Diagnosing Insulin Resistance in the General Population

KIRSTEN A. MCAULEY, MBCHB[1]
SHEILA M. WILLIAMS, BSC(HONS)[2]
JIM I. MANN, DM, PHD, FRACP[1]
ROBERT J. WALKER, MD, FRACP[3]
NICK J. LEWIS-BARNED, FRACP[4]
LARA A. TEMPLE, BSC[1]
ASHLEY W. DUNCAN, BSC, NZCS[1]

OBJECTIVE — Difficulties in measuring insulin sensitivity prevent the identification of insulin-resistant individuals in the general population. Therefore, we compared fasting insulin, homeostasis model assessment (HOMA), insulin-to-glucose ratio, Bennett index, and a score based on weighted combinations of fasting insulin, BMI, and fasting triglycerides with the euglycemic insulin clamp to determine the most appropriate method for assessing insulin resistance in the general population.

RESEARCH DESIGN AND METHODS — Family history of diabetes, BMI, blood pressure, waist and hip circumference, fasting lipids, glucose, insulin, liver enzymes, and insulin sensitivity index (ISI) using the euglycemic insulin clamp were obtained for 178 normoglycemic individuals aged 25–68 years. Product-moment correlations were used to examine the association between ISI and various surrogate measurements of insulin sensitivity. Regression models were used to devise weights for each variable and to identify cutoff points for individual components of the score. A bootstrap procedure was used to identify the most useful predictors of ISI.

RESULTS — Correlation coefficients between ISI and fasting insulin, HOMA, insulin-to-glucose ratio, and the Bennett index were similar in magnitude. The variables that best predicted insulin sensitivity were fasting insulin and fasting triglycerides. The use of a score based on

$$\text{Mffm/I} = \exp[2.63 - 0.28\ln(\text{insulin}) - 0.31\ln(\text{TAG})]$$

rather than the use of fasting insulin alone resulted in a higher sensitivity and a maintained specificity when predicting insulin sensitivity.

CONCLUSIONS — A weighted combination of two routine laboratory measurements, i.e., fasting insulin and triglycerides, provides a simple means of screening for insulin resistance in the general population.

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Insulin resistance is an important risk factor for type 2 diabetes and cardiovascular disease (1). There is increasing evidence supporting the fact that by the time glucose tolerance or fasting glucose levels become impaired, appreciable β-cell destruction may have already occurred (2). Thus, it seems likely that attempts to prevent type 2 diabetes will be more successful if intervention is commenced when blood glucose levels are still in the normal range. Therefore, a simple test for identifying insulin-resistant individuals is important both for population-based research and clinical practice. The euglycemic insulin clamp and the intravenous glucose tolerance test (IVGTT) are standard methods for the measurement of insulin resistance in research, but they are impractical in clinical practice and are difficult to perform in population-based research studies (3). Fasting insulin, homeostasis model assessment (HOMA), insulin-to-glucose ratio, and the Bennett index are all used to predict insulin sensitivity; and several other individual variables, such as family history of diabetes, BMI, blood pressure (BP), waist and hip circumference, fasting triglycerides, HDL, glucose, insulin, and hepatic enzymes, are known to correlate with insulin resistance (4–7). Combinations of variables used to predict insulin resistance have been assessed in a small number of studies, and most studies have assessed prediction in individuals with impaired glucose tolerance (IGT) and diabetes. Few studies have specifically evaluated the prediction of insulin resistance in a significant number of individuals with normal glucose tolerance (4,8). We have compared the standard techniques, several individual variables, and a score based on a weighted combination of selected variables with the euglycemic insulin clamp to evaluate the best method of predicting insulin resistance in normoglycemic individuals.

RESEARCH DESIGN AND METHODS

— Participants who previously volunteered for various research projects were recruited. A total of 178 normoglycemic men and women aged 25–68 years, similar to the general population of New Zealand with respect to BP, BMI, and waist-to-hip ratio (WHR) (9), gave informed consent for a euglycemic insulin clamp to be performed (10).

