Insulin sensitivity index in type 1 diabetes and following human islet transplantation: comparison of the minimal model to euglycemic clamp measures

Michael R. Rickels, Stephanie M. Kong, Carissa Fuller, Cornelia Dalton-Bakes, Jane F. Ferguson, Muredach P. Reilly, Karen L. Teff, and Ali Naji

1Division of Endocrinology, Diabetes & Metabolism, Department of Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania; 2Division of Cardiovascular Medicine, Department of Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania; 3Monell Chemical Senses Center, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania; and 4Division of Transplantation, Department of Surgery, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania

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Insulin resistance is an underappreciated feature of type 1 diabetes (T1D) (7, 13, 32, 33), resulting at least in part from the absence of endogenous insulin secretion, frequent periods of sustained hyperglycemia (12, 21, 31), and impaired sensitivity of lipolysis to inhibition by insulin, resulting in elevated free fatty acids (FFA) (24, 33). Islet transplantation restores endogenous insulin secretion that can correct the hyperglycemia of T1D and normalize FFA metabolism (15, 20, 27), effects that have been associated with improved insulin sensitivity as derived from an insulin-modified frequently sampled intravenous glucose tolerance (FSIGT) test in T1D recipients of islet transplants. More recently, employing the hyperinsulinemic-euglycemic clamp technique with a stable glucose isotope, our group has confirmed this correction of impaired insulin sensitivity in T1D by islet transplantation and shown that the improvement is mediated by effects at the liver and skeletal muscle (18). Extension of these findings to larger populations and to other therapeutic interventions for T1D may be more readily accomplished using the FSIGT test that can be more easily standardized across clinical sites.

Whereas the minimal model index of insulin sensitivity, S\textsubscript{SI}, can be derived in T1D subjects using an insulin-modified FSIGT with good parameter resolution (10, 20, 28), S\textsubscript{SI} has not before been evaluated against measures of insulin sensitivity derived from the gold-standard minimal model indexes of insulin sensitivity (16, 19). We sought to determine how well the FSIGT minimal model-derived S\textsubscript{SI} can be derived in T1D subjects using an insulin-modified frequently sampled intravenous glucose tolerance (FSIGT) test in T1D recipients of islet transplants.

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Address for reprint requests and other correspondence: M. R. Rickels, Perelman School of Medicine at the Univ. of Pennsylvania, 12-134 Smilow Center for Translational Research, 3400 Civic Center Blvd., Philadelphia, PA 19104 (e-mail: rickels@mail.med.upenn.edu).

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MATERIALS AND METHODS

T1D subjects included those with long-standing C peptide-negative disease complicated by hypoglycemia unawareness and frequent severe hypoglycemia events who had normal kidney function and were initially considered as potential candidates for islet alone transplantation (n = 21). A subgroup of these subjects received intrahepatic islet transplants (n = 12) as part of the Clinical Islet Transplantation (CIT) Consortium protocols being conducted at the University of Pennsylvania (1). The study protocols were approved by the Institutional Review Board of the University of Pennsylvania, and all subjects gave their written informed consent to participate.

The islet transplant recipients included all 11 subjects participating in the CIT07 protocol from our institution that included thymoglobulin and etanercept for induction immunosuppression (19) and one of two participants who experienced early islet graft failure with the CIT05 protocol consisting of thymoglobulin and rituximab for induction and was later retransplanted under an Edmonton protocol with basiliximab induction. The transplant recipients underwent one or two intraperitoneal infusions of islets to achieve insulin independence. Maintenance immunosuppression consisted of low-dose tacrolimus (12-h basiliximab induction. The transplant recipients underwent one or two intraperitoneal infusions of islets to achieve insulin independence. Maintenance immunosuppression consisted of low-dose tacrolimus (12-h blood trough target 5–6 μg/l) and sirolimus (24-h blood trough target 10–15 μg/l for the first 3 mo and 8–12 μg/l thereafter).

