Validation of Insulin Resistance Indexes in a Stable Renal Transplant Population

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OBJECTIVE — The purpose of this study was to investigate the validity of established insulin resistance indexes, based on fasting blood parameters, in a stable renal transplant population.

RESEARCH DESIGN AND METHODS — Fasting insulin, homeostasis model assessment (HOMA), the quantitative insulin sensitivity check index (QUICKI), and McAuley's index were assessed for correlation and agreement with whole-body glucose uptake (*M* value) divided by prevailing serum insulin concentrations (*I* value) assessed during a hyperinsulinemic-euglycemic clamp in 51 stable renal transplant recipients, who were at a median of 7.5 years after transplant. Multivariate linear regression analyses were used to determine independent risk factors for insulin resistance.

RESULTS — The *M/I* value correlated with fasting insulin concentration ($r = -0.56$), HOMA ($r = -0.53$), QUICKI ($r = 0.52$), and McAuley's index ($r = 0.61$) (all $P < 0.01$). Linear regression showed agreement between all indexes and insulin resistance. However, McAuley's index showed the strongest agreement irrespective of age, sex, renal allograft function, and obesity. In multivariate analysis, fasting insulin concentration ($\beta = -0.59$, $P = 0.002$), fasting triglyceride concentration ($\beta = -0.33$, $P = 0.04$), and BMI ($\beta = -1.22$, $P = 0.05$) were independently associated with the *M/I* value.

CONCLUSIONS — All investigated insulin resistance indexes were valid estimates of insulin resistance in the long-term stable renal transplant population. However, correlation and agreement were strongest for McAuley's index. In addition to fasting insulin and triglyceride concentrations, of which McAuley's index is composed, only BMI seemed to be independently associated with insulin resistance in this population.

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The incidence and prevalence of cardiovascular disease have been estimated to be three to five times greater in the renal transplant population than in the general population (1,2). A recent study showed that the majority of renal transplant outpatients have a constellation of cardiovascular risk factors, i.e., obesity, dyslipidemia, hypertension, and posttransplant diabetes, which are consistent with the metabolic syndrome (3). According to preliminary data of the ALERT (Assessment of Lescol in Renal Transplantation) trial, metabolic syndrome is associated with an increased risk of cardiovascular mortality (4).

Insulin resistance is thought to be the central pathophysiological feature underlying the metabolic syndrome (5). To study the role of insulin resistance in the high incidence of cardiovascular morbidity and mortality in this population, validated insulin resistance indexes are needed. Insulin resistance indexes have not yet been validated in comparison to the hyperinsulinemic-euglycemic clamp in the stable renal transplant population. Indexes that are based on fasting blood parameters alone have distinct advantages over other methods of quantifying insulin resistance in that they are less cumbersome and less time consuming for large-scale epidemiological studies at outpatient clinics. However, established indexes have been derived from correlates of insulin resistance in nontransplant populations. Evidence suggests that insulin resistance in the renal transplant population may be caused by other risk factors as well, such as immunosuppression and antihypertensive medication (6). Consequently, it remains uncertain whether these indexes are applicable to the stable renal transplantation population.

The primary objective of this study was, therefore, to validate established insulin resistance indexes based on fasting blood parameters in a stable renal transplant population. The second objective was to investigate which risk factors, both traditional and those specifically related to the transplant population, are associated with insulin resistance.

RESEARCH DESIGN AND METHODS

— The institutional review board approved the study protocol (METc 01/039), which was in adherence with the Declaration of Helsinki (7). Patients from the renal transplant outpatient population, who were part of a previous study cohort (3), were randomly invited to participate. Recruitment was performed in a stratified manner so that similar numbers of male and female subjects and similar numbers of participants with a high and a low waist-to-hip ratio would be included. Subjects were eligible for participation in the present study if they had received a renal allograft at our center at least 2 years before the start of the study and used cyclosporine microemulsion (Neoral; in combination with prednisolone and/or azathioprine, mycophenolate mofetil, or rapamycin) as part of their immunosuppressive regimen. Inclusion required a stable allograft function, defined as a 24-h urinary creatinine clearance of >30 ml/min and a difference in 24-h urinary creatinine clearance over the

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Abbreviations: CMV, cytomegalovirus; HOMA, homeostasis model assessment; PAP, *p*-aminophenazone; QUICKI, quantitative insulin sensitivity check index.

