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Comparison of insulin sensitivity assessment indices with euglycemic-hyperinsulinemic clamp data after a dietary and exercise intervention in older adults

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Abstract

Multiple indices to assess insulin sensitivity calculated from mathematical equations based on fasting blood parameters or oral glucose tolerance data have been developed. Although these indices have frequently been validated using euglycemic-hyperinsulinemic clamp data, the utility of each equation in measuring change in insulin sensitivity over time remains uncertain. We examined change in insulin sensitivity in response to a 12-week diet and exercise intervention in 31 older men and women with impaired glucose tolerance using a euglycemic-hyperinsulinemic clamp and 10 commonly used insulin sensitivity equations. Mean glucose disposal as calculated from clamp data was significantly higher after the intervention compared with baseline (5.92 ± 0.38 vs 5.18 ± 0.30 mg · kg fat free mass^{-1} · min^{-1}, $P = .013$). In contrast, none of the examined indices indicated a significant change in insulin sensitivity over time (all $P > .3$). A limits of agreement approach to compare insulin sensitivity calculated from each equation with the measure of glucose disposal from the clamp indicated overall imperfect agreement between measures (agreement limits ranged from ± 2.48 to ± 4.23 mg · kg fat free mass^{-1} · min^{-1}) despite significant bivariate correlations between indices and clamp data. The wide variability in the 95% prediction limits of agreement among equations suggests that these equations vary substantially from a euglycemic-hyperinsulinemic clamp in their ability to assess insulin sensitivity. Despite the observed limited agreement using this statistical approach, changes in several calculated indices were significantly correlated with changes in clamp data, suggesting that these indices may have some utility in tracking improvements in insulin sensitivity. Further research is necessary to examine agreement between indices and clamp data in larger, more heterogeneous populations and in response to other interventions where the magnitude of change in insulin sensitivity may be larger.

1. Introduction

A primary characteristic of individuals at risk for type 2 diabetes mellitus is reduced insulin sensitivity, characterized by impaired glucose uptake by peripheral tissues and elevated endogenous glucose production. Although the euglycemic-hyperinsulinemic clamp technique [1] is generally considered the best available method of assessing insulin sensitivity [2], the relative expense and difficulty of completing this measurement in settings other than the research laboratory have necessitated the development of alternative techniques. Several mathematical equations based on fasting data or an oral glucose tolerance test (OGTT) have been proposed as easier and more readily available substitute measures for clamp-assessed insulin sensitivity. These equations typically have been validated against clamp data and demonstrated to correlate significantly with clamp-assessed insulin sensitivity; thus, these

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indices have been proposed as adequate surrogate measures of insulin sensitivity obtained using the clamp. However, the utility of these equations in assessing change in insulin sensitivity over time is uncertain.

In a recent analysis, Duncan et al [3] demonstrated that the quantitative insulin sensitivity check index (QUICKI) did not accurately reflect changes in insulin sensitivity after a 6-month aerobic exercise intervention in 15 nondiabetic, middle-aged subjects. Although QUICKI results were significantly correlated with insulin sensitivity as measured using the minimal model analysis by Bergman et al [4] of a frequently sampled intravenous glucose tolerance test at baseline and at follow-up, correlations of Δ (ie, difference) values were not significant. In contrast, Katsuki et al [5,6] reported that changes in QUICKI and the homeostasis model assessment (HOMA) equation were significantly correlated with changes in clamp data in response to a 6-week diet and exercise intervention in 60 subjects with type 2 diabetes mellitus. Although differences in the subject populations and the exact insulin sensitivity assessment technique used as the standard of comparison in these studies may explain the discrepant results, further examination of changes in insulin sensitivity indices in response to an experimentally induced change in insulin action appears to be warranted. In addition, similar analyses of other insulin sensitivity equations have not been completed, and a regression-based predicted limits of agreement approach has been rarely used by previous investigators in assessing the agreement of insulin sensitivity index (ISI) and clamp data, although this method may be a superior assessment of agreement between 2 measurement techniques compared with simple correlation-based procedures [7].