Healthy nondiabetic control subjects for the FSIGT (n = 11) were selected for gender, age, and body mass index (BMI) from other studies conducted by our group (23, 25) to match that of the T1D subjects.

Metabolic studies. All 21 T1D subjects underwent FSIGTs and hyperinsulinemic-euglycemic clamps between 2 days and 1 mo apart. When performed the same week, the FSIGT was conducted on the first day, and menstruating women underwent both tests during the follicular phase of their menstrual cycle (26). The 12 subjects who underwent islet transplantation each repeated the FSIGT between 2.5 and 7 mo posttransplant and the euglycemic clamp between 6 and 7 mo posttransplant. The median (interquartile range) of time between the posttransplant FSIGT and euglycemic clamp studies was 3 (2.5–3.5) mo. For both the euglycemic clamp and FSIGT, T1D subjects and insulin-dependent islet transplant recipients were admitted to the University of Pennsylvania Clinical and Translational Research Center (CTRC) the afternoon before study and fasted overnight after 2000 for 12 h before testing. At 2100 subjects were converted from subcutaneous insulin to a low-dose intravenous insulin infusion protocol to target blood glucose at 81–115 mg/dl. Insulin-independent islet transplant recipients and normal controls had the option of fasting overnight either in the CTRC or at home with arrival in the CTRC by 0630 the morning of study. By 0700, one cather was placed in an antecubital vein for infusions, and one catheter was placed in a hand vein for blood sampling, with the hand placed in a thermoregulated box (−50°C) or heating pad to promote arterialization of venous blood.

FSIGT. When used overnight, the insulin infusion was discontinued 20 min before testing. All other medications were withheld until later in the morning. After baseline blood sampling at t = 0, −1, −5, and −1 min, 0.3 g/kg of 50% glucose was injected over 1 min starting at time (t) = −30 s, and 0.03 U/kg of insulin (1 U/ml solution) was injected over 30 s starting at t = 20 min. Additional blood samples were collected at t = 1, 2, 3, 4, 5, 7, 10, 12, 14, 16, 18, 20, 22, 25, 30, 40, 50, 70, 100, 140, and 180 min after the injection of glucose (20, 22, 26). All samples were centrifuged at 4°C, separated, and frozen at −80°C for subsequent analysis. Serum glucose was measured by the glucose hexokinase method using an automated glucose analyzer (Roche Module P; Roche Diagnostics, Indianapolis, IN) and serum insulin by two-site immune-enzymometric assay using a Tosoh 2000 autoanalyzer (Tosoh Biosciences, San Francisco, CA) at the Northwest Lipid Research Laboratory (University of Washington, Seattle, WA).

Euglycemic clamp. At t = −120 min a primed (5 mg/kg · fasting plasma glucose in mg/dl × 0.05 mg/dl over 5 min) continuous (0.05 mg/kg · min−1 for 355 min) infusion of the stable glucose isotope tracer [6,6-2H2]glucose (99% enriched; Cambridge Isotope Laboratories, Andover, MA) was administered to assess endogenous glucose production before and during the induction of hyperinsulinemia (4, 18). When used overnight, the insulin infusion was continued during this period to maintain stable normoglycemia until t = 0. After baseline blood sampling at −20, −10, and −1 min, at t = 0 min a continuous infusion of insulin was initiated at 1 ml/kg · min−1 for 240 min to produce hyperinsulinemia. Subsequently, a variable-rate infusion of 20% glucose was administered according to the glycemic clamp technique (8) to maintain the plasma glucose about 90 mg/dl. To reduce changes in plasma enrichment of [6,6-2H2]glucose during the clamp, the 20% glucose solution was enriched to 2.0% with [6,6-2H2]glucose (4). Morning immunosuppression medications were taken after baseline blood sampling if applicable. Blood samples were taken every 5 min, centrifuged, and measured at bedside with an automated glucose analyzer (YSI 2300; Yellow Springs Instruments, Yellow Springs, OH) to adjust the glucose infusion rate and achieve the desired plasma glucose concentration. Additional blood samples were taken every 20 min for biochemical analysis. All samples were collected on ice in chilled tubes containing EDTA and Protease Inhibitor Cocktail (Sigma-Aldrich, St. Louis, MO), centrifuged at 4°C, separated, and frozen at −80°C for subsequent analysis. Plasma glucose was verified in duplicate by the glucose oxidase method using an automated glucose analyzer (YSI 2300; Yellow Springs Instruments, Yellow Springs, OH), which was measured in duplicate by double-analyte radioimmunoassay (Millipore, Billerica, MA) as previously described (18). Enrichment of [6,6-2H2]glucose was measured by gas chromatography-mass spectrometry at Metabolic Solutions (Nashua, NH) or the Metabolic Tracer Resource at the University of Pennsylvania.

