Relationship of Insulin Sensitivity, Insulin Secretion, and Adiposity With Insulin Clearance in a Multiethnic Population

The Insulin Resistance Atherosclerosis Study

CARLOS LORENZO, MD
ANTHONY J.G. HANLEY, PHD
LYNNE E. WAGENKNECHT, DRPH
MARIAN J. REWERS, MD

DARKO STEFANOVSKI, PHD
MARK O. GOODARZI, MD
STEVEN M. HAFFNER, MD

OBJECTIVE—We aimed to examine insulin clearance, a compensatory mechanism to changes in insulin sensitivity, across sex, race/ethnicity populations, and varying states of glucose tolerance. RESEARCH DESIGN AND METHODS—We measured insulin sensitivity index ($S_I$), acute insulin response (AIR), and metabolic clearance rate of insulin (MCRI) by the frequently sampled intravenous glucose tolerance test in 1,295 participants in the Insulin Resistance Atherosclerosis Study.

RESULTS—MCRI was positively related to $S_I$ and negatively to AIR and adiposity across sex, race/ethnicity populations, and varying states of glucose tolerance, adiposity, and family history of diabetes. Differences in MCRI by race/ethnicity (lower in African Americans and Hispanics compared with non-Hispanic whites) and glucose tolerance were largely explained by differences in adiposity, $S_I$, and AIR.

CONCLUSIONS—Insulin sensitivity, insulin secretion, and adiposity are correlates of insulin clearance and appear to explain differences in insulin clearance by race/ethnicity and glucose tolerance status.

Reduced insulin clearance has been demonstrated in experimental models of insulin resistance (1) and conditions associated with insulin resistance (2–5). Insulin clearance partially explains the variability of fasting insulin independently of the effect of insulin resistance, insulin secretion, adiposity, and plasma glucose (6). In response to their higher insulin resistance, minority populations have lower insulin clearance than non-Hispanic whites (4,5,7). In these studies, however, results were not adjusted for insulin resistance. Therefore, we aimed to examine insulin clearance across sex, race/ethnicity populations, and varying states of glucose tolerance in the Insulin Resistance Atherosclerosis Study (IRAS) (8).

RESULTS—MCRI was not related to $S_I$ and inversely to adiposity, plasma glucose, fasting insulin, and AIR. Comparison with impaired glucose tolerance, MCRI was higher in

RESEARCH DESIGN AND METHODS—The design and methods of the IRAS have previously been described in detail (8). The present report includes information on 1,295 participants, none of whom were treated with glucose-lowering medications.

Insulin sensitivity, insulin secretion, and insulin clearance were measured by the frequently sampled intravenous glucose tolerance test. Insulin sensitivity, expressed as the insulin sensitivity index ($S_I$), was calculated using mathematical modeling methods (MINMOD version 3.0 [1994]; Harms Software, Los Angeles, CA). Acute insulin secretion (AIR) was calculated as the mean of 2- and 4-min insulin concentrations after glucose administration. MCRI was calculated as the ratio of the insulin dose over the incremental area under the curve of insulin from 20 min to infinity (9).

Statistical analyses were performed using the SAS statistical software (version 9.2; SAS Institute, Cary, NC). Means ± SE or proportions (95% CI) were calculated by one-way ANCOVA or logistic regression to account for the effect of covariates (age, sex, race/ethnicity, and clinic). Pearson correlation analysis was used to examine the relationship of MCRI with $S_I$, AIR, fasting insulin, and waist circumference. Independent relationships of relevant variables with MCRI were established using the GENMOD procedure to account for the effect of categorical and standardized continuous variables. Log-transformed values of age, insulin, $S_I$, AIR, and MCRI were used to meet statistical assumptions.

RESULTS—MCRI was not related to age and sex (Table 1). Minority populations and family history of diabetes were associated with lower MCRI. MCRI was directly related to $S_I$ and inversely to adiposity, plasma glucose, fasting insulin, and AIR. Compared with impaired glucose tolerance, MCRI was higher in
BMI (kg/m²) 29.2
Family history of diabetes 42.8 (40.2 – 1.8, P < 0.001), and AIR (0.001), waist circumference (S = 0.61) (Supplementary Fig. 1).