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

past year of ≤20 ml/min to participate. Excluded from invitation were subjects with diabetes, defined as plasma glucose concentration ≥7.0 mmol/l and/or use of antidiabetic medication. Sources funding this project did not play a role in either data collection or analysis or in submission and publication of the manuscript.

Subjects were admitted at 8:00 A.M. to our clinical research unit after an 8-h overnight fasting period. Fasting blood samples were drawn first, after which patients were allowed to take their immunosuppressive medication. Weight, height, and waist (midway between the iliac crest and the 10th rib) and hip (at the level of the trochanter major) circumference were measured secondly. Blood pressure was reported as the average of five automated measurements taken at 3-min intervals (Dinamap; GE Medical Systems, Milwaukee, WI).

Hyperinsulinemic-euglycemic clamp

Insulin resistance was measured using the hyperinsulinemic-euglycemic clamp technique. The clamps were performed as described by previous investigators (8). To give a brief summary of the procedure, exogenous insulin (Velosulin; Novo Nordisk, Bagsvaerd, Denmark) was infused at a continuous rate of 50 $mU \cdot kg^{-1} \cdot h^{-1}$ for 120 min. A glucose concentration of 5 mmol/l was maintained by adjusting the rate of a 20% D-glucose and 1% KCl infusion based on plasma glucose measurements performed at 5-min intervals. Whole-body glucose uptake (*M* value in milligrams per kilogram per minute) was determined by the total amount of glucose infused during the last 60 min of the clamp. The steady-state insulin concentration (*I* value in picomoles per liter) was determined as the mean of two plasma samples at 90 and 120 min. Insulin sensitivity was defined as the whole-body glucose uptake (*M* value) divided by the prevailing serum insulin concentrations (*I* value) during the clamp (milligrams per kilogram per minute per picomoles per liter). Insulin resistance is the reciprocal of insulin sensitivity. Clamp-assessed insulin resistance is therefore the reciprocal of the *M/I* value. For convenience, the *M/I* value was multiplied by 100.

Insulin resistance indexes

The following indexes were validated against the clamp: fasting insulin concentration (in microunits per milliliter) (9), homeostasis model assessment (HOMA): [glucose (in millimoles per liter) × insulin (in microunits per milliliter)]/22.5 (10), Quantitative insulin sensitivity check index (QUICKI): 1/[log glucose (in milligrams per deciliter) + log insulin (in microunits per milliliter)] (11), and McAuley's index: exp[2.63 − 0.28 ln (insulin [in microunits per milliliter]) − 0.31 ln (triglycerides [in millimoles per liter])] (12).

Analytical methods

Fasting serum insulin and insulin levels during the clamp were determined using a radioactive immunoassay (DSL-1600; Diagnostic Systems Laboratories, Webster, TX). The intra- and interassay coefficients of variation at 16.9 μU/ml are 4.5 and 9.9%, respectively, and at 53.4 μU/ml are 6.4 and 4.7%, respectively. Total cholesterol concentration was assessed using the cholesterol oxidase–*p*-aminophenazone (PAP) method, and serum triglyceride level was measured using the glutathione peroxidase–PAP method (both on a MEGA AU 510; Merck Diagnostica, Darmstadt, Germany). HDL cholesterol concentration was determined using the cholesterol oxidase–PAP method on a Technikon RA-1000 (Bayer Diagnostics, Mijdrecht, the Netherlands). LDL cholesterol concentration was calculated using the Friedewald formula (13). Total protein concentration was analyzed using the biuret reaction (MEGA AU 510; Merck Diagnostica). Creatinine clearance was calculated using 24-h urinary creatinine excretion and serum creatinine.

Transplant-related factors

Relevant donor, recipient, and transplant characteristics were extracted from the Groningen Renal Transplant Database. This database holds information on all renal transplantations that have been performed at our center since 1968. Parameters used for analysis were donor and recipient age and sex, dialysis modality and duration, date of transplantation, delayed graft function (i.e., days of oliguria or necessity of dialysis treatment), weight 6 months after transplantation (to calculate posttransplant weight gain), human leukocyte antigen mismatches, cold and warm ischemia times, cytomegalovirus (CMV) seropositivity of donor and recipient, acute rejection treatment, and immunosuppressive medication.