Calculations and statistics. Basal levels of glucose and insulin were calculated from the mean of the baseline samples preceding t = 0 for the FSIGT. Intravenous glucose tolerance was evaluated from the FSIGT by the glucose disappearance rate Kgl = ln[gln-glucose/min × 100, calculated as the slope of the natural log of glucose values between 10 and 40 min with least-squares linear regression (29) using Origin software (Northampton, MA). The FSIGT parameters for the acute insulin response to the injection of glucose (AIRg), insulin sensitivity (SI), disposition index (DI = AIRg × SI), and glucose effectiveness (SG) were derived from Bergman’s minimal model using MINMOD Millennium software (6) as previously described (20, 25, 26).

The rate of appearance (Ra) of glucose during the euglycemic clamps was calculated using Steele’s nonsteady state equation modified for the use of stable isotopes: Ra = [(E1−E2)+(t2−t1)]/[E1−E2][E1−E2]+E2]2, where C1 and C2 are the glucose concentrations at the times 2 and 1, respectively (in mg/ml), V is the fractional volume of distribution of glucose (40 ml/kg), F is the tracer infusion rate, and E represents the isotopic enrichment at the respective time points (30). The rate of disposal (Rd) of glucose during the euglycemic clamps was calculated using Steele’s non-steady-state equation Rd = V[(C2−C1)/2]+E1]/E1(1−t1)], where C1 and C2 are the glucose concentrations at the times 2 and 1, respectively (in mg/ml). Total body insulin sensitivity was calculated from the final hour of the euglycemic clamp as SI(clamp) = M/(ΔG × G) where M is the glucose infusion rate (GIR), ΔG is the change in insulin concentration from basal to the steady-state condition during the final hour of insulin infusion, and G is the steady-state glucose concentration during the final hour (2). Accounting for space correction (SC), such that M = GIR − SC where SC = (G2 − G1) × 1.9((t2 − t1)) calculates the glucose removed from or added to the glucose space between each time interval where G2 and G1 are the glucose concentrations at the times 2 and 1, respectively (in mg/dl) (8), resulted in nearly identical measures for SI(clamp) (r2 = 0.997; P < 0.00001). Peripheral (primarily skeletal muscle) insulin...
sensitivity was calculated using the steady-state tracer-derived glucose disposal as $\text{SI}_{\text{P(clamp)}} = \Delta R_g/\Delta (\Delta I \times G)$ (3).

