Validation of Steady State Insulin Sensitivity Indices in Chronic Kidney Disease
Running Title: Steady State Insulin Sensitivity Indices in CKD

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Abstract

Objective: Insulin resistance may contribute to cardiovascular disease and the progression of renal insufficiency in patients with chronic kidney disease (CKD). However, feasible methods for estimating insulin sensitivity in large-population CKD studies have not been validated. The purpose of this study was to attempt to validate several commonly used steady state insulin sensitivity indices in a CKD population.

Research design and methods: Twenty seven subjects with estimated glomerular filtration rate (eGFR) ranging from 70 to <10 ml/minute/1.73m$^2$ (median eGFR=48 ml/min/1.73m$^2$) underwent a frequently sampled intravenous glucose tolerance test (FSIVGTT) on a single occasion. Correlations were obtained between the minimal model-derived insulin sensitivity parameter from the FSIVGTT (SI-FSIVGTT) and seven steady state insulin sensitivity indices derived from fasting insulin and glucose data obtained just prior to the FSIVGTT.

Results: Each of the seven steady state indices was significantly correlated with SI-FSIVGTT. For indices obtained using the mean of 4 fasting insulin and glucose values over 15 minutes, Pearson correlation coefficients (|r|) ranged from 0.51 to 0.87 (p<0.01 for each). For indices using single fasting insulin and glucose values, |r| ranged from 0.51 to 0.72 (p<0.01 for each). By both the four and one time point approaches, $1/I_0$ had the highest correlation with SI-FSIVGTT. The correlation with SI-FSIVGTT did not change significantly according to eGFR level for any of the SI-SS indices.

Conclusions: Steady state insulin sensitivity indices are valid surrogates for SI-FSIVGTT in the CKD population. Their use will expand the range of testable hypotheses in CKD cohort studies.
Chronic kidney disease (CKD) affects up to 20 million Americans and has high morbidity and mortality due to atherosclerotic cardiovascular disease (CVD) (1-4). Prevention of CVD in this high risk population depends on accurate identification and aggressive modification of risk factors. While large-scale observational studies have identified CVD risk factors in the general population and provide the basis for current CVD risk assessment and prevention (5), such data are much less robust in the CKD population. Because the strong association of CKD with CVD is explained only in part by traditional CVD risk factors (6), it is hypothesized that other metabolic or inflammatory features of renal disease contribute to CVD in this population. Insulin resistance has been independently linked with CVD in both non-diabetics and those with type 2 diabetes mellitus (7) and commonly clusters with other CVD risk factors to carry a particularly potent CVD risk (8). Insulin resistance is highly prevalent in CKD patients (9, 10) and is plausibly a risk factor for both CVD and for CKD progression (11). However, the longitudinal associations of insulin resistance with other metabolic syndrome features and with clinical outcomes are largely unknown in this population.

Dynamic tests, such as the hyperinsulinemic-euglycemic clamp and the Frequently Sampled Intravenous Glucose Tolerance Test, are considered the gold standard for insulin sensitivity estimation (SI-clamp, SI-FSIVGTT) but are impractical in a large-study setting (12, 13). Insulin resistance is usually estimated in epidemiologic studies by fasting insulin concentration (I₀), or by steady-state insulin sensitivity (SI-SS) indices derived from the relationship between I₀ and fasting glucose (G₀) values (14, 15). SI-SS indices such as those based on the homeostasis model assessment (HOMA) have been found to be appropriate surrogate variables for SI-Clamp or SI-FSIVGTT across a broad spectrum of insulin sensitivity and glucose tolerance (16-18) and are considered suitable for use in epidemiologic studies by the American Diabetes Association (19).