We examined the agreement of 10 insulin sensitivity indices with euglycemic-hyperinsulinemic clamp data in a small sample of older individuals before and after a 12-week diet and exercise intervention designed to increase insulin action. We used a limits of agreement approach, as well as bivariate correlation statistical methods, to compare the agreement of each index with clamp data at baseline and at follow-up, as well as the agreement of changes in each index with change in clamp data. Both correlations and the limits of agreement approach were used to examine potential differences in the results or conclusions obtained using each specific data analytic technique. We hypothesized that each equation would agree closely with clamp data both before and after a 12-week intervention, and that changes over time in equation and clamp data would agree closely as well.

2. Research design and methods

2.1. Subjects

Thirty-six older men and women were recruited from the greater Little Rock area using newspaper advertisements inviting participation in a 12-week study designed to test the influence of a low-fat diet and aerobic exercise training on insulin sensitivity, as described elsewhere [8]. All subjects provided written informed consent before study participation, and study procedures were approved by the Institutional Review Board of the University of Arkansas for Medical Sciences and the Research and Development Committee of the Central Arkansas Veterans Healthcare System. Glucose tolerance was assessed using an OGTT (details provided below), with those subjects exhibiting a blood glucose concentration of 140 or higher and less than 200 mg/dL 2 hours after consumption of the oral glucose load eligible to participate. Subjects were generally healthy (aside from glucose intolerance), sedentary, overweight, and did not take medications known to influence glucose or energy metabolism. Two subjects withdrew from the study for personal reasons, and 3 subjects were excluded because of missing data, leaving a final sample size of 31 (18 females/13 males—analyses in males and females separately were very similar and, thus, data are reported for both sexes combined). Partially missing OGTT insulin data for 3 subjects resulted in smaller sample sizes for analyses involving certain specific insulin sensitivity indices because of an inability to accurately calculate these indices.

2.2. Study protocol

Following screening procedures, the overall study design involved baseline testing procedures (week 0), followed by assignment of subjects into 1 of 3 study groups, using a stratified (by sex) randomly permuted block randomization plan: control diet (41% fat, 45% carbohydrate, 14% protein), low-fat diet (18% fat, 63% carbohydrate, 19% protein), or low-fat diet (as above) plus aerobic exercise training (exercise, 4 d/wk, 45 min/d, 75%-80% peak heart rate). The dietary and exercise intervention occurred over weeks 1 through 12, and postintervention testing was completed at week 13, with subjects continuing to consume their study diets. Additional details have been described elsewhere [8]. Note that differences in the change in glucose disposal among the 3 groups were not significant, nor were differences by group in insulin sensitivity at baseline or follow-up. Because similar changes were observed in all 3 groups, we combined the groups into a single cohort for the present analyses.

2.3. Metabolic measures

2.3.1. Glucose tolerance

For screening and baseline OGTT measures, subjects arrived at the laboratory in the morning after an overnight fast and after being instructed to consume a carbohydrate-rich diet for 3 days before the test. Postintervention OGTTs were performed 1 day after the final exercise session (in subjects randomized to the exercise group) and with subjects maintaining their study diet. Seventy-five grams of chilled dextrose (Sun-Dex 75, Fisher Healthcare, Houston, TX) was administered orally after placement of an antecubital intra-

venous catheter and collection of baseline blood samples, and additional blood samples were collected at 30-minute intervals for 2 hours after dextrose administration. Blood samples were drawn into Vacutainers (Becton Dickinson, Franklin Lakes, NJ) containing sodium heparin, with an aliquot of whole blood assayed immediately for glucose concentration (YSI 2300 Stat Plus, YSI, Yellow Springs, OH). Remaining blood was centrifuged at 1200*g* for 20 minutes at 4°C, and plasma was stored at −20°C for future analysis. Insulin concentration was measured from thawed plasma samples using either a double-antibody radioimmunoassay (Linco Research, St Charles, MO) or an immunochemiluminometric assay (MLT Research, Wales, UK) because of changes in protocol in our General Clinical Research Center laboratory. Subjects' pre- and postintervention insulin samples were measured simultaneously using the same assay to maintain qualitative integrity, and samples representing each study group were measured using each insulin assay methodology to minimize bias due to possible methodological differences.