Whereas both minimal model ($S_I$) and clamp ($S_{IC(clamp)}$, and $S_{IP(clamp)}$) measures reflect insulin sensitivity that is dominated by extrahepatic effects of insulin (3), they are not directly comparable because they are expressed in different units $[(\mu U/ml)^{-1} \text{ min and } \text{ g} \cdot \text{min}^{-1} \cdot \text{kg}^{-1} \text{ per U/ml}$, respectively]. This is due to each parameter being normalized to a different measure of body size, with the volume of distribution of glucose used in the minimal model and body weight in the clamp calculations. To convert them to a common index of insulin sensitivity, $S_{IC}$, reflecting the unitary change in insulin to cause a given increment in glucose clearance (dl/min per $\mu$ U/ml), we followed the procedure reported by Bergman’s group (3, 22) such that $S_{IC(minmod)} = S_I \times V_D$ where the volume of distribution of glucose is calculated as $V_D = (\text{dose of glucose injected in milligrams divided by } G_0 - G_b = \text{mg/dl, where } G_0 = \text{the peak and } G_b = \text{the basal glucose derived from the minimal model, } S_{IC(clamp)} = S_{IC(clamp)} \times \text{body weight in kilograms, and } S_{IP(clamp)} = S_{IP(clamp)} \times \text{body weight in kilograms.}$

Because the conversion factors used for the minimal model and clamp-derived estimates of insulin sensitivity are independent, this procedure excludes bias in the statistical comparison of the two methods for measuring $S_{IC}$ (3).

All data are expressed as means ± SE. Comparison of results between pre- and posttransplant T1D subjects was performed with paired Student’s t-tests or Wilcoxon Match Pairs tests for nonparametric data, and comparison of results between each T1D group and controls was performed with unpaired Student’s t-tests or the Mann-Whitney U-test as appropriate using Statistica software (StatSoft, Tulsa, OK). Comparison of the minimal model and clamp-derived indexes of insulin sensitivity were performed by least-squares linear regression using Origin software. Significance was considered at $P < 0.05$ (2-tailed).

RESULTS

Subject characteristics. The T1D subjects were of comparable gender distribution, age, body weight, and BMI to the control subjects (Table 1). Those T1D subjects who underwent islet transplantation had a decrease in body weight with resulting decrease in BMI ($P < 0.01$; Table 1), although values of both remained not different from normal. The T1D subjects had ~30 years of disease duration and an insulin requirement.

Table 1. Subject characteristics at the time of FSIGT testing

<table>
<thead>
<tr>
<th>TID</th>
<th>Allevated (n = 21)</th>
<th>Pretransplant (n = 12)</th>
<th>Posttransplant (n = 12)</th>
<th>Normal Controls (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>9/12</td>
<td>5/7</td>
<td>5/7</td>
<td>6/5</td>
</tr>
<tr>
<td>Age, yr</td>
<td>46 ± 2</td>
<td>46 ± 3</td>
<td>47 ± 3*</td>
<td>40 ± 2</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>70 ± 3</td>
<td>71 ± 3</td>
<td>66 ± 3*</td>
<td>71 ± 3</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25 ± 1</td>
<td>25 ± 1</td>
<td>23 ± 1*</td>
<td>24 ± 1</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>6.8 ± 0.2</td>
<td>7.1 ± 0.2</td>
<td>5.5 ± 0.1*</td>
<td>ND</td>
</tr>
<tr>
<td>TID duration, yr</td>
<td>31 ± 2</td>
<td>29 ± 4</td>
<td>31 ± 4*</td>
<td>ND</td>
</tr>
<tr>
<td>Insulin use, U/kg·day⁻¹</td>
<td>0.50 ± 0.03</td>
<td>0.48 ± 0.05</td>
<td>0.02 ± 0.02*</td>
<td>ND</td>
</tr>
<tr>
<td>IE/kg</td>
<td>9.648 ± 666</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tacrolimus, μg/l</td>
<td>4.8 ± 0.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sirolimus, μg/l</td>
<td>9.2 ± 0.7*</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are means ± SE; n, no. of subjects. FSIGT, frequently sampled intravenous glucose tolerance; TID, type 1 diabetes; M, males; F, females; BMI, body mass index; IE/kg, islet equivalents transplanted/kg recipient body wt whereby an IE approximates a standard islet diameter of 150 μm. *$P < 0.01$ for comparison with TID pretransplant. †One subject was converted from sirolimus to mycophenolate mofetil because of the development of interstitial pneumonia 4 wk posttransplant that subsequently resolved (19).