The validity of SI-SS indices has, however, not been established in the CKD population. The kidney plays an important role in insulin metabolism (20), and the mechanisms underlying insulin resistance in CKD may differ from those in patients with normal kidney function (21). Further, SI-SS indices are not effective surrogates for dynamic test-derived insulin sensitivity estimates in all populations (22, 23). Therefore, we hypothesized that SI-SS indices might not provide effective estimation of insulin sensitivity in patients with CKD, particularly in those with advanced renal failure. To evaluate this hypothesis, we assessed the correlation between SI-SS indices and SI-FSIVGTT in non-diabetic subjects across a broad spectrum of CKD. Many of these subjects are also participants in the NIH-sponsored Chronic Renal Insufficiency Cohort (CRIC) Study, an ongoing prospective cohort study of 3000 CKD patients to identify determinants of CVD and CKD progression in this population (24). The ultimate goal of our study was to establish the validity of SI-SS indices for future use in CRIC and other epidemiologic studies of patients with CKD.

Research Design and Methods

Study Subjects: Eligible subjects were 18-75 years old and (1) had an estimated glomerular filtration rate (eGFR) <75 ml/min/1.73 m², by the 4 variable MDRD estimating equation using a single serum creatinine value standardized to the Cleveland Clinic Foundation laboratory or (2) received maintenance hemodialysis (HD) for ESRD. Exclusion criteria included pregnancy, known
diabetes mellitus or fasting blood glucose > 125 mg/dl at screening, corticosteroid use within the past 6 months, or a terminal diagnosis. Subjects were recruited by advertisement and by investigator-initiated query at primary care clinics, nephrology clinics, and maintenance hemodialysis facilities at or affiliated with the Hospital of the University of Pennsylvania, Philadelphia, PA, or the Philadelphia Veterans Administration Medical Center, Philadelphia, PA. Written informed consent was obtained from each subject in compliance with institutional review boards at these institutions.

Procedure: The study procedure took place during a single admission to the General Clinical Research Center at the Hospital of the University of Pennsylvania. After an overnight fast, subjects underwent a 3-hour FSIVGTT as previously described (25) with the dose of insulin administered modified to be 0.01, 0.02, or 0.03 units/kg (based on eGFR <30, 30 to <60, or >60 ml/min/1.73m², respectively).

Analytical procedures and data analysis: Demographic variables and body weight and height were collected. Plasma immunoreactive insulin was measured in duplicate by double-antibody radioimmunoassay (Linco Research Inc, MO). Plasma glucose was measured by an automated glucose meter (YSI Inc., Yellow Springs, OH.) at bedside during the FSIVGTT. SI-FSIVGTT was derived using MINMOD Millennium (version 6.02) software (26).

Letting \( I_0 \) and \( G_0 \) equal the mean of 4 fasting plasma insulin and glucose values measured at time= -15, -10, -5 and -1 minute (immediately prior to the FSIVGTT), the following SI-SS indices were derived: RI-HOMA = \( (I_0(\mu U/ml) \times G_0(mM))/22.5 \); \( \log(\text{RI-HOMA}) \); SI-HOMA = 1/(RI-HOMA); and Quantitative Insulin Sensitivity Check Index (QUICKI) = \( 1/ [\log(I_0)+\log(G_0)] \). \( I_0 \), \( \log(I_0) \) and \( 1/I_0 \) were also considered. SI-SS values based only on single insulin and glucose measurements, obtained at the -1 minute time point, were also examined. Glucose values were converted to mM for SI-SS calculations.

Statistical Methods: Standard descriptive statistics were used. The assumption of normal distribution across the independent variables was examined. Treating SI-FSIVGTT as the dependent variable, univariable linear regression models for each SI-SS index were fit. Pearson correlation coefficients (r) were tested using one-sample t-tests against a null hypothesis that the population correlation coefficient (\( \rho \)) = 0. Interactions between these correlations and potential co-variables including eGFR, age, race (black vs. non-black), gender and body mass index (BMI) were explored as discussed in Results. In supplemental analyses, Spearman’s rank correlations (\( r_s \)) were also obtained. A two-tailed p-value < 0.05 was the criterion for statistical significance. Analyses were performed using STATA 9.0.