After a 10-h overnight fast, each participant's weight, height, and BP were measured and recorded. Intravenous cannulae were inserted into the cubital vein for the administration of insulin and glucose (25% dextrose) and into the dorsal aspect of the hand for arterialized sampling. Basal samples were obtained for the measurement of fasting insulin and lipid

From the [1]Department of Human Nutrition, [2]Department of Preventive and Social Medicine, and [3]Department of Medicine, Otago University, Dunedin, New Zealand; and the [4]Department of Diabetes and Endocrinology, Gloucestershire Royal Hospital, Gloucester, U.K.

Address correspondence and reprint requests to Dr. Kirsten McAuley, Department of Human Nutrition, Otago University, P.O. Box 56, Dunedin, New Zealand. E-mail: kirsten.mcauley@stonebow.otago.ac.nz.

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Abbreviations: AST, aspartate aminotransferase; BP, blood pressure; HOMA, homeostasis model assessment; IGT, impaired glucose tolerance; ISI, insulin sensitivity index; IVGTT, intravenous glucose tolerance test; *M*, glucose disposal rate; Mbw/I, ISI corrected for total body weight divided by average insulin; Mffm/I, ISI corrected for fat-free mass divided by average insulin; PSEP, prognostic separation index; TAG, triglycerides; WHR, waist-to-hip ratio.

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

profile and for glucose and liver function tests. Insulin (Actrapid) was infused at 40 $mU \cdot m^{-2} \cdot min^{-1}$ to achieve hyperinsulinemia. Arterialized samples, achieved using the heated-hand technique, were taken from the dorsum of the hand every 10 min for immediate glucose measurements using a Yellow Springs Instruments Sidekick Glucose Analyzer (calibrated before and during the test). A variable rate glucose infusion was given for 115 min and adjusted every 10 min according to a negative feedback algorithm used in the Otago Clamp Method (11). Blood glucose levels were maintained as close as possible to 4.5 mmol/l. Plasma insulin levels were measured at 0, 60, 90, and 120 min. The glucose disposal rate (*M*) (milligrams per kilogram per minute) was calculated from measurements taken during the final 60 min of the clamp. The ISI using total body weight (Mbw/I) was calculated by dividing the average *M* by the average plasma insulin concentration over the final 60 min (*M* per milliunit per liter). The ISI corrected for fat-free mass (Mffm/I) was also calculated (12).

HOMA was calculated as described by Matthews et al. (5). The Bennett index was calculated by 1/ln(glucose 0)ln(insulin 0) (13).

Plasma insulin was determined using the Coat-A-Count ^{125}I radioimmunoassay (Diagnostics Products, Los Angeles, CA). This is a polyclonal assay with a cross-reactivity with proinsulin at the midcurve of 40%. The interassay coefficient of variation is <10%, and the detection limit is ~1.2–1.5 mU/ml. Cholesterol concentration in plasma and lipoprotein fractions was measured enzymatically with Boehringer kits and calibrators. Triglyceride and liver function tests were measured enzymatically using Roche kits and reagents on a Cobas Fara analyzer. HDL cholesterol was measured in the supernatant after precipitation of apolipoprotein B–containing lipoproteins with phosphotungstate/magnesium chloride solution.

BP was measured in a sitting position after a 10-min rest. Waist girth was measured as the minimum circumference between iliac crest and rib cage, and hip girth was measured at the maximum width over the greater trochanters (available for 99 participants). WHR was calculated from these measurements. BMI (kg/m^2) was also calculated. A positive family history of type 2 diabetes was defined as having a first-degree relative with diabetes diagnosed after 30 years of age and not requiring insulin during the first 6 months from diagnosis (available for 101 participants).