$-0.5 \text{ U·kg}^{-1} \cdot \text{day}^{-1}$ that was substantially reduced ($P < 0.01$; Table 1) following receipt of 9,648 ± 666 islet equivalents/kg recipient body weight with 10 of the 12 islet recipients insulin independent at the time of posttransplant assessment. HbA1c, which was elevated in TID, was normalized in the group posttransplant (Table 1), of which seven were insulin-independent following one islet infusion, three were insulin-independent following two islet infusions, one was insulin-dependent while awaiting a second islet infusion, and one remained insulin-dependent after two islet infusions. Subjects maintained appropriate levels of tacrolimus and sirolimus (Table 1) except for one who was converted from sirolimus to mycophenolate mofetil (19).

FSIGT. Basal glucose was higher in the T1D subjects pre- compared with posttransplant and normal ($P < 0.05$ for both; Table 2 and Fig. 1A) and was also higher in the posttransplant subjects than in controls ($P < 0.05$; Table 2 and Fig. 1A), whereas basal insulin was similar in all groups (Table 2). The $V_D$ for the injected glucose was higher in the T1D subjects pre- compared with posttransplant and normal ($P < 0.05$ for both; Table 2), and $K_g$ was slower in the T1D subjects pre-compared with posttransplant and normal ($P < 0.01$ for both; Table 2). Islet transplantation restored previously absent endogenous insulin secretion with the first-phase AIRg not significantly different from normal (Table 2 and Fig. 1B). $S_i$ was reduced in T1D pre- compared with posttransplant and normal ($P < 0.01$ for both; Table 2). The resulting $D_I$ was not significantly different in the islet transplant recipients compared with controls (Table 2). $S_G$ was also reduced in T1D pre-compared with posttransplant and with normal ($P < 0.01$ for both; Table 2).

Euglycemic clamp. The steady-state glucose concentration and change in insulin concentration were similar in all groups during the final hour of the clamp, with one posttransplant subject not completing the clamp because of intravenous line failure (Table 2) (18). The GIR was less pre- than posttransplant ($P < 0.05$; Table 2), with similar results for the change in $R_g$ ($P < 0.05$; Table 2). As a result, both total body, $S_{IC(clamp)}$, and peripheral, $S_{IP(clamp)}$, insulin sensitivity were lower in T1D pre- compared with posttransplant ($P < 0.05$ for both; Table 2).

When the data were adjusted for BMI using a linear mixed model, the change in BMI did not have a significant effect on the change in FSIGT or euglycemic clamp-derived insulin sensitivity measures.

Comparison of FSIGT to euglycemic clamp-derived insulin sensitivity. Before correction, $S_{IC(minmod)}$ was reasonably predictive of $S_{IC(clamp)}$ ($r^2 = 0.50; P < 0.001$; Fig. 2A) and $S_{IP(clamp)}$ ($r^2 = 0.59; P < 0.0001$; Fig. 2B) for all 21 T1D subjects, including those not transplanted ($n = 9$) and those pretransplant ($n = 12$). When considering the untransplanted subjects ($n = 9$) and those posttransplant ($n = 11$), the predictive value of $S_{IC(minmod)}$ was weaker for $S_{IC(clamp)}$ ($r^2 = 0.19; P < 0.05$; Fig. 2C) and $S_{IP(clamp)}$ ($r^2 = 0.44; P < 0.001$; Fig. 2D). This is explained by distinct relationships appearing between the untransplanted and posttransplant subjects such that, when each group is considered separately, $S_{IC(minmod)}$ was more predictive of $S_{IC(clamp)}$ ($r^2 = 0.63$ and 0.62, respectively; $P < 0.01$; Fig. 2C) and $S_{IP(clamp)}$ ($r^2 = 0.69$ and 0.66, respectively; $P < 0.01$; Fig. 2D) than when considering the untransplanted and posttransplant subjects together.
planted (clamp) when examining all 21 T1D subjects, those not transplanted (n = 12) for comparison of SIC(minmod) with both SIC(clamp) (P = 0.66; Fig. 3A) and SICP(clamp) (P = 0.70; Fig. 3C) and SICP(clamp) (r = 0.70; P < 0.00001; Fig. 3D).

