RESEARCH ARTICLE | Obesity, Diabetes and Energy Homeostasis

Variable reliability of surrogate measures of insulin sensitivity after Roux-en-Y gastric bypass

Kirstine N. Bojsen-Møller,1,2 Carsten Dirksen,1,2 Maria S. Svane,1,2 Nils B. Jørgensen,1,2 Jens J. Holst,2,3 Erik A. Richter,4 and Sten Madsbad1,2

1Department of Endocrinology, Hvidovre Hospital, Hvidovre, Denmark; 2Novo Nordisk Foundation Center for Basic Metabolic Research, University of Copenhagen, Copenhagen, Denmark; 3Department of Biomedical Sciences, University of Copenhagen, Copenhagen, Denmark; and 4Department of Nutrition, Exercise and Sports Sciences, Faculty of Science, University of Copenhagen, Copenhagen, Denmark

Submitted 1 July 2016; accepted in final form 9 February 2017

Roux-en-Y gastric bypass (RYGB) is an effective treatment for severe obesity and markedly improves glycemic control in patients with type 2 diabetes (11, 30). Insulin resistance (i.e., reduced insulin sensitivity) is closely linked to obesity and is a hallmark of diabetes pathophysiology (7). The term is used to describe impaired glucose disposal in skeletal muscle and fat tissue (i.e., peripheral insulin sensitivity) as well as impaired hepatic insulin sensitivity resulting in inadequate suppression of hepatic glucose production (HGP).

The hyperinsulinemic-euglycemic clamp (HEC) is the gold standard for assessment of peripheral insulin sensitivity in particular (7, 8), whereas an index of hepatic insulin sensitivity can be derived from tracer estimation of HGP (23). However, these methods are not always feasible in clinical settings. Instead, surrogate indices of insulin sensitivity calculated from insulin and glucose concentrations at fasting or after an oral glucose tolerance test (OGTT) are frequently used, but have not been validated after RYGB. Our aim was to evaluate whether surrogate indices reliably estimate changes in insulin sensitivity after RYGB. Four fasting surrogates (inverse-HOMA-IR, HOMA2-%S, QUICKI, revised-QUICKI) and three OGTT-derived surrogates (Matsuda, Gutt, OGIS) were compared with HEC-estimated peripheral insulin sensitivity index (Rd or Rd/I, depending on how the index was originally validated) and the tracer-determined hepatic insulin sensitivity index (HISI) in patients with preoperative type 2 diabetes (n = 10) and normal glucose tolerance (n = 10) 1 wk, 3 mo, and 1 yr postoperatively. Post-RYGB changes in inverse-HOMA-IR and HOMA2-%S did not correlate with changes in Rd at any visit, but were comparable to changes in HISI at 1 wk. Changes in QUICKI and revised-QUICKI correlated with Rd/I after surgery. Changes in the Matsuda and Gutt indices did not correlate with changes in Rd/I and Rd, respectively, whereas OGIS changes correlated with Rd changes at 1 yr post-RYGB. In conclusion, surrogate measures of insulin sensitivity may not reflect results obtained with gold standard methodology after RYGB, underscoring the importance of critical reflection when surrogate endpoints are used. Fasting surrogate indices may be particularly affected by post-RYGB changes in insulin clearance, whereas the validity of OGTT-derived surrogates may be compromised by surgical rearrangements of the gut.

Roux-en-Y GASTRIC BYPASS (RYGB) surgery is an effective treatment for severe obesity and markedly improves glycemic control in patients with type 2 diabetes. In patients that have undergone an RYGB operation, neither fasting nor OGTT-derived indices have been systematically validated against the HEC. The extensive rearrangements of the upper gastrointestinal tract after RYGB could in particular affect the validity of OGTT-derived indices due to accelerated passage of nutrients to the small intestine resulting in accelerated systemic glucose appearance and exaggerated postprandial insulin secretion associated with excessive glucagon-like peptide-1 (GLP-1) secretion. Moreover, OGTT-derived indices may reflect both hepatic and peripheral insulin sensitivity, whereas OGTT-derived indices may reflect both hepatic and peripheral insulin sensitivity. Instead, surrogate indices of insulin sensitivity calculated from insulin and glucose concentrations at fasting or after an oral glucose tolerance test (OGTT) are frequently used, but have not been validated after RYGB. Our aim was to evaluate whether surrogate indices reliably estimate changes in insulin sensitivity after RYGB. Four fasting surrogates (inverse-HOMA-IR, HOMA2-%S, QUICKI, revised-QUICKI) and three OGTT-derived surrogates (Matsuda, Gutt, OGIS) were compared with HEC-estimated peripheral insulin sensitivity index (Rd or Rd/I, depending on how the index was originally validated) and the tracer