Statistical analysis

Analyses were performed using SPSS version 12.0 software (SPSS, Chicago, IL). The Kolmogorov-Smirnov test was used to assess the normality assumption of continuous distribution. Parametric values are presented as means ± SD, whereas nonparametric values are displayed as median (interquartile range). A two-sided *P* value of ≤0.05 was considered to indicate statistical significance. All indexes and *M/I* values were log transformed before analysis.

The study sample was compared with the population from which participants were recruited (3) with regard to age, sex, time after transplantation, BMI, blood pressure, renal allograft function, and proteinuria, using Student's *t* test for parametric variables and the Mann-Whitney *U* test for nonparametric variables. Correlation between the indexes and log-transformed *M/I* values of the clamps were analyzed by Pearson's test for parametric variables. Agreement between the indexes and the clamps was assessed by linear regression of the insulin resistance index under investigation against the *M/I* values with a 95% prediction interval, as suggested by Bland and Altman (14) when methods have different units.

To determine whether age, sex, BMI, or renal allograft function influenced the association between the indexes and clamp-assessed insulin resistance, correlation was reassessed after stratification along the median of the above-mentioned variables. For differences in correlation, linear regression was performed to determine whether effect modification existed between the above-mentioned variables and the indexes.

To determine which traditional and transplant-related risk factors were associated with insulin resistance, all putative factors that were univariately associated with log-transformed *M/I* values at a *P* value ≤0.1 were entered simultaneously in a backward linear regression model with log-transformed *M/I* values as the dependent variable. The variables that were retained in the crude model were subsequently tested for interaction among covariates, goodness of fit, and higher-order (e.g., polynomial) regression by ANOVA. Residual terms were tested to determine whether distribution was normal.

RESULTS — Table 1 shows baseline characteristics of the 51 subjects. Age was 53 ± 11 years, 55% were male, median time after transplantation was 7.5 years, and the majority (90%) had received a cadaveric allograft. Forty percent were overweight (BMI between 25 and 30 kg/m^2) and 20% were obese (BMI >30 kg/

Table 1—*Population characteristics*

Characteristics	Value
n	51
Recipient demographics	
Age (years)	53 ± 11
Male sex	28 (55)
Time since transplantation (years)	7.5 (5.2–12.0)
Cadaveric donor	46 (90)
Body composition	
BMI (kg/m^2)	26.0 (23.8–28.6)
Waist circumference (cm)	101 ± 12
Waist-to-hip ratio	1.03 (0.92–1.09)
Renal function and proteinuria	
Creatinine clearance (ml/min)	65 (57–78)
Serum creatinine (μmol/l)	134 (106–149)
Proteinuria (g/24 h)	0.1 (0.0–0.2)
Blood pressure	
Systolic blood pressure (mmHg)	145 ± 15
Diastolic blood pressure (mmHg)	85 ± 11
Lipids	
Total cholesterol (mmol/l)	5.4 ± 0.9
LDL cholesterol (mmol/l)	3.3 ± 0.8
HDL cholesterol (mmol/l)	1.3 (0.9–1.7)
Triglycerides (mmol/l)	1.7 (1.1–2.4)
Medication	
Antihypertensive	
β-Blocker	6 (12)
ACE inhibitor	20 (40)
Angiotensin II antagonist	4 (7)
Calcium antagonist	19 (38)
Diuretics	22 (44)
Lipid-lowering drugs	
Statine	37 (72)
Immunosuppresion	
Prednisolone dose (mg/day)	10 (7.5–10)
Cyclosporine	51 (100)
Trough-level (μg/l)	109 (78–143)
Azathioprine	10 (20)
Mycophenolate mofetil	13 (25)
Trough level (μg/l)	1.5 (1.1–3.6)
Rapamycine	1 (2)

Data are means ± SD, *n* (%), or median (interquartile range).

m^2). Creatinine clearance was 65 (57–78) ml/min. Average blood pressure was 145/85 mmHg. The subjects in the study sample did not differ significantly from the population from which they were recruited with respect to age, sex, time after transplantation, BMI, blood pressure, or renal allograft function (data not shown). Only proteinuria was significantly lower in the study sample (0.1 g/24 h [0.0–0.2] vs. 0.2 [0.0–0.5], $P = 0.001$).

The hyperinsulinemic-euglycemic clamp was performed with glucose concentrations of 5.04 ± 0.16 mmol/l during the last hour of the clamp. Insulin levels were raised to 550 pmol/l (391–751), yielding an *M* value of 4.9 ± 1.8 mg · kg^{-1} · min^{-1} and an *M/I* value of 0.83 mg · kg^{-1} · min^{-1} per pmol/l (0.57–1.39).