Results: Table 1 provides demographic and clinical characteristics of the 27 study subjects categorized by eGFR level. Median age was 47 (range 21 to 73) years, median BMI was 30.0 (range 18.2 to 73.3) kg/m², 67% (18/27) of subjects were male, and 63% (17/27) were African American. Four subjects had ESRD requiring maintenance HD. Among the others, eGFR ranged from 16 to 70ml/minute/1.73m² (overall median 48 ml/min/1.73m²).

\( I_0 \), \( G_0 \), RI-HOMA, and SI-FSIVGTT are also summarized in Table 1. \( I_0 \) and \( G_0 \) are reported as the within-subject mean of measurements at 4 time points over 15 minutes. The median (range) of these insulin and glucose values were 12.8 (2.8-48.7)
μU/ml and 77 (57 to 129) mg/dL, respectively. Between subject variability, expressed as coefficient of variation (CV = (standard deviation/mean) x 100), was much larger for insulin, 71%, than for glucose, 19%. There was moderate within-subject variability in fasting insulin levels, consistent with assay characteristics and known fluctuations in plasma insulin levels over short periods of time (27). The median (range) intra-subject CV for fasting insulin levels was 10% (4 to 40%), and three of the 27 subjects had CV>20% (22, 24, and 40%). By contrast, the median (range) intra-subject CV for fasting glucose levels was 3% (0.5 to 9%).

**Correlations between SI-FSIVGTT and SI-SS indices:**

The two-way distributions of SI-FSIVGTT and six of the SI-SS indices are provided graphically in Figure 1, and Pearson correlation coefficients are listed in Table 2. All correlations were statistically significant. For indices obtained using the mean of 4 fasting insulin and glucose values over 15 minutes, Pearson correlation coefficients (|r|) ranged from 0.51 to 0.87 (p<0.01 for each). For indices using single fasting insulin and glucose values, |r| ranged from 0.51 to 0.72 (p<0.01 for each). Indices employing log or reciprocal transformations to limit the impact of outlying data [log(RI-HOMA), SI-HOMA, QUICKI, log(I₀), and 1/I₀] were more highly correlated with SI-FSIVGTT than indices using untransformed data (RI-HOMA and I₀).

In general, indices based on I₀ alone were at least as highly correlated with SI-FSIVGTT as indices derived from both I₀ and G₀ data. By both the four and one time point approaches, 1/I₀ had the highest (or nearly highest) correlation with SI-FSIVGTT (r=0.87 and 0.71, respectively).

Use of one time point rather than four to derive I₀ and G₀ substantially attenuated the correlations with SI-FSIVGTT for indices employing reciprocal transformations [SI-HOMA, QUICKI, and 1/I₀], but had more modest impact on the correlations with SI-FSIVGTT for the other indices. This finding was principally explained by one subject whose fasting plasma insulin levels were highly variable (CV 40% for the four fasting insulin values). After exclusion of this subject, Pearson correlation coefficients with SI-FSIVGTT for all SI-SS indices derived from single time point values differed by <2% from the corresponding correlation coefficients based on 4 time point values.

Because SI-FSIVGTT was not normally distributed, Spearman’s rank correlations (rₛ) were also obtained. |rₛ| was ≥ 0.77 (p<0.0001) for all indices assessed by both the 4- and 1-time point approaches.

