Minimal Model–Derived Insulin Sensitivity Index Underestimates Insulin Sensitivity in Black Americans

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OBJECTIVE

To examine the ethnic differences in insulin sensitivity (S_I) as measured by the minimal model approach (S_I-MM) and the reference method, the euglycemic-hyperinsulinemic clamp (EHC).

RESEARCH DESIGN AND METHODS

In a prospective study design, thirty Black Americans (BA) were age, sex, and BMI matched with non-Hispanic Whites (NHW). Participants underwent frequently sampled intravenous tolerance test (FSIVGTT) and EHC on 2 separate days during a single visit.

RESULTS

S_I-MM values were significantly lower in BA when compared with NHW (0.035 ± 0.025 vs. 0.058 ± 0.036 [dL/min]/[μU/mL]; $P = 0.003$). However, there were no ethnic differences in S_I measured by EHC (0.028 ± 0.012 vs. 0.035 ± 0.019 [dL/min]/[μU/mL]; $P = 0.18$).

CONCLUSIONS

S_I-MM systematically underestimates S_I in BA when compared with NHW. These findings suggest that studies inferring lower S_I in BA based on FSIVGTT and S_I-MM should be interpreted cautiously.

The higher death rate and clinical severity among Black Americans (BA) during the ongoing coronavirus disease 2019 (COVID-19) pandemic have highlighted the increased prevalence of type 2 diabetes in this population. It is widely accepted that the lower insulin sensitivity (S_I) in BA accentuates their risk for diabetes compared with non-Hispanic White (NHW) Americans (1,2). Understanding ethnic phenotypic variability of S_I is vital in ensuring robust outcomes in preventing, diagnosing, and treating metabolic disorders. Therefore, it is crucial to obtain accurately quantified S_I measures, especially within high-risk populations.

The reference test for the measurement of S_I is the euglycemic-hyperinsulinemic clamp (EHC) technique. Deemed more feasible because of clinical accessibility and lower costs, minimal model analysis of a frequently sampled intravenous glucose tolerance test (FSIVGTT) is often used to infer S_I (S_I-MM). Widely cited studies, primarily using FSIVGTT, have reported lower S_I in BA (1,2). Ethnicity affects the predictive ability of some surrogate indices of insulin resistance that rely on ambient

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glucose and insulin concentrations (3). Whether ethnicity similarly affects the reliability of S_I-MM to accurately predict S_I as determined by EHC is unknown. In this study, we examined the ethnic differences in the ability of S_I-MM to predict S_I as measured by EHC.

RESEARCH DESIGN AND METHODS

This study protocol was approved by the Institutional Review Board of the National Institute of Diabetes and Digestive and Kidney Diseases and was conducted at the Clinical Research Center, National Institutes of Health, in Bethesda, Maryland. Thirty BA and 30 NHW, matched for age, sex, and BMI, were prospectively enrolled in the Study of the Phenotype of Overweight and Obese Adults (ClinicalTrials.gov identifier NCT00428987). Written informed consent was attained from all participants. Participants were admitted for a 3-night visit to the National Institutes of Health Metabolic Research Unit. After an overnight fast, S_I was evaluated by the EHC (glucose disposal rate [GDR]) and insulin-modified FSIVGTT (S_I-MM) on different days in random order as previously described (4). The rate of glucose disposal (*M*), a measure of S_I was defined as the average of the glucose infusion rate during the steady state (GDR in milligrams per minute) corrected for estimated metabolic body size. The steady-state period of the clamp was defined as a $\geq$20-min period, 90 min after the initiation of the clamp, where the coefficient of variation for plasma glucose and glucose infusion rate was $<$5%. Prior to EHC, basal hepatic glucose production (HGP) and hepatic insulin resistance index were measured by using a stable isotope tracer (4). Because of the interruption in pharmacy compounding services and access to tracers, we could conduct tracer studies in only 43 individuals (BA n = 21; NHW n = 22). In addition, we measured circulating IGF binding protein 1 (IGFBP-1), a marker for hepatic S_I. Minimal model analysis of the FSIVGTT was used to estimate glucose effectiveness (Sg) and S_I-MM values as previously described using MINMOD software (version 6.02) (MinMOD Millenium, Los Angeles, CA) (4). Precision of parameter estimates from S_I-MM was assessed by fractional SD. Mean fractional SD of parameter estimates were $<$10%. Measures of S_I from EHC (Sc-Clamp) and S_I-MM (Sc-MM), specifically, change in glucose clearance per change in plasma insulin concentration, were expressed in the same units as originally described (5). A model-independent index of S_I (calculated S_I) was calculated and is related to KG/AUC_D (6). KG is the rate of glucose disappearance (slope of log glucose), and AUC_D is defined as the dynamic area under the insulin curve in FSIVGTT (0–50 min).

Statistical Analyses

Variables are expressed as mean ± SD. Comparisons between groups were assessed by the independent unpaired *t* test or Wilcoxon-Mann-Whitney test. A P value $<$0.05 was considered statistically significant. Data were analyzed with JMP software (version 13.0) (SAS Institute, Cary, NC) and GraphPad Prism 7 software (GraphPad Software, Inc, La Jolla, CA).

RESULTS

Percentage body fat, total body fat, fat-free mass, and fasting plasma glucose and insulin concentrations were similar between the groups (Table 1). BA had a significantly greater A1C than NHW. Six BA and three NHW had impaired fasting glucose (P = 0.27). Fifteen BA and four NHW had prediabetes based on A1C levels (P = 0.002). QUICKI, a surrogate measure of S_I based on fasting glucose and insulin concentrations, was not significantly different between the groups (P = 0.07) (Table 1). Direct measurement of S_I by EHC was similar between NHW and BA (Table 1). However, S_I-MM values were significantly lower in BA when compared with NHW (Table 1). Similarly, when these parameters were expressed in the same units, Sc-Clamp was not significantly different between the groups, but Sc-MM was lower in BA (Table 1). Simple linear regression analyses revealed a modest but significant relationship between log-transformed S_I-MM and GDR values in BA (r = 0.44; P = 0.04) and NHW (r = 0.62; P = 0.003). Indeed, Deming regression analysis, which assumes measurement error in Sc-MM and Sc-Clamp, showed a fixed bias (*y*-intercept) between ethnic groups (P = 0.002). Indeed, a factor of 1.65 applied to Sc-MM in BA (Sc-MM * 1.65) corrects the bias between the ethnic groups. Like S_I-MM and Sc-MM values, calculated S_I was lower in BA (BA 0.90 ± 0.58; NHW 1.41 ± 0.95 $10^{-4} \cdot [\mu U/mL]^{-1} \cdot min^{-1}$; P = 0.04). We did not observe any significant ethnic differences in estimated whole-body glucose effectiveness by clamp (BA 0.037 ± 0.016; NHW 0.033 ± 0.020 $dL \cdot min^{-1} \cdot kg^{-1}$; P = 0.40) or IVGTT (BA 0.019 ± 0.008; NHW 0.015 ± 0.006 min^{-1}; P = 0.12). In a subset of our cohort, hepatic insulin resistance index was not different between the groups (BA 6.81 ± 2.77; NHW 6.82 ± 2.91 [mg/kg/min] · [ng/mL]; P = 0.94). Concentrations of circulating IGFBP-1 were similar (BA 11.7 ± 9.4; NHW 12.3 ± 6.7 ng/mL; P = 0.26).

CONCLUSIONS

In this study, despite similar *M* and Sc-Clamp in both groups, S_I determined by S_I-MM was ~40% lower in BA. Sc-MM and Sc-Clamp are comparable, but not equivalent. S_I is a measure of insulin-mediated glucose uptake and inhibition of HGP. In normal individuals, only ~17% of S_I is due to insulin inhibition of HGP, while the rest is due to insulin-stimulated glucose disposal (5). Nevertheless, measures of hepatic S_I were similar in both groups and thus do not explicate the lower S_I from S_I-MM in BA. GDR from the clamp represents peripheral insulin- and glucose-dependent glucose disposal (glucose effectiveness). We did not observe any significant difference in estimated whole-body glucose effectiveness measures using the clamp or S_I-MM. These results suggest that there is no ethnic bias in the measures of glucose disposal during EHC.

In S_I-MM, S_I is mathematically represented as the partial derivative of glucose disappearance on glucose insulin. Because of the inverse relationship between S_I and insulin concentrations, the model likely underestimates S_I in individuals who display higher insulin response, especially first-phase insulin secretion (AIR) (Table 1). The robust AIR (approximately 2-fold) and impaired clearance of insulin (337 ± 90 vs. 432 ± 208 $mL \cdot m^{-2} \cdot min^{-1}$; P = 0.01) in BA may thus play a role in affecting the lumped parameters in the model and estimation of S_I (7). Indeed, we recently reported that in simulated FSIVGTT, S_I-MM underestimated S_I because of its inverse relationship

Table 1—Clinical and metabolic characteristics in NHW and BA

	NHW (n = 30)	BA (n = 30)	P*
Age (years)	38 ± 10	36 ± 11	0.49
Sex (% female)	47	47	—
BMI (kg/m^2)	29.2 ± 6.3	29.3 ± 6.8	0.98
Total body fat (%)	33.6 ± 11.5	30.4 ± 11.7	0.29
Fat-free mass (kg)	56.9 ± 10.1	61.4 ± 12.7	0.13
Fasting plasma glucose (mg/dL)	89.5 ± 6.1	90.9 ± 8.2	0.42
Fasting plasma insulin (μU/mL)	9.4 ± 6.8	12.1 ± 6.9	0.06
Fasting C-peptide (ng/mL)	2.8 ± 1.3	2.8 ± 1.2	0.82
Hemoglobin A1C (%)	5.3 ± 0.4	5.7 ± 0.4	0.001
Hemoglobin A1C (mmol/mol)	34.9 ± 3.8	38.3 ± 3.8	0.001
Total cholesterol (mg/dL)	179 ± 37	172 ± 28	0.63
LDL cholesterol (mg/dL)	96 ± 38	98 ± 22	0.74
HDL cholesterol (mg/dL)	59 ± 19	57 ± 10	0.69
Triglycerides (mg/dL)	122 ± 77	80 ± 31	0.03
QUICKI	0.35 ± 0.03	0.34 ± 0.04	0.07
Acute insulin response to glucose ($\mu U \cdot mL^{-1} \cdot min^{-1}$)	524 ± 618	1,127 ± 825	0.0004
S_I-MM ($10^{-4} \cdot [\mu U/mL]^{-1}\ min^{-1}$)	3.88 ± 2.45	2.31 ± 1.54	0.01
GDR, M (mg/kg fat-free mass + 17.7/min)	12.8 ± 4.7	12.6 ± 3.2	0.54
Sc-MM ([dL/min]/[μU/mL])†	0.058 ± 0.036	0.035 ± 0.025	0.003
Sc-Clamp ([dL/min]/[μU/mL])‡	0.035 ± 0.019	0.028 ± 0.012	0.18

Data are presented as arithmetic mean ± SD. *An unpaired, two-tailed Student t test (or Mann-Whitney U test for values that were not normally distributed) was used to test differences between ethnic groups. P values indicate significance for comparisons between ethnic groups. †Sc-MM is obtained by multiplying S_I-MM by V_D, where V_D is the apparent volume of distribution of glucose and is equal to the ratio of the glucose dose to the increment in plasma glucose during FSIVGTT. ‡Sc-Clamp was defined as GDR/(G × ΔI), where G is steady-state blood glucose concentration (mg/dL), and ΔI is the difference between basal and steady-state plasma insulin concentrations (μU/mL).

with AIR. This underestimation was context dependent and observed only when high AIR was the result of an increased size of the rapidly releasable pool of insulin (7). Consistent with our results, other studies using EHC have not demonstrated differences in S_I between BA and NHW (3,8–10). In a systematic review of S_I-MM studies, BA were more likely to demonstrate lower S_I (2). However, presented here is the first prospectively designed study to demonstrate lower S_I in BA by FSIVGT, but not EHC, in age-, sex-, and BMI-matched ethnic cohorts. Pisprasert et al. (3) showed that BA were more insulin resistant when assessed by the Matsuda index, HOMA for insulin resistance, and fasting insulin level, despite similar S_I levels by EHC. These studies together question the reliability of surrogate measures in assessing S_I in BA. Strengths of our study include the prospective study design, BMI matching, and use of the gold-standard EHC technique to compare S_I. Limitations include self-reporting of ethnicity and small sample size. Nevertheless, a priori sample size calculation suggested that a sample size of $n = 30$ was sufficient to detect a 20% difference in S_I (by EHC) between groups at a power of 80% and a type I error of 5%.

In conclusion, our results suggest ethnic differences exist in the predictive ability of S_I-MM, and studies inferring lower S_I in BA without diabetes based on FSIVGTT and minimal modeling should be interpreted cautiously.

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