2.3.2. Euglycemic-hyperinsulinemic clamp

A 2-hour single-stage euglycemic-hyperinsulinemic clamp [1] was used to assess insulin-mediated glucose disposal at baseline and week 13. Baseline clamp measurements were performed after 2 days of standardized dietary intake (35% fat, 45% carbohydrate, 20% protein), and postintervention clamps were completed while subjects continued their study diets, as well as 3 days after the final exercise session (in those subjects randomized to the exercise group). A primed continuous infusion (priming dose, 18 μmol/kg; infusion, 0.22 μmol · kg^{-1} · min^{-1}) of [6,6-$^2H_2$]glucose (Cambridge Isotope Labs, Andover, MA) was administered for the duration of the clamp to allow measurement of endogenous glucose production. Insulin (Humulin, Eli Lilly, Indianapolis, IN) was infused at a rate of 40 mU · m^2 · min^{-1} after a 10-minute stepped priming infusion. Glucose (20% dextrose) was infused using a variable-speed infusion pump (Harvard Apparatus, Holliston, MA) controlled with a computerized algorithm to maintain plasma glucose values at approximately ±3% (mean range, 1.5%-4.7%) of baseline value. A spike of [6,6-$^2H_2$]glucose (800 mg) was added to the exogenously administered glucose to maintain a constant plasma glucose isotopic enrichment. Blood samples were obtained every 5 minutes for determination of plasma glucose in duplicate by the glucose oxidase method (Glucose Analyzer 2, Beckman Coulter, Brea, CA); samples were also drawn every 15 to 30 minutes for analyses of plasma insulin and glucose isotope enrichment. Arterialized venous blood samples were obtained by placing the subject's catheterized hand in a heated box. Mean glucose disposal (calculated as glucose infusion rate plus isotopically derived endogenous glucose production, normalized for fat free mass [GDFFM; mg · kg FFM^{-1} · min^{-1}] or body weight [GDBW; mg · kg BW^{-1} · min^{-1}]) during the final 30 minutes of the clamp, was used to assess insulin-mediated glucose disposal. Steady-state plasma insulin concentrations were calculated as the mean insulin value over the final 30 minutes of the clamp.

2.3.3. Body weight/fat free mass

Fasting body weight was measured in each subject on the morning of the clamp procedure, and body composition was measured 1 day before the clamp using air displacement plethysmography, as described previously [8].

2.3.4. Index calculations

The insulin sensitivity indices examined in the present study were calculated either from fasting glucose and insulin values (QUICKI [9], HOMA [10]) or glucose and insulin values obtained during the OGTT [11-16] using the formulas listed in each original citation (Table 1). Given the observed nonlinear relationship between HOMA and clamp data, a log-transformed HOMA index was calculated and used in subsequent analyses; all other relationships between indices and clamp data were approximately linear. The index by Mari et al [14] (oral glucose insulin sensitivity [OGIS] index) was calculated using a spreadsheet downloaded from an Internet World Wide Web page maintained by the index authors. The areas under the OGTT glucose

