validation cohorts from the same population, we were better able to match the 2 groups and maximized the extent to which the demographic characteristics were similar for the development and validation groups. Other limitations include the restriction of the study population to Western geographic regions.

Future efforts toward producing an improved scoring system for risk of insulin resistance should include testing the variables found in our randomized cohort to be associated with the magnitude of HOMA-IR: history of hypertension, cigarette smoking, C-reactive protein, and HgbA1c. Of note, neither C-reactive protein nor HgbA1c was evaluated by Stern. Stern's research would suggest that family history should also be considered.

In conclusion, we have developed 2 instruments that incorporate routine clinical variables to predict risk for insulin resistance in men and women aged 40 years and older with a recent ischemic stroke or TIA. However, we were not able to demonstrate improved performance over a simpler instrument that used a more accurate gold standard in a diverse population. We recommend that future studies developing instruments to predict insulin resistance use the euglycemic–hyperinsulinemic clamp as the measure of insulin resistance. We also recommend that future studies incorporate family history of diabetes and hypertension, cigarette smoking, C-reactive protein, and HgbA1c into their analyses. With high enough sensitivity and specificity, these prediction instruments could help clinicians identify patients

at high risk for insulin resistance in order to prevent important downstream complications including diabetes mellitus, coronary disease, and ischemic stroke.

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Table 1

Characteristics of development and validation cohorts (n = 7262)

Feature	Cohort	
	Development N = 4357	**Validation N =2905**
Demographic features		
Age (years, mean)	64 ± 11	64 ± 11
Male (%)	64%	65%
Black race (%)	11%	11%
Hispanic ethnicity (%)	3%	4%
Physical examination		
BMI (kg/m^2, mean)	28 ± 5	28 ± 6
Abdominal obesity	52%	51%
SBP (mmHg, mean)	136 ± 19	137 ± 19
DBP (mmHg, mean)	81 ± 11	81 ± 11
Modified Rankin Scale score (mean)	.9 ± 1.0	.9 ± 1.0
Laboratory data		
HOMA-IR (mean)	4.5 ± 4.1	4.4 ± 3.3
LDL (mmol/L, mean)	88 ± 32	89 ± 32
HDL (mmol/L, mean)	49 ± 13	50 ± 15
TG (mg/dL, mean)	128 ± 67	129 ± 69
TG/HDL (mean)	3.0 ± 2.1	3.0 ± 2.4
Fasting glucose (mg/dL) (mean)	97 ± 13	97 ± 16
Fasting insulin (μU/mL) (mean)	18 ± 13	18 ± 11
Randomized into IRIS (no.)	2245	1465

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein; SBP, systolic blood pressure; TG, triglyceride.

Missing data:
Development: race (14); ethnicity (14); BMI (20); abdominal obesity (54); SBP (12); DBP (12); modified Rankin Scale (4); LDL (45); HDL (17); TG (16); TG/HDL ratio (17).
Validation: race (18); ethnicity (20); BMI (13); abdominal obesity (54); SBP (7); DBP (7); modified Rankin Scale (1); LDL (29); HDL (11); TG (10); TG/HDL ratio (11).

Table 2

Bivariate analysis

Feature	No.	Median HOMA-IR	R*	*P* value
Age				
<65	2339	3.9		
≥65	2018	3.5	.08	<.0001
Male gender				
No	1568	3.6		
Yes	2789	3.7	.04	.01
Race				
White	3625	3.6		
Black	501	3.8		
Other	169	3.9		
Uncertain	48	3.6	.02	.07
Hispanic ethnicity				
No	4192	3.7		
Yes	151	4.1	.04	.02
Modified Rankin Scale grade	4353		.03	.06
Body mass index (kg/m^2)				
<25	1149	2.7		
25–29	1788	3.6		
30–34	940	4.6		
35+	459	5.4	.41	<.0001
Abdominal obesity†				
Absent	2078	3.0		
Present	2225	4.1	.33	<.0001
Waist-to-hip ratio obesity‡				
Absent	2966	3.5		
Present	1325	4.1	.13	<.0001
Systolic BP (mmHg)				
<130	1683	3.5		
130+	2661	3.8	.07	<.0001
Diastolic BP (mmHg)				
<85	2825	3.5		
85+	1519	4.0	.09	<.0001
Glucose (mg/dL)				
<100	2886	3.2		
100+	1470	4.9	.38	<.0001
TG/HDL				
<1.6	1029	2.8		
1.6–2.3	1067	3.4		

Feature	No.	Median HOMA-IR	R*	*P* value
2.4–3.5	1105	3.9		
3.6+	1138	4.7	.35	<.0001

Abbreviations: BP, blood pressure; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; TG, triglyceride.