Table 1—*Clinical and metabolic descriptors of the study population*

	n	Geometric mean ± SD	Range
Age (years)	178	46.8 ± 7.8	25–68
Weight (kg)	178	76.1 ± 17.3	48–149
BMI (kg/m^2)	178	27.5 ± 5.3	18.4–50.6
Waist (cm)			
Women	68	95.8 ± 14.5	69.0–132.5
Men	31	104.2 ± 12.7	72.8–130.6
WHR			
Women	68	0.86 ± 0.06	0.71–1.02
Men	31	0.97 ± 0.05	0.84–1.06
BP	177	125/81 ± 17/10	90/58–208/110
TAG (mmol/l)	178	1.47 ± 0.73	0.44–5.50
HDL (mmol/l)	178	1.31 ± 0.37	0.55–2.69
Insulin (mU/l)	178	10.0 ± 9.5	2–73
AST (U/l)	73	14.3 ± 6.5	9–56
Mbw/I	178	4.3 ± 2.4	1.2–18.6
Mffm/I	178	6.7 ± 3.4	2.3–25.9
HOMA	178	2.1 ± 2.2	0.3–15.9
Insulin-to-glucose ratio	178	2.1 ± 1.9	0.4–14.9
Bennett index	178	0.29 ± 0.1	0.1–1.1

Statistical analysis

Product-moment correlations were used to examine the association between ISI and fasting insulin, HOMA, insulin-to-glucose ratio, Bennett index, and other individual variables previously listed. A log transformation was applied to all of the variables apart from age, family history, and BP.

An ISI of $\leq 6.3\ M \cdot mU^{-1} \cdot l^{-1}$ defined individuals with insulin resistance. This corresponded to the lowest quartile for the lean population (BMI <27 kg/m^2). Two approaches were used to select the variables to be included in the risk score. The first approach involved regression analysis with backward elimination, which estimated the association between ISI and explanatory variables. This method started with all explanatory variables in the model and progressively deleted those not meeting prespecified statistical criteria. The second approach used a bootstrap procedure to reveal the variables that were most important. This involved drawing 500 samples of the same size from the original sample, with subsequent replacement (14). Regression analysis with backward elimination was repeated for each sample. The most frequently selected variables were regarded as the most important.

Three possible scoring systems were evaluated. In the first, the log-transformed values of Mffm/I and the predictor variables were analyzed as continuous variables. By regarding a predicted value $\leq 6.3\ M \cdot mU^{-1} \cdot l^{-1}$, obtained from regressing Mffm/I on the other variables singly or in combination, it was possible to evaluate sensitivity and specificity of the scoring test and, when used singly, to identify cutoff points for the variables.

In the second scoring system, Mffm/I was divided into two groups, with values $\leq 6.3\ M \cdot mU^{-1} \cdot l^{-1}$ constituting a diagnosis of insulin resistance. In this case, we used logistic regression, which estimates the probability of a diagnosis. Prediction probabilities ≥0.5 were taken as positive, so that the sensitivity and specificity could be calculated. Again, it was possible to identify cutoff points when the variables were used one at a time. The third model divided each predictor into two groups using the cutoff points identified in the other two models.

It is well known that scoring systems established in one set of data may not predict as well in a new sample; therefore, using the selected variables, another bootstrap procedure was used to carry out internal validation (15,16). The median values of the sensitivity and specificity, rather than those obtained using only the original sample, are more realistic predictors of how the test will perform on a new set of data. The 2.5 and 97.5 percentiles were used as CIs.

Finally, values for the prognostic sep-

aration index (PSEP) were provided. PSEP is based on the difference between the positive and negative predictive values of a test and can be derived from its sensitivity and specificity. The positive predictive value of a test shows the probability of someone with a positive test actually having the disease. The greater the difference or separation between the positive and negative predictive values, the better the PSEP and the more useful the test or score for discriminating between individuals with and without the disease.

RESULTS — Clinical and metabolic descriptors of the study population are shown in Table 1. Correlation coefficients among Mbw/I and Mffm/I, commonly used indexes, and individual variables known to be associated with insulin resistance are presented in Table 2. A total of 75 (42%) people in our sample met the criteria for insulin resistance. The correlation between Mbw/I and Mffm/I was 0.95. The variables most strongly correlated with insulin sensitivity were fasting insulin, fasting triglycerides, aspartate aminotransferase (AST), waist circumference, and BMI. To determine whether sensitivity and specificity for predicting insulin sensitivity could be improved, all variables considered in a score, i.e., age, WHR, BP, HDL cholesterol, liver enzymes, and those previously listed, were considered in various combinations. The combination of insulin and triglycerides proved to be the best predictor and was a better predictor than insulin alone. The addition of other variables did not improve the prediction of insulin sensitivity. BMI was considered because it is regarded as an important determinant of insulin resistance, and the results for this are shown. The scores used to predict Mffm/I as a continuous variable are as follows:

$$\text{Score } 1A\text{: Mffm/I} = \exp[3.29 - 0.25\ln(\text{insulin}) - 0.22\ln(\text{BMI}) - 0.28\ln(\text{TAG})]$$

$$\text{Score } 1B\text{: Mffm/I} = \exp[2.63 - 0.28\ln(\text{insulin}) - 0.31\ln(\text{TAG})]$$

The scores used to predict Mffm/I as a categorical variable were based on the following:

$$\text{Score } 2A = -3.62 + 1.90\ln(\text{insulin}) - 0.43\ln(\text{BMI}) + 1.30\ln(\text{TAG})$$

$$\text{Score } 2B = -4.93 + 1.81\ln(\text{insulin}) + 1.24\ln(\text{TAG})$$

The first two scores give values for ISI. The second two scores, where ISI is a categorical variable, can be translated into probabilities. More precise estimates of the probability of having insulin resistance for scores 2*A* and 2*B* are obtained from the following:

$$\text{Score } 2A\text{: the probability (insulin resistant)} = \frac{\exp[-3.62 + 1.90\ln(\text{insulin}) - 0.43\ln(\text{BMI}) + 1.30\ln(\text{TAG})]}{1 + \exp[-3.62 + 190\ln(\text{insulin}) - 0.43\ln(\text{BMI}) + 1.30\ln(\text{TAG})]}$$

$$\text{Score } 2B\text{: the probability (insulin resistant)} = \frac{\exp[-4.93 + 1.81\ln(\text{insulin}) + 1.24\ln(\text{TAG})]}{1 + \exp[-4.93 + 1.81\ln(\text{insulin}) + 1.24\ln(\text{TAG})]}$$

A score >0 corresponds to a >50% chance of insulin resistance, a score >1 corresponds to a 73% chance, and a score >2 corresponds to an 88% chance.

The sensitivity and specificity derived from regressing each of these variables alone and in combination are shown in Table 3. Insulin alone has a specificity of 0.82; the sensitivity, however, increased from 0.57 to 0.64, either when all three variables were part of the score or when only insulin and triglycerides were used. The bootstrap procedures used to examine the internal validity of this score showed that there was little shrinkage and provided 95% CIs for sensitivities of 0.53–0.73 and specificities of 0.74–0.88. Table 3 shows that the sensitivity and specificity are similar to the values obtained when Mffm/I was used as a continuous variable. However, the validation studies show that much more shrinkage occurs when Mffm/I is categorical. This means that the score will not be able to divide individuals into two groups on a new sample as accurately as it did on the sample used to establish the score. The PSEP values show that the greatest separation between groups is provided by insulin. A modest but significant increase occurs with the addition of triglycerides. Although the score is maintained when Mffm/I is used as a categorical variable, the validation procedure suggests that this is because of a trade-off that occurs between sensitivity and specificity.

Table 2—*Product moment correlation coefficients between Mbw/I and Mffm/I using the euglycemic insulin clamp method are commonly used indexes and risk factors for insulin resistance*

	n	Mbw/I	Log(Mbw/I) and log(variable)	Mffm/I	Log(Mffm/I) and log(variable)
Insulin (mU/l)	178	−0.40	−0.56	−0.37	−0.50
HOMA	178	−0.42	−0.53	−0.39	−0.51
Insulin-to-glucose ratio	178	−0.41	−0.47	−0.34	−0.47
Bennett index	178	0.42	0.45	0.33	0.48
BMI (kg/m^2)	178	−0.51	−0.59	−0.35	−0.42
Waist (cm)	99	−0.53	−0.55	−0.41	−0.43
WHR	99	−0.26	−0.27	−0.24	−0.26
TAG (mmol/l)	178	−0.40	−0.48	−0.37	−0.45
HDL (mmol/l)	178	0.36	0.40	0.30	0.35
AST (U/l)	73	−0.20*	−0.44	−0.21*	−0.44
ALT (U/l)	73	−0.22*	−0.20*	−0.24	−0.19*
GGT (U/l)	73	−0.31	−0.26	−0.32	−0.28
Family history	101	0.14*	0.11*†	0.17*	0.16*†
BP	177	−0.19	−0.21†	−0.11*	−0.13*†