When examining the change in uncorrected insulin sensitivity measures in the transplanted subjects (n = 11), \( \Delta S_I \) (minmod) correlated with \( \Delta S_{IC(clamp)} \) (r = 0.61; P < 0.05; Fig. 4A) and more weakly with \( \Delta S_{IP(clamp)} \) (r = 0.50; P = 0.07; Fig. 4B) for the change in corrected insulin sensitivity measures from pre- to posttransplant (n = 11), \( \Delta S_I \) (minmod) correlated with both \( \Delta S_{IC(clamp)} \) (r = 0.60; P < 0.05; Fig. 4C) and with \( \Delta S_{IP(clamp)} \) (r = 0.63; P < 0.05; Fig. 4D) similar to the results with \( \Delta S_i \) (minmod) (Table 2), after adjusting for VD of the injected glucose, insulin sensitivity measured as SIC(minmod) to euglycemic clamp, peripheral insulin sensitivity. To convert glucose to mmol/l, multiply by 0.05551; and to convert insulin to pmol/l, multiply by 6. *Data from the euglycemic clamp have been previously published for the 12 T1D subjects who underwent islet transplantation (18). †n = 11 Posttransplant for measures of steady-state glucose, \( \Delta S_i \), steady-state GIR, \( \Delta R_a \), \( S_i(clamp) \), and \( S_i(pclamp) \). ‡P < 0.05 compared with T1D pretransplant. §P < 0.05 compared with T1D pretransplant. ‡P < 0.01 compared with T1D pretransplant. ¶P = 0.05 compared with T1D pretransplant.
derived measures of insulin sensitivity in T1D and islet transplant recipients. These results confirm prior reports of improved insulin sensitivity following islet transplantation for T1D that used minimal model-derived estimates from the FSIGT (15, 20) and validate the minimal model-derived SI as a measure of both total body and peripheral insulin sensitivity in T1D. In fact, the correlations shown here were slightly stronger with clamp-derived peripheral insulin sensitivity, SIP(clamp), based on tracer-calculated glucose disposal, Rd, than clamp-derived total body insulin sensitivity, SI(clamp), based on glucose infusion rate. Importantly, the relationships between the minimal model and clamp-derived estimates were stronger when considering the volume-corrected SIC, particularly when evaluating untransplanted and posttransplant subject together, an effect explained by the different VD for the injected glucose between these groups. Indeed, the SIC measure is more appropriate than the standard SI when comparing T1D subjects with varying VD, since similar relationships were present using SIC whether considering only T1D subjects or including those postislet transplantation.

Prior reports from our group and others have established that the minimal model can adequately resolve the parameter S1 in T1D (10, 20, 28), despite a late rise in glucose during the FSIGT as seen in our study (Fig. 1). Other studies involving T2D have encountered estimates of SI equal to zero, a problem avoided in the present work we believe by the use of an overnight insulin infusion targeting near-normal glycemia that was present at the start of testing. It is important to note that the minimal model SI underestimates insulin sensitivity as measured by the clamp when the values were normalized to identical units with the slope for correlations of SIC(minmod) against SIC(clamp) and SICP(clamp) both being around 0.5 (Fig. 2). A similar underestimation was also reported for the analysis comparing the minimal model and clamp-derived measures of insulin sensitivity in subjects that ranged from normal with those with impaired glucose tolerance, including overt T2D (22). This underestimation is likely explained by the difference in the effect on glucose disposal of an insulin bolus, as given with the FSIGT, compared with a continuous infusion of insulin