Fasting insulin concentration was 16.5 μU/ml (12.0–23.5), fasting glucose concentration was 4.5 ± 0.6 mmol/l, HOMA was 6.4 (5.2–9.3), QUICKI was 0.32 (0.30–0.34), and McAuley's index was 5.4 ± 1.2. Correlation coefficients between the indexes and the *M/I* value were $r = -0.56$ for fasting insulin, $r = -0.53$ for HOMA, $r = 0.52$ for QUICKI, and $r = 0.61$ for McAuley's index, all at $P < 0.01$. Figure 1*A*–*D* shows the regression analyses with 95% prediction intervals. Agreement was reached for all indexes. HOMA and QUICKI had two (~4%) subjects outside the prediction interval. Fasting insulin concentration and McAuley's index had one subject outside the interval.

The correlation coefficients between the indexes and clamp-assessed insulin resistance did not change significantly after stratification along the median for age and renal allograft function. However, a difference was observed after stratification for BMI and sex. In the lower BMI (<26.0 kg/m^2) and female sex groups, the correlations of fasting insulin, HOMA, and QUICKI with clamp-assessed insulin resistance lost statistical significance (data not shown). Only McAuley's index remained significantly correlated with *M/I* values in all subgroup analyses (low BMI group $r = 0.41$, $P < 0.05$; high BMI group $r = 0.63$, $P < 0.01$; male subjects $r = 0.64$, $P < 0.01$; female subjects $r = 0.60$, $P < 0.01$). No effect modification was found for BMI and sex in the linear regression analyses.

Putative determinants of insulin resistance were analyzed, first univariately and later multivariately, in a backward linear regression model. Table 2 shows that only fasting insulin concentration, BMI, HDL cholesterol concentration, fasting triglyceride level, and waist circumference were univariately associated with the *M/I* value. All other putative variables did not reach the $P \leq 0.10$ level, specifically, sex, age, posttransplant weight gain, LDL cholesterol concentration, use of lipid-lowering drugs, systolic and diastolic blood pressure, use of blood pressure medication (diuretics, β-blockers, angiotensin inhibitors, or angiotensin receptor blockers and total number of antihypertensive drugs), fasting glucose concentration, creatinine clearance, daily prednisolone dosage, cyclosporine trough levels, mycophenolate mofetil or azathioprine use, cold and warm ischemia times, delayed graft function, human leukocyte antigen mismatches, cold and warm ischemia times, CMV seropositivity of donor and recipient, and acute rejection treatment with high-dose corticosteroids or monoclonal antibodies.

Variables that were significantly associated with *M/I* values were entered together with age and sex in a backward linear regression model. The crude model was subsequently tested for interaction terms, higher-order regression, and goodness of fit with ANOVA. These subsequent models were not significantly better, so the crude model was accepted