Table 1
Insulin sensitivity index equations

Index	Equation	Reference
Log HOMA	log {[FPI (μU/mL) × FPG (mmol/L)]/22.5}	[10]
QUICKI	1/[log FPI (μU/mL) + log FPG (mg/dL)]	[9]
ISI-Belfiore	2/[({[0.5 × FPG (mmol/L)] + OGTT 1-h PG + (0.5 × OGTT 2-h PG)}/11.36) × ({[0.5 × FPI (pmol/L)] + OGTT 1-h PI + (0.5 × OGTT 2-h PI)}/638) + 1]	[11]
ISI-Ceder	[(75 000/120) + ({[FPG (mmol/L) − OGTT 2-h PG] × 1.15 × 180 × 0.19 × body weight (kg)}/120)]/[OGTT glucose AUC (mmol · min^{-1} · L^{-1})/120]/log[OGTT insulin AUC (mU · min^{-1} · L^{-1})/120]	[12]
ISI-Gutt	{75 000 + [FPG (mg/L) − OGTT 2-h PG] × 0.19 × body weight (kg)/120}/[(FPG + OGTT 2-h PG)/2]/log{[FPI (mU/L) + OGTT 2-h PI]/2}	[13]
ISI-Matsuda	$10\,000/\sqrt{[\text{FPG (mg/dL)} \times \text{FPI } (\mu\text{U/mL})] \times (\text{mean OGTT PG} \times \text{mean OGTT PI})}$	[15]
ISI-Stumvoll	0.226 − [0.0032 × BMI (kg/m^2)] − [0.0000645 × OGTT 2-h PI (pmol/L)] − [0.00375 × OGTT 1.5-h PG (mmol/L)]	[16]

Note that the AUC-glu and AUC-ins indices were calculated using the trapezium rule [17], and the OGIS index was calculated using a spreadsheet downloaded from an Internet World Wide Web page maintained by the index authors [14]. FPI indicates fasting plasma insulin; FPG, fasting plasma glucose; PG, plasma glucose; PI, plasma insulin.

and insulin curves (AUC-glu and AUC-ins, respectively) were calculated using the trapezium rule [17]. Note that different units of measurement were used for each equation to match the units used in the original citation.

2.4. Statistical analyses

Two related statistical analytic approaches were used to examine the agreement between calculated insulin sensitivity indices and clamp data. The first approach included a scatterplot with correlation analysis, which has been commonly and historically used to assess the agreement of 2 measurement techniques. The second approach used a regression-based 95% prediction interval, which has been suggested to be a superior analytic method of comparing 2 measurements [7]. The prediction interval was calculated by first regressing the clamp measurement on each index measurement, and then using the equation

$$1.96\sqrt{s^2\left\{1+(1/n)+\left[(\chi_i-\chi_{\text{bar}})^2/\sum(\chi_i-\overline{\chi})^2\right]\right\}},$$

where s = standard error of the regression equation, n = number of observations, χ_i = ith index value, and χ_{bar} = mean index value to obtain the approximate 95% range of possible clamp values predicted by each mean index value. The reported prediction interval values reflect the upper and lower boundaries of the calculated interval—this width of the prediction interval reflects the agreement between clamp and index data. This approach is useful in that the interval numbers have the same scale as the comparison method (eg, for the clamp index, the prediction units are in mg · kg^{-1} · min^{-1}) and thus the interval is more intuitively related to the error associated with indirect prediction of clamp values by the indices, but the approach may be limited by the fact that acceptable agreement (ie, an acceptable prediction interval width) is a matter of clinical and not statistical judgment. Our goal in using 2 different statistical approaches was to examine whether different conclusions would likely be drawn using one approach vs the other. The correlation analyses were included to provide results in a comparable format to those published by many previous investigators. Correlation, however, does not assess any potential systematic bias between 2 variables, nor is the magnitude or significance of the correlation coefficient an adequate assessment of the magnitude of the differences between 2 variables (the overall objective of this study), and for this reason the alternative approach described above was also used [7].