Fig. 2. Correlations between total body insulin sensitivity estimated by the minimal model [S(minmod)] total body insulin sensitivity based on glucose infusion rate, M, from the euglycemic clamp [S(clamp); on the left], and peripheral insulin sensitivity based on glucose disposal rate, Rd, from the euglycemic clamp [SIP(clamp); on the right]. The predictive relationships of S(minmod) to S(clamp) and SIP(clamp) were stronger when considering all 21 T1D subjects (A and B) than when considering those not transplanted and those posttransplant (C and D).
during the euglycemic clamp since insulin-stimulated glucose disposal increases with time (9). This same difference in insulin administration may also explain the greater magnitude of increase in insulin sensitivity seen with the minimal model than with euglycemic clamp measures and suggests that the FSIGT may be a more sensitive methodology for identifying changes in insulin sensitivity in T1D. Given these differences in performance characteristics, the minimal model SI should still be regarded as an index of insulin sensitivity and not be directly substituted for direct measures obtained from euglycemic clamp studies.

This is the first study to show that the impaired $S_G$ seen in T1D (10, 28) can be normalized following islet transplantation. The low $S_G$ derived from the FSIGT in T1D may in part be a consequence of absent insulin secretory function, since greater $AIR_g$ in normal subjects may lead to an overestimation of $S_G$ by the minimal model approach (11). In our prior study of islet transplant recipients where $S_G$ was less than normal, the $AIR_g$ was significantly reduced (20). In the present study, $AIR_g$ was not different from normal, although individual subjects did have reduced responses, and so demonstrates that, in the presence of near-normal $\beta$-cell function, there is no impairment of $S_G$ in islet transplant recipients. Glucose effectiveness is comprised of peripheral and hepatic components, with glucose autoregulation of glucose production by the liver contributing importantly to overall endogenous glucose production (5). Because glucose effectiveness describes the capacity for glucose to mediate its own disposal independent from insulin, the normalization of $S_G$ reported here provides additional evidence to the already reported improvements in hepatic and peripheral insulin sensitivity (18) against a detrimental effect of the intrahepatic site of transplantation or immunosuppression regimen on the maintenance of glucose homeostasis in islet recipients.

In conclusion, the minimal model-derived index of total body insulin sensitivity, $S_{IC}$, is highly predictive of clamp-derived measures of both total and peripheral insulin sensitivity in T1D and following islet transplantation. When employing the FSIGT to generate the minimal model $S_I$, simultaneous

![Graph A](image1)

![Graph B](image2)

![Graph C](image3)

![Graph D](image4)

Fig. 3. Correlations between corrected measures of $S_{IC(minmod)}$ and $S_{IC(clamp)}$ (on the left), and $S_{ICP(clamp)}$ (on the right). The minimal model and clamp-derived measures were each independently converted to a common index of insulin sensitivity, $S_{IC}$, reflecting the unitary change in insulin to cause a given increment in glucose clearance and expressed $\times 10^2$ in $dl/min$ per $\mu U/ml$. The resulting predictive relationships of $S_{IC(minmod)}$ to $S_{IC(clamp)}$ and $S_{ICP(clamp)}$ were robust both when considering all 21 T1D subjects ($A$ and $B$), and when considering those not transplanted and those posttransplant ($C$ and $D$).
generation of $S_G$ is possible, with both indexes impaired in T1D and capable of correction as shown here with islet transplantation. The FSIGT parameter $AIR_g$ also provides a measure of islet graft $\beta$-cell function that is predictive of insulin requirements (14) and so may also be of interest during postislet transplant metabolic assessment. Thus, our data indicate the usefulness of the minimal model for longitudinal or cross-sectional studies in T1D populations when performance of the euglycemic clamp is not feasible for economic or practical reasons. Finally, the FSIGT may be the desired methodological approach in T1D for additional consideration of potential therapeutic effects on glucose effectiveness and $\beta$-cell function.

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DISCLOSURES

No potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS


REFERENCES