*Spearman rank correlation coefficient.

†Greater than 88 cm for women and greater than 102 cm for men.

‡Greater than .9 in men and greater than .85 in women.

Table 3

Multivariate analyses

	Basic model		Enhanced model	
Feature	**Coefficient**	**Points**	**Coefficient**	**Points**
Male gender	.72	2		
Body mass index (kg/m^2)				
25–29	.77	2	.49	1
30–35	1.62	4	1.14	2
35+	2.47	8	1.92	4
Abdominal obesity *	.57	2	.54	1
Waist-to-hip ratio obesity †	.65	2		
Systolic BP ≥130 mmHg	.32	1		
Glucose ≥100 mg/dL			1.99	4
Triglycerides/HDL				
1.6–2.3			.35	1
2.4–3.5			.83	2
3.6+			1.71	4
Total possible points	0–15		0–13	

Abbreviations: BP, blood pressure; HDL, high-density lipoprotein.

* Greater than 88 cm for women and greater than 102 cm for men.

† Greater than .9 in men and greater than .85 in women.

Table 4

Performance of the basic instrument

Development cohort (n = 4280)					
Score cutoff (greater than or equal to)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	No. of patients with score less than cutoff
0	100	0	63	—	0
1	99	5	65	79	107
2	97	11	65	70	243
3	92	24	68	64	581
4	84	41	71	60	1072
5	76	53	74	56	1477
6	63	69	78	52	2091
7	54	75	79	48	2435
8	38	86	83	45	3024
9	31	90	84	43	3288
10	18	95	86	40	3724
11	16	96	87	40	3793
12	13	97	88	39	3891
13	9	98	87	38	3996
14	2	99	84	37	4212
15	1	99	80	37	4240
Validation cohort (n = 2844)					
Score cutoff (greater than or equal to)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	No. of patients with score less than cutoff
0	100	0	64	—	0
1	99	3	64	72	47
2	98	9	66	72	127
3	93	22	68	65	349
4	86	44	73	64	713
5	78	55	75	58	970
6	63	71	79	52	1399

7	55	76	80	49		1600
8	40	87	85	45		1976
9	32	91	86	43		2165
10	18	96	89	40		2483
11	16	96	89	39		2515
12	13	98	92	39		2584
13	10	99	93	38		2656
14	3	100	93	37		2783
15	2	100	92	36		2807

Abbreviations: NPV, negative predictive value; PPV, positive predictive value.

Table 5

Performance of the enhanced instrument

Development cohort (n = 4278)					
Score cutoff (greater than or equal to)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	No. of patients with score less than cutoff
0	100	0	64	—	0
1	97	15	67	77	312
2	93	32	70	72	688
3	85	50	75	66	1184
4	77	61	78	60	1579
5	68	73	81	56	2019
6	55	83	85	52	2509
7	44	91	89	48	2921
8	31	95	92	44	3364
9	24	97	93	42	3591
10	14	99	95	40	3888
11	9	99	97	39	4016
13	3	100	97	37	4190
Validation cohort (n = 2837)					
Score cutoff (greater than or equal to)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	No. of patients with score less than cutoff
0	100	0	64	—	0
1	98	16	68	81	204
2	93	35	72	75	480
3	86	53	76	68	799
4	78	64	80	62	1066
5	68	74	82	56	1337
6	55	84	86	51	1664
7	44	90	88	47	1941
8	29	95	92	43	2255
9	24	97	94	42	2370

10	14	99	96	39		2569
11	9	100	98	38		2672
12	2	100	100	36		2797
13	2	100	100	36		2798

Abbreviations: NPV, negative predictive value; PPV, positive predictive value.