Demographic and clinical variables are reported as mean ± SEM and were summarized using standard descriptive statistics. Visual inspection of each continuous variable using normal probability plots failed to reveal any serious departures from normality. For all analyses, the threshold P value that was considered to be statistically significant was .05. Differences between pre- and postintervention values were examined using a paired-samples t test. A Pearson product moment correlation was used to examine the correlation of each calculated ISI with insulin-mediated glucose disposal assessed using the clamp. For the Bland-Altman statistical approach, the 95% prediction interval was plotted on each scatterplot, and the approximate numeric interval was calculated using the central value of the standard error for each equation variable. Statistical analyses were performed using SPSS 12.0 (SPSS, Chicago, IL). Equivalence among correlation coefficients (ie, correlational pattern hypothesis testing) was examined using MULTICORR 2.4 [18].

3. Results

3.1. Clinical characteristics of subjects

Subject descriptive characteristics, clamp data, and insulin sensitivity indices calculated at pre- and postintervention are shown in Table 2. Mean weight and BMI

Table 2
Subject descriptive characteristics and insulin sensitivity indices (n = 31, except where indicated)

	Preintervention	Postintervention
Age (y)	67.8 ± 3.6	–
Weight (kg)	86.8 ± 2.6	84.3 ± 2.6*
BMI (kg/m^2)	30.7 ± 0.7	29.8 ± 0.7*
GDBW (mg · kg^{-1} · min^{-1})	3.02 ± 0.17	3.64 ± 0.27*
GDFFM (mg · kg^{-1} · min^{-1})	5.18 ± 0.30	5.92 ± 0.38*
Steady-state insulin (μU/mL)	93.1 ± 3.8	99.4 ± 4.5
Steady-state glucose (mg/dL)	104.8 ± 2.3	103.2 ± 2.4
Basal EGP (μmol · kg^{-1} · min^{-1})	16.1 ± 1.1	15.9 ± 1.0
Steady-state EGP (μmol · kg^{-1} · min^{-1})	0.44 ± 0.06	0.53 ± 0.08*
HOMA	2.9 ± 0.3	3.7 ± 0.8
Log HOMA	0.37 ± 0.06	0.39 ± 0.07
QUICKI	0.34 ± 0.01	0.34 ± 0.01
OGTT fasting glucose (mg/dL)	96.3 ± 2.2	95.8 ± 2.6
OGTT fasting insulin (μU/mL)	12.1 ± 1.1	15.6 ± 3.8
OGTT 2-h glucose (mg/dL)	160.4 ± 6.5	158.7 ± 6.9
OGTT 2-h insulin (μU/mL)	77.5 ± 8.6	73.1 ± 8.5
OGTT glucose AUC (mg · min^{-1} · L^{-1})	19132 ± 567	18470 ± 814
OGTT insulin AUC (μU · min^{-1} · L^{-1})[a]	7913 ± 769	7518 ± 699
ISI-Belfiore[b]	0.81 ± 0.05	0.84 ± 0.05
ISI-Ceder[a]	35.6 ± 2.0	36.3 ± 2.1
ISI-Gutt	39.3 ± 1.5	39.5 ± 1.9
ISI-Matsuda[a]	3.8 ± 0.4	4.2 ± 0.4
OGIS[b]	378 ± 8	386 ± 12
ISI-Stumvoll	0.062 ± 0.006	0.066 ± 0.005

Data are mean ± SEM. Conversion factors are as follows: glucose, 1 mg/dL = 0.05551 mmol/L; insulin, 1 μU/mL = 6.0 pmol/L. GDBW indicates insulin-mediated glucose disposal per kilogram of body weight; GDFFM, insulin-mediated glucose disposal per kilogram of fat free mass; steady-state insulin, mean plasma insulin concentration over the final 30 minutes of the clamp procedure; steady-state glucose, mean plasma glucose concentration over the final 30 minutes of the clamp procedure; EGP, endogenous glucose production.

[a] n = 28.

[b] n = 30.

* P < .05, significantly different from preintervention value.