Findings among subjects stratified according to eGFR level were comparable to those combining subjects across eGFR levels. For indices based on the mean of 4 fasting time points, the log- or reciprocal-transformed indices were most highly correlated with SI-FSIVGTT at both higher and lower eGFR levels, while for indices based on a single fasting time points the log-transformed indices were most highly correlated with SI-FSIVGTT. By the four-time-point approach, Pearson correlation coefficients (|r|) with SI-FSIVGTT among 13 subjects with eGFR < 48 ml/min/1.73 m² (the median eGFR value) were 0.47 (p=0.11) for RI-HOMA, 0.63 (p=0.02) for log RI-HOMA, 0.49 (p=0.09) for I₀, and ranged from 0.69 to 0.86 (all p<0.01) for the other four SI-SS indices. Among 14 subjects with eGFR ≥ 48 ml/min/1.73 m², the Pearson correlation coefficient (|r|) was 0.63 (p=0.02) for RI-HOMA and 0.85 to 0.89 (all p<0.01) for the other six indices. In keeping with these findings, tests for whether the association of each SI-SS with SI-FSIVGTT changed according to eGFR level < or ≥ 48 ml/min/1.73 m² were not significant (p values 0.32 to 0.97). In additional analyses, the Pearson correlation coefficients (|r|) were 0.73 to 0.96 for eGFR 60 to 70 ml/min/1.73 m² (CKD Stage 2, n=4), 0.53 (RI-HOMA;
p=0.02) to 0.89 (1/I₀; p<0.0001) for eGFR 15 to <60 ml/min/1.73m² (CKD Stage 3 to 4, n=19), and 0.31 to 0.45 for eGFR <15 ml/min/1.73m² (CKD Stage 5, n=4). The precision of the estimates and the significance levels for CKD Stages 2 and 5 were limited due to the small sample size in these categories.

Each SI-SS index retained statistically significant association with SI-FSIVGTT in multivariable linear regression models (p <0.01 for each SI-SS index, in separate models). In the same models, age, BMI, and eGFR level were not significantly associated with SI-FSIVGTT, while black race was associated with greater insulin resistance by SI-FSIVGTT than non-black race (all p≤0.05). In a series of exploratory analyses, correlations between SI-FSIVGTT and each SI-SS index also did not vary significantly when stratified by age, race, gender, or BMI.

\( \beta \)-cell function and fasting glucose in CKD:

Significant inverse correlations were found between \( G₀ \) and FSIVGTT-derived parameters of pancreatic \( \beta \)-cell function including both the disposition index (DI=AIR\(_{\text{gluc}} \times \text{SI} \)) and the acute insulin response to glucose (AIR\(_{\text{gluc}} \)) as follows (Figure 2): DI (r = -0.59, p=0.001), AIR\(_{\text{gluc}} \) (r = -0.49, p=0.009). Conversely, no correlation was seen between \( G₀ \) and SI-FSIVGTT (r = 0.02, p=0.93).

**Conclusions**

This study demonstrates, in subjects with CKD, a strong and significant correlation between insulin sensitivity estimates derived from fasting glucose and insulin data and the MINMOD-derived parameter of SI-FSIVGTT. Validity of these indices has been demonstrated in the general population (14, 15) and in some (28, 29), but not all (23), select populations. A single study has validated the use of SI-SS indices in renal transplant recipients (30), but the relevance of that study to the non-transplant CKD population is limited by important factors. These include the impact of immune-suppressive agents on glucose metabolism (31) and the excellent graft function of its subjects which impairs its relevance to the setting of advanced renal insufficiency. In contrast, 23/27 subjects in the current study had K/DOQI stage 3-5 (glomerular filtration rate<60ml/min/1.73m²) CKD (32). An additional study did correlate RI-HOMA with SI-clamp in a population that contained a minority of subjects with elevated serum creatinine (17/113=15%), but did not report correlation specifically in this group with renal insufficiency (33). Therefore, the current study provides the first specific validation of SI-SS indices across a wide spectrum of CKD in non-transplant subjects.

The sample size of this study was relatively small and replication of these results at other centers will strengthen these conclusions. However, the overall correlations demonstrated here between SI-SS indices and SI-FSIVGTT are statistically significant, and similar in strength to those seen in multiple studies across diverse populations (16, 28-30). Our results specifically support the utility of the SI-SS indices in Stage 3 CKD, a critical group because of both its large size (3) and the substantial associated risk of CVD (4). This suggests that CKD does not disrupt the correlation between hepatic insulin sensitivity, which the SI-SS indices principally reflect, and insulin sensitivity at peripheral tissues including skeletal muscle and adipose which contribute substantially to insulin sensitivity estimated with dynamic methods such as the FSIVGTT (16, 34). The small number of subjects with Stage 5 CKD precludes any conclusion specifically pertaining to this group.