*NS; †the Mbw/I and Mffm/I have been log-transformed, but the variable has not been log-transformed.

Table 3—*Sensitivity, specificity, PSEP, and shrinkage analysis for measures of insulin sensitivity (expressed Mffm/I) using three different methods*

	Cutoff	Sensitivity	Specificity	PSEP
Method *A*				
Insulin	12.2 mU/l	0.57	0.82	0.42
BMI	29.3 kg/m^2	0.56	0.76	0.33
TAG	1.5 mmol/l	0.53	0.75	0.29
Insulin, BMI, and TAG	—	0.63	0.82	0.46
Validation estimates	—	0.64	0.81	0.46
95% CI	—	0.53–0.73	0.74–0.88	0.40–0.52
Insulin and TAG	—	0.62	0.84	0.40
Validation estimates	—	0.64	0.83	0.49
95% CI	—	0.53–0.73	0.74–0.88	0.44–0.52
Method *B*				
Insulin	12.1 mU/l	0.56	0.84	0.45
BMI	30.0 kg/m^2	0.52	0.78	0.31
TAG	1.6 mmol/l	0.53	0.79	0.34
Insulin, BMI, and TAG	—	0.61	0.85	0.50
Validation estimates	—	0.45	0.91	0.50
95% CI	—	0.32–0.6	0.85–0.96	0.45–0.55
Insulin and TAG	—	0.61	0.84	0.49
Validation estimates	—	0.49	0.92	0.51
95% CI	—	0.32–0.6	0.86–0.95	0.47–0.54
Method *C*				
Insulin	12.0 mU/l	0.71	0.69	0.39
BMI	30.0 kg/m^2	0.69	0.64	0.33
TAG	1.5 mmol/l	0.63	0.58	0.20
Insulin, BMI, and TAG	—	0.65	0.79	0.45
Validation estimates	—	0.52	0.83	—
95% CI	—	0.0–0.65	0.72–1.0	—

Method *A*, ISI and predictors analyzed continuously; method *B*, categorical ISI ($\leq 6.3\ M \cdot mU^{-1} \cdot l^{-1}$) and continuous predictors; method *C*, categorical ISI and predictors. Cutoffs have been derived from the equations for each variable.

CONCLUSIONS — Predicting insulin sensitivity in normoglycemic individuals is important, as diabetes intervention programs are more likely to be successful at this stage rather than after the development of impaired glucose tolerance. Most studies have investigated predictors of insulin resistance; however, almost all studies have included people with IGT and diabetes, rather than normoglycemic individuals in the general population (5–7,13,17). In our study, fasting insulin alone was as accurate at predicting insulin resistance in the normoglycemic population as HOMA, insulin-to-glucose ratio, and the Bennett index. Our finding is comparable with that of Laakso (4), who demonstrated that fasting insulin alone was less variable and had a higher correlation with ISI in individuals with normoglycemia than in individuals with IGT and diabetes. Thus, any method to predict insulin sensitivity in normoglycemic individuals should be compared with fasting insulin. Cross-reactivity with proinsulin is unlikely to alter these findings, because proinsulin levels are low in insulin-resistant normoglycemic individuals, and the pattern of response is similar to that of specific insulin (18,19).