Table 3
Correlations of insulin sensitivity indices and euglycemic clamp data (n = 31, except where indicated)

	Preintervention		Postintervention		Δ	
	GDBW	GDFFM	GDBW	GDFFM	GDBW	GDFFM
Log HOMA	−0.381*	−0.504*	−0.247	−0.241	−0.286	−0.276
QUICKI	0.354	0.490*	0.214	0.209	0.214	0.223
AUC-glu	−0.149	−0.131	−0.256	−0.278	−0.290	−0.228
AUC-ins[a]	−0.604*	−0.536*	−0.726*	−0.701*	−0.363	−0.342
ISI-Belfiore[b]	0.738*	0.650*	0.780*	0.737*	0.456*	0.408*
ISI-Ceder[a]	0.552*	0.489*	0.563*	0.563*	0.408*	0.351
ISI-Gutt	0.572*	0.484*	0.531*	0.519*	0.489*	0.475*
ISI-Matsuda[a]	0.636*	0.617*	0.654*	0.652*	0.515*	0.413*
OGIS[b]	0.413*	0.361	0.405*	0.430*	0.417*	0.379*
ISI-Stumvoll	0.661*	0.517*	0.717*	0.671*	0.447*	0.416*

The Δ values were calculated as the difference between post- and preintervention data.
[a] n = 28.
[b] n = 30.
* $P < .05$, significant correlation.

values at postintervention were significantly lower than at baseline (note that 12 subjects maintained a stable weight by study design). Mean insulin-mediated glucose disposal (normalized for body weight [GDBW] or fat free mass [GDFFM]) significantly increased over the intervention. However, none of the differences between baseline and postintervention insulin sensitivity indices were significant. GDBW and GDFFM were each used as "reference" variables to explore whether different conclusions would be obtained depending on which variable was used because these variables are often used essentially interchangeably by multiple researchers. Similar results were observed using glucose disposal normalized for body surface area as the reference variable (131.3 ± 6.6 vs 154.8 ± 10.7 mg · m^{-2} · min^{-1}, $P = .008$) and when glucose disposal was calculated without the isotopic data (5.05 ± 0.30 vs 5.77 ± 0.37 mg · kg FFM^{-1} · min^{-1}, $P = .014$). Similar correlation and prediction limit results were also observed using glucose disposal values normalized for plasma steady-state insulin concentration (data not shown).

3.2. Correlation and agreement of ISI indices and clamp data

Pearson bivariate correlations of each ISI with clamp data are shown in Table 3. At preintervention, ISI-Belfiore [11] was highly correlated with clamp data, whether normalized for body weight, fat free mass, or body surface area, as were ISI-Stumvoll [16], ISI-Gutt [13], and ISI-Matsuda [15] (all $P \leq .003$). Only AUC-glu was not significantly correlated with either GDBW or GDFFM at preintervention. At postintervention, all indices except log HOMA, AUC-glu, and QUICKI were significantly correlated with at least 1 clamp variable, with ISI-Belfiore again having the strongest significant correlation coefficient. The correlation of Δ index values with Δ clamp data resulted in a different finding—ISI-Gutt and ISI-Matsuda had the strongest significant correlations, followed by ISI-Belfiore, ISI-Stumvoll, OGIS, and ISI-Ceder, and although several correlations were significant, all Δ correlations in general were weaker than those at baseline and at follow-up. Several

Table 4
Approximate 95% prediction limits of agreement for each ISI in comparison with euglycemic clamp data, calculated using the mean value of each standard error (n = 31, except where indicated)

	Preintervention		Postintervention		Δ	
	GDBW	GDFFM	GDBW	GDFFM	GDBW	GDFFM
Log HOMA	1.77	2.96	2.99	4.20	2.16	3.04
QUICKI	1.79	2.98	3.02	4.23	2.20	3.08
AUC-glu	1.90	3.39	2.98	4.15	2.15	3.08
AUC-ins[a]	1.48	2.66	2.17	3.04	2.20	3.11
ISI-Belfiore[b]	1.27	2.57	1.96	2.92	2.03	2.94
ISI-Ceder[a]	1.54	2.75	2.61	3.52	2.15	3.10
ISI-Gutt	1.57	2.99	2.62	3.69	1.96	2.78
ISI-Matsuda[a]	1.43	2.48	2.39	3.23	2.02	3.02
OGIS[b]	1.74	3.20	2.82	3.89	2.07	2.97
ISI-Stumvoll	1.44	2.93	2.15	3.20	2.01	2.88