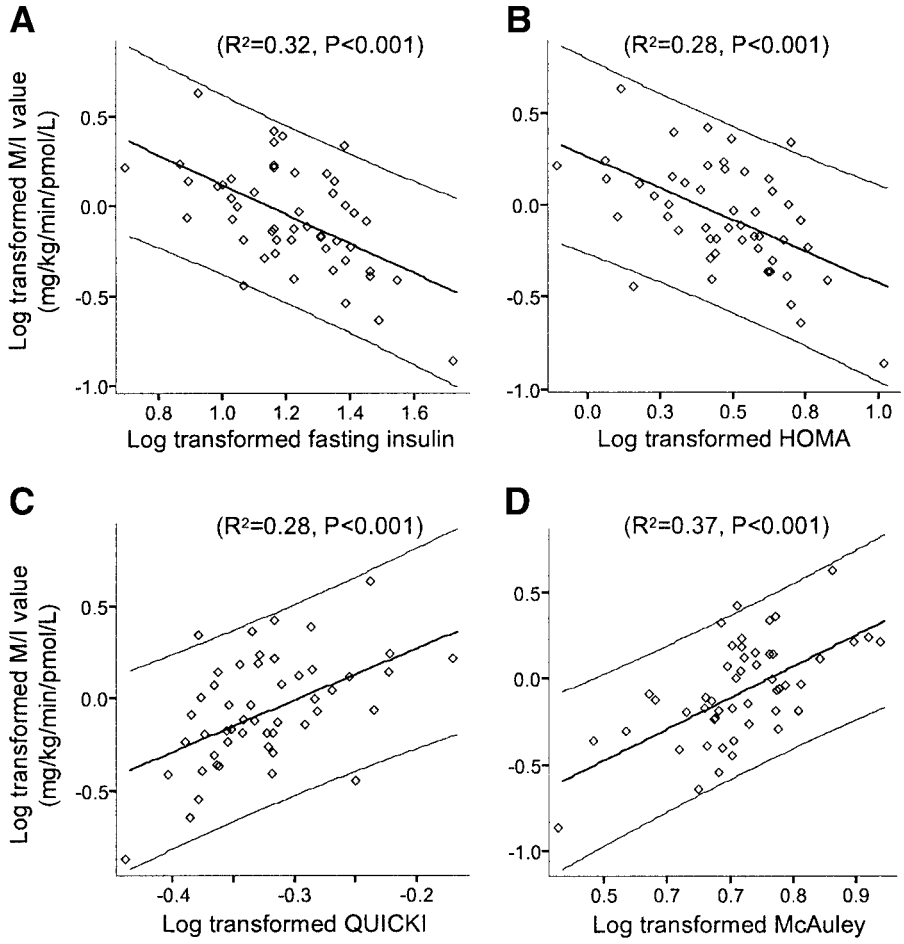

Figure 1—*Regression analyses of fasting insulin, HOMA, QUICKI, and McAuley against* M/I *value. Data are presented as best-fit regression line with prediction interval.*

as the final model. In this model, only log-transformed insulin (β −0.59, [95% CI −0.96 to −0.22], $P = 0.002$), log-transformed fasting triglycerides (β −0.33 [−0.64 to −0.01], $P = 0.04$), and log-transformed BMI (β −1.22, [−2.27 to 0.00], $P = 0.05$) remained independently associated with *M/I* values ($R^2 = 0.44$, *F* test = 12.2, degrees of freedom [df] 47, $P < 0.001$) as shown in Table 2.

CONCLUSIONS — This study shows that four commonly used insulin resistance indexes, based on risk factors for insulin resistance in nontransplant populations, are valid estimates of clamp-assessed insulin resistance in a stable renal transplant outpatient population. Incidence and prevalence of cardiovascular disease are high in the renal transplant population (1,2). Insulin resistance is an independent risk factor for cardiovascular mortality in the general population (15) and has been hypothesized to play a role in the development of chronic renal allograft dysfunction as well (16). Consequently, validated insulin resistance indexes are needed to study the role of insulin resistance in the development of cardiovascular morbidity and mortality. Fasting blood–based indexes have the advantage that they are practical and easy to use for large-scale epidemiological studies.

The finding that McAuley's index, which consists of fasting triglycerides and fasting insulin, performed best was additionally supported by our multivariate linear regression analyses, which revealed that only fasting insulin concentration, fasting triglyceride levels, and BMI were associated with insulin resistance in the long term after renal transplantation. HOMA and QUICKI yielded weaker correlations and lesser agreement in comparison with both McAuley's index and fasting insulin concentration but did compare similarly to each other. This is most likely due to the fact that they are mathematically comparable. The presence of glucose in the HOMA and QUICKI indexes clearly did not increase the strength of the association with insulin resistance compared with fasting insulin concentration alone. This finding was additionally supported by the fact that glucose was not associated with clamp-assessed insulin resistance in the linear regression analysis. This lack of significant relationship is probably caused by the fact that the current study population was nondiabetic.

Correlations between the indexes and *M/I* values were significant, irrespective of age and renal allograft function. In contrast, fasting insulin concentration, HOMA, and QUICKI did not correlate significantly with *M/I* values in female subjects and in the nonobese (low BMI) subgroups. However, further analyses by linear regression analyses could not demonstrate any significant effect modification of sex or degree of obesity. McAuley's index was the only index that remained significantly correlated with clamp-

Table 2—*Univariate and backward multivariate regression analyses*

	β	95% CI	*P* value
Univariate analysis			
Log-transformed insulin	−0.83	−1.18 to −0.47	<0.001
Log-transformed BMI	−2.24	−3.69 to −1.19	<0.001
Log-transformed HDL cholesterol	0.69	0.14–1.24	0.01
Log-transformed triglycerides	−0.55	−0.90 to −0.19	0.003
Waist circumference (cm)	−0.02	−0.04 to −0.01	0.004
Multivariate analysis			
Log-transformed insulin	−0.59	−0.96 to −0.22	0.002
Log-transformed triglycerides	−0.33	−0.64 to −0.01	0.04
Log-transformed BMI	−1.22	−2.27 to 0.00	0.05

Log-transformed *M/I* values were entered as the dependent variable in univariate and backward multivariate regression analysis. In univariate analysis only variables at $P < 0.10$ are shown. $R^2 = 0.44$, $F = 12.2$, total df = 47, $P < 0.001$.

assessed insulin resistance in all stratified analyses; again showing that it performed best.