A number of clinical and metabolic abnormalities have been associated with insulin resistance (1). Mykkanen et al. (6) has confirmed that low insulin sensitivity is associated with "clusters" of metabolic disorders and that the ISI (measured by an IVGTT) decreased with an increased number of disorders. The metabolic disorders were classified as dyslipidemia, hypertension, and IGT. Howard et al. (17) compared several alternative methods for measuring insulin sensitivity to predict cardiovascular risk. Many of the methods, including the modified Galvin method and other methods based on the frequently sampled IVGTT, are invasive and time consuming, and they are not appropriate for general population screening. However, they did confirm that the best method was dependent on glucose status. The Galvin and the HOMA methods were the most useful across all glucose levels. In addition, the data for individuals with normal glucose tolerance from these two methods were consistent with our own method, showing that a fasting insulin was as good, if not better, than HOMA, insulin-to-glucose ratio, or the Bennett index. Berglund and Lithell (7) have used BMI and either triglycerides (TAG) or a serum alanine-amino transferase to predict insulin resistance in hypertensive patients. They found either combination to be as useful as a fasting insulin, but they did not add fasting insulin to either combination. However, glucose status was not reported in all of the groups they evaluated. More recently, Strumvoll et al. (8) assessed 104 nondiabetic individuals to determine whether age, BMI, WHR, and glucose and insulin levels during an oral glucose tolerance test could predict insulin sensitivity (measured using a euglycemic insulin clamp). They found that BMI, insulin at 120 min, and glucose at 90 min best predicted insulin sensitivity. These parameters appeared robust in individuals with normal glucose tolerance (n = 65), as well as in individuals with IGT. Other studies have not found a 120-min insulin measurement as useful as a fasting insulin measurement (3,4). It is worth noting that in the Strumvoll et al. study (8), the correlation coefficient between fasting insulin and ISI (−0.59) was remarkably similar to that between ISI and 120-min insulin (−0.62), suggesting little difference between fasting insulin and 120-min insulin as predictors. In summary, simple predictors of insulin resistance have often been applied to those with a range of glucose tolerance, and there is evidence that the best method depends on glucose status.

When measures of obesity, i.e., BMI, waist circumference, and WHR, are assessed as predictors of insulin resistance (measured by a euglycemic insulin clamp), it is important that glucose disposal is expressed for fat-free mass rather than for total body weight, because the contribution of fat mass to glucose disposal is small (12). Muscle is the primary site for glucose disposal, and if total body weight is used in the calculation of glucose disposal, then insulin resistance is considerably overestimated in overweight individuals (12). It is possible that if other

studies had corrected for fat-free mass, BMI would not have been as important in predicting insulin resistance. In our study, the correction for fat-free mass reduced the correlation between ISI and BMI from −0.59 to −0.41. The correlation of ISI and waist circumference, a crude measure of central adiposity, was reduced to a lesser extent (from −0.55 to −0.43) after the correction for fat-free mass. It is difficult to draw any conclusions about the usefulness of waist circumference compared with BMI, given the reduced number of measurements of waist circumference in this sample; however, this should be considered in future studies.

In our study, a fasting insulin of >12.2 mU/l in normoglycemic individuals is a remarkably specific test for insulin resistance. Our aim was to discover whether the addition of other variables that correlate well with insulin resistance improved on a fasting insulin alone. The variables (other than fasting insulin) that best predicted insulin sensitivity (Mffm/I) were fasting triglycerides, AST, waist circumference, and BMI. The addition of triglycerides to a fasting insulin increases sensitivity from 0.57 to 0.64 and maintains good specificity. When glucose disposal is corrected for fat-free mass, rather than for total body weight, BMI does not increase the sensitivity or specificity of this combination. Waist circumference and AST also appear to be important associated variables and warrant further assessment; however, because of the small number of these measurements in this study, no further conclusions can be made.

This study shows that the best predictors of insulin sensitivity in the general population were the log-transformed values for fasting insulin and fasting triglycerides. We found that it is important to use continuous variables, because in our study the shrinkage was small, which means the score (1*B*) should perform well on future samples. Many prediction models suggested for clinical use prefer to use categories, rather than continuous variables, for simplicity and ease of calculation. However, this study shows that when categories are used, there is considerable shrinkage, which means the score may not predict well in new samples. The equation predicting insulin sensitivity using continuous variables is just as easily applied as that for categories using a simple computer program and does not sacrifice valuable information.

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