The Δ values were calculated as the difference between post- and preintervention data.
[a] n = 28.
[b] n = 30.

variables were not significantly correlated with Δ clamp data, namely, log HOMA, AUC-glu, AUC-ins, and QUICKI. The Δ variable correlations were further analyzed by testing for equivalence according to the procedure of Steiger [18,19], and no correlation coefficient among the Δ variables was significantly different from any other using the same clamp data variable as a covariate (all $P > 0.10$ [n = 28]). This suggests that no particular Δ correlation is superior to any other, even if one particular correlation is significant and another is not.

When 95% prediction limits were used to examine agreement between insulin sensitivity indices and insulin-mediated glucose disposal, slightly different results were observed depending on the exact reference variable used (ie, GDBW or GDFFM), although overall results were similar to those observed for the correlation analyses. Results for preintervention data, postintervention data, and for the difference between post- and preintervention variables (Δ data) are shown in Table 4. ISI-Belfiore generally had the smallest prediction limit at pre- and postintervention, and ISI-Gutt had the smallest limit when Δ data were analyzed. This pattern was consistent for both of the differently normalized clamp variables examined. Limits of agreement between indices and GDBW were generally smaller compared with limits of agreement between indices and GDFFM, but this difference is due to the numerically smaller GDBW values (the prediction interval has the same units as the clamp). Given that the significant change in insulin sensitivity measured by the clamp in the present study was in the range of 0.62 mg · kg^{-1} · min^{-1} (body weight) and 0.74 mg · kg^{-1} · min^{-1} (fat free mass), it is apparent that the limits of agreement are not narrow enough to reliably distinguish a significant change in insulin sensitivity, at least in this population and in response to the specific intervention that we used.

4. Discussion

Our results indicate that small but significant changes in insulin-mediated glucose disposal as assessed by the euglycemic-hyperinsulinemic clamp are inadequately estimated by many common insulin sensitivity indices. Although correlations of insulin sensitivity indices and clamp data collected at baseline and follow-up were moderately strong and significant, correlations of Δ index and Δ clamp scores (Δ scores calculated as the difference between pre- and postintervention values) were weaker and often not significant, suggesting that use of these indices in lieu of the clamp may underestimate the effectiveness of dietary and exercise interventions in improving insulin sensitivity. Tests of equivalence among Δ correlation coefficients showed that no particular index was better correlated with change in clamp data compared with any other index. Similarly, the limits of agreement analysis indicated stronger agreement at baseline and follow-up compared with Δ values, with the *widest* prediction interval among variables at baseline (1.90 mg · kg^{-1} · min^{-1}, normalized for body weight) equal to the *narrowest* prediction interval among Δ variables. Among the specific indices examined, those proposed by Belfiore et al [11] and Gutt et al [13] were most strongly correlated with clamp-assessed insulin sensitivity, and had the narrowest prediction limits of agreement, suggesting that these indices performed best as substitute measures of clamp-assessed insulin sensitivity compared with the other examined indices. In general, indices calculated from OGTT data were better predictors of the clamp-assessed change in insulin sensitivity vs indices calculated from fasting blood parameters.