### Table 1—Characteristics in the overall population by tertiles of MCRI

| Overall population | 1st tertile | 2nd tertile | 3rd tertile | P trend |
|--------------------|-------------|-------------|-------------|---------|
| BMI (kg/m²)* | 29.2 ± 0.2 | 33.0 ± 0.2 | 28.6 ± 0.2 | 0.001 |
| Waist circumference (cm) | 92.5 ± 0.4 | 101.3 ± 0.5 | 91.9 ± 0.5 | 0.001 |
| Fasting glucose (mmol/L) | 6.09 ± 0.50 | 6.62 ± 0.08 | 5.59 ± 0.08 | 0.001 |
| 2-h glucose (mmol/L) | 8.74 ± 0.12 | 10.35 ± 0.20 | 8.51 ± 0.19 | <0.001 |
| Fasting insulin (pmol/L)* | 84.9 ± 1.6 | 142.6 ± 4.3 | 84.8 ± 1.7 | 0.001 |
| S_i (×10⁻⁷ min⁻¹ · μU⁻¹ · mL⁻¹)* | 1.37 ± 0.04 | 0.51 ± 0.03 | 1.29 ± 0.05 | <0.001 |
| AIR (μU/mL)* | 42.3 ± 1.0 | 56.8 ± 2.3 | 42.5 ± 1.7 | <0.001 |

Data are mean ± SE or % (95% CI) unless otherwise indicated. Results adjusted for age, sex, race/ethnicity, and center. *Log-transformed variables and back transformed for presentation. †Nonadjusted results.

normal glucose tolerance (5.64 ± 0.10 vs. 4.53 ± 0.12 mL/kg/min, P < 0.001) and lower in diabetes (3.94 ± 0.11 mL/kg/min, P < 0.001).

MCRI correlated directly with S_i in both nondiabetic (r = 0.77) and diabetic (r = 0.58) individuals and inversely with fasting insulin (r = −0.69 and −0.64, respectively), waist circumference (r = −0.56 and −0.46), AIR (r = −0.47 and −0.61) (Supplementary Fig. 1).

The relation of race/ethnicity, family history of diabetes, and glucose tolerance to MCRI was no longer statistically significant after adjustment for BMI, waist circumference, S_i, and AIR (Supplementary Table 1). BMI (β = −7.2 ± 1.7, P < 0.001), waist circumference (β = −3.9 ± 1.8, P < 0.05), S_i (β = 27.4 ± 1.1, P < 0.001), and AIR (β = −12.5 ± 0.9, P < 0.001) were independently related to MCRI. The relation of BMI, S_i, and AIR to MCRI was consistent across sex, race/ethnicity populations, and varying states of glucose tolerance, adiposity, and family history of diabetes (Supplementary Table 2).

**CONCLUSIONS**—Our study has several novel findings: 1) insulin clearance is not associated with age or sex; 2) insulin sensitivity, insulin secretion, and adiposity are independently related to insulin clearance across sex, race/ethnic populations, varying states of glucose tolerance and adiposity, and family history of diabetes; and 3) insulin sensitivity, insulin secretion, and adiposity appear to explain differences in insulin clearance by race/ethnicity and glucose tolerance status.

In the fasting state, the liver clears ~40–60% of the insulin concentration in the portal blood (10). Results from a study of intentional weight gain in men with normal weight (change in BMI from 21.8 to 23.8 kg/m² in 15 weeks) suggest that reduced insulin clearance may be the most important compensatory mechanism for explaining the increase in basal and stimulated insulin concentrations (11). Insulin clearance has also been described as the first compensatory mechanism to experimental fat-induced insulin resistance (1), even though insulin clearance is not altered by acute hyperglycemia (12). The reduction in insulin clearance enhances glucose uptake and suppresses lipolysis by increasing insulin levels. Consequently, it has been hypothesized that insulin clearance is reduced in insulin-resistant states to lessen the demands on the β-cell (1).

In an animal model of alloxan-induced selective decrease in β-cell mass, insulin secretion decreases in proportion to β-cell mass (13). Insulin secretion after meal ingestion is impaired along with worsening of hepatic insulin clearance. Human studies have also shown that skeletal muscle contributes to peripheral insulin clearance (14,15). Physiological hyperinsulinemia recruits skeletal muscle capillaries, but insulin clearance is reduced because of the saturation of the trans endothelial insulin transport (a rate-limiting process for insulin action) (14). Obesity has been shown to impair microvascular recruitment (15). The cross-sectional nature of our study precludes us from making causal inferences. However, our results suggest that there is a complex relationship between insulin secretion and insulin clearance independently of the effect of obesity and insulin sensitivity.

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C.L. contributed to the study concept and design, wrote the manuscript, contributed to discussion, and reviewed and edited the manuscript. A.J.G.H. and L.E.W. contributed to discussion, and reviewed and edited the manuscript. M.O.G. contributed to discussion, and reviewed and edited the manuscript. C.L. contributed to discussion, and reviewed and edited the manuscript. M.J.R. and D.S. contributed to discussion and reviewed and edited the manuscript. S.M.H. contributed to discussion and reviewed and edited the manuscript. M.O.G. contributed to discussion and reviewed and edited the manuscript. C.L. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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