Our data indicate that valid insulin sensitivity estimates can be effectively derived from single fasting insulin and glucose measurements in non-diabetic CKD
subjects. This is in agreement with data from a diabetic population (15) and greatly enhances the feasibility of using SI-SS indices in large CKD studies. Further, and as seen in other studies (29, 30, 35), parameters derived from both insulin and glucose values were not superior to either raw fasting insulin values or transformations of fasting insulin (LogI₀, 1/I₀). Fasting glucose concentration may contribute relatively little information regarding insulin sensitivity in non-diabetic populations as it is maintained in a relatively restricted range while fasting insulin concentrations vary widely according to insulin sensitivity (35). This was reflected in the current study by the much larger between-subject CV for insulin than for glucose. Finally, SI-SS indices employing logarithmic or inverse transformations were uniformly more highly correlated with SI-FSIVGTT than untransformed SI-SS indice (RI-HOMA and I₀), suggesting that data transformation should be employed. Overall, our findings indicate that measurement of a single fasting insulin value will permit effective insulin sensitivity estimation in non-diabetic CKD subjects. As fasting blood glucose did correlate significantly with FSIVGTT-derived parameters of β-cell function but did not correlate with SI-FSIVGTT, it is likely that β-cell function plays a much more important role than insulin sensitivity in determining fasting blood glucose concentration in this non-diabetic CKD population. This inverse correlation between fasting blood glucose and β-cell function has been observed in subjects with normal glucose tolerance and impaired fasting glucose (36) as well as in pancreatic islet transplant recipients (37). This is consistent with the postulate that insulin secretion will compensate for insulin resistance in the setting of CKD if β-cell function is adequate.

Insulin sensitivity estimation has been employed in large scale studies for multiple purposes. These include exploration of the association between insulin resistance and cardiovascular disease (38-42) as well as the investigation of other potential emerging CVD risk factors (17) and the physiologic impact of genetic variations within metabolically active genes (18, 43). Therefore, the use of these indices will significantly expand the hypotheses that may be addressed in CRIC and other CKD population-based studies, including those exploring the relationship between insulin resistance and both CVD and the progression of renal insufficiency in this select population.

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References


Table 1 - Subject Characteristics by eGFR Category

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<td>30 to &lt;45</td>
<td>15 to &lt;30</td>
<td>&lt;15 **</td>
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<td>6</td>
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<td>4</td>
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<td>(1.1, 13.9)</td>
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Where indicated (*) data are median (range).  ** Receiving maintenance hemodialysis. BMI, body mass index; eGFR, estimated glomerular filtration rate; I_0, fasting insulin (average); G_0, fasting glucose (average); RI-HOMA, homeostasis model insulin resistance parameter; SI-MINMOD, minimal model derived parameter of insulin sensitivity.
Table 2: Correlation of SI-SS and FSIVGTT derived SI

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<td>r* (p-value)</td>
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<td>-0.51 (0.007)</td>
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<td>1/(l₀)</td>
<td>0.87 (&lt;0.0001)</td>
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* r=Pearson’s correlation coefficient between SI-SS index and SI-FSIVGTT
Figure Legends

Figure 1: Correlation between SI-FSIVGTT and SI-SS parameters in CKD. The intravenous glucose tolerance test-derived insulin sensitivity parameter (SI-FSIVGTT) and several steady state parameters (A-F) of insulin sensitivity (SI-SS) are correlated. Data are presented as x-y scatter plots with best fit regression line along with the strength (r) and significance (p) of correlation derived from Pearson’s correlation analysis.
Figure 2: Correlation between pancreatic β-cell function and fasting blood glucose in CKD. Fasting blood glucose is correlated with FSIVGTT-derived parameters of β-cell function including the disposition index (A: DI-FSIVGTT) and the acute insulin response to glucose (B: AIR-glucose). Data are presented as x-y scatter plots with best fit regression line along with the strength (r) and significance (p) of correlation derived from Pearson’s correlation analysis.