A previous study validated insulin resistance indexes in renal transplant recipients at 10 weeks posttransplant (6). In that study, McAuley's index performed best of all indexes based on fasting blood parameters as well (17). In that study not only BMI and triglyceride concentrations but also daily prednisolone dose and active CMV infection were associated with insulin resistance (6). The explanation for this difference may lie in the time period after transplantation in which that study was performed. The period immediately after transplantation is characterized by use of high doses of immunosuppressant drugs to prevent and treat acute rejection. The consequences of use of high doses of immunosuppressant drugs are opportunistic infections. In that particular study at 10 weeks posttransplant, cyclosporine trough levels were more than double the levels in our study (242 ± 60 vs. 108 ± 42 μg/l) (6). Cyclosporine is thought to increase insulin resistance and reduce insulin secretion (18). Additionally, daily prednisolone dosage was almost double in the study of Hjelmesæth et al. (6) compared with that in ours (15 ± 7 vs. 8.7 ± 2.0 mg/day). This difference may have an influence because the same group recently showed that a reduction in the daily prednisolone dose from 16 (10–30) to 9 (5–12.5) mg/day was accompanied by an average decrease in insulin resistance of 24% (19). Moreover, the majority of participants in that study had received methylprednisolone boluses of 125–500 mg/day for 4–5 consecutive days for treatment of acute rejection episodes (6). As mentioned before, Hjelmesæth et al. found active CMV infection to be associated with insulin resistance as well. Although this finding may constitute an epiphenomenon of immunosuppresion, CMV infection may add directly to an insulin-resistant state through release of cytokines such as tumor necrosis factor-α (20,21).

When the immunosuppression regimen is tapered and opportunistic infections become less prevalent in the long term after transplantation, obesity may become a more predominant factor that influences insulin resistance. Most renal transplant recipients experience at least a 10% weight gain after transplantation (22). In the study of Hjelmesæth et al. (6), average BMI was 23.5 ± 3.8 kg/m^2 at 3 months posttransplant. Our study subjects had a similar BMI of 23.7 ± 3.4 kg/m^2 at 1 month posttransplant, which had increased to 26.6 ± 3.8 kg/m^2 by the time they participated in this study. Because obesity is an important determinant of insulin resistance, this weight gain might have a large effect on insulin resistance. The inclusion of BMI in an estimate of insulin resistance could further increase the accuracy of such an index as was shown in our multivariate linear regression analyses.

This study had some limitations, however. All of our subjects had a cyclosporine-based immunosuppressive regimen and relatively preserved renal allograft function. We wanted to study a homogenous population because cyclosporine is thought to influence insulin secretion as well as resistance. It remains unknown whether our findings are applicable to subjects receiving other immunosuppressive regimens and those with less preserved renal allograft function. Both cyclosporine treatment and impaired renal function have been shown to be associated with hypertriglyceridemia (23,24). Consequently, our finding that McAuley's index, which includes triglyceride levels in its equation, correlated and agreed strongest with clamp-assessed insulin resistance may only hold true for renal transplant recipients receiving a cyclosporine-based immunosuppressive regimen with relatively preserved renal allograft function. However, because both cyclosporine trough levels and renal allograft function were not found to be associated with *M/I* values in this study and because fasting insulin concentration, BMI, and triglyceride levels appeared to be the only determinants of insulin resistance in the long term, we hypothesize that our results may be generalized to subjects receiving other immunosuppressive regimens and to subjects with less preserved renal allograft function.

In summary, all insulin resistance indexes investigated in this study were valid estimates of clamp-assessed insulin resistance in a stable renal transplant population. Only fasting insulin concentration, triglyceride levels, and BMI were independently associated with insulin resistance. These results underscore our finding that McAuley's index performed best in the present population with a cyclosporine-based immunosuppressive regimen and relatively preserved renal function.

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