Previous studies have demonstrated a limited ability of certain indices to evaluate change in insulin sensitivity over time in response to a specific intervention [3], although results have been mixed [5,6,20]. Katsuki et al [5,6] reported that both QUICKI and HOMA were reliable and accurate methods for assessing change in insulin sensitivity after dietary and exercise therapy in Japanese subjects with type 2 diabetes mellitus. In contrast, Duncan et al [3] found that QUICKI was not able to accurately track exercise-induced changes in insulin sensitivity in 15 middle-aged subjects. The results of Duncan et al [3] may have been limited by the use of an unmodified frequently sampled intravenous glucose tolerance test as the standard measure of comparison [21], whereas the studies of Katsuki et al [5,6] and Mather et al [20] used the clamp as the comparison measurement. Our results confirm those of Duncan et al in that QUICKI was neither correlated nor in close agreement with the measure of change in insulin sensitivity as assessed by the clamp. We extended these findings by observing that none of the examined simple insulin sensitivity indices adequately tracked exercise- and dietary-induced changes in clamp-assessed insulin sensitivity in this population. The average improvement in insulin-mediated glucose disposal observed by Katsuki et al was 2.5 mg · kg^{-1} · min^{-1}, or about 300% larger than the change observed in our study (0.62 mg · kg^{-1} · min^{-1}). It may be that the improvement in insulin sensitivity observed in their study was large enough for simpler measures like QUICKI and HOMA to accurately assess, whereas the relatively small change in our study was too minor for simpler measures to track. However, given that interventions such as lifestyle modification have been shown to result in minor improvement in insulin sensitivity [22] and also to delay or prevent the progression to type 2 diabetes mellitus in subjects with impaired glucose tolerance [23], the ability to track small changes using simpler methods is important.

Our results further suggest that simple correlation-based methods of comparing indices with standard measures such as the clamp may be inadequate. In the present study, most of the insulin sensitivity indices we examined were highly and significantly correlated with clamp-assessed insulin sensitivity at pre- and postintervention, with weaker but still significant correlations observed among Δ variables. These results are similar to those previously reported. Using a test

of equivalence [18,19], however, we found that no particular correlation among Δ variables was significantly different from any other Δ correlation, suggesting that the presence of a significant bivariate correlation may not indicate a true ranking or preference among these measures. In addition, the predicted limits of agreement approach, which has been suggested to be a preferable method of assessing agreement between different measurement techniques [7,24], indicated that no index provided a suitable assessment of change in insulin-mediated glucose disposal over time. It should be noted that the identification of suitable agreement between measurements using the limits of agreement approach is a matter of clinical judgment and is not a statistical consideration [24], and thus may introduce a level of subjectivity. In our judgment, no index appeared to be an adequate predictor of change in glucose disposal, at least given the relatively small change in insulin sensitivity observed in our study population and after our intervention. It should also be noted that our results were obtained from a small number of specifically characterized subjects, and only cautious generalization to other populations is possible.

The relatively poor agreement of changes in examined insulin sensitivity indices with changes in clamp-assessed insulin-mediated glucose disposal may be due to several factors. It is possible that the small changes in insulin sensitivity observed in our study may be primarily a reflection of improved peripheral insulin action, especially given the exercise component of the intervention, and thus indices that primarily measure hepatic and other splanchnic tissue insulin sensitivity (such as HOMA and QUICKI) are less able to detect these changes. In addition, the variable insulin response to an oral glucose load may mask changes in insulin sensitivity that are detected when insulin concentrations are more tightly controlled (such as during a clamp), thus making indices calculated from OGTT data also less able to detect these changes. It is also possible that the accuracy of the HOMA and QUICKI assessments would have been improved by the use of mean fasting values obtained from multiple baseline OGTT samples.

In conclusion, our results indicate that a number of indices designed to assess insulin sensitivity using fasting or OGTT data were unable to track a small but significant improvement in insulin sensitivity observed using euglycemic-hyperinsulinemic clamp data in a sample of older adults after a dietary and exercise intervention designed to improve glucose tolerance. The generally significant correlation of each index with values derived from the glucose clamp at pre- and postintervention is not evidence that indices are useful assessors of change in insulin action. Given the importance of quantifying insulin sensitivity in research and clinical settings where standard assessment techniques are impractical or prohibitive, further examinations of commonly used indices in measuring change in insulin sensitivity over time are of vital interest and appear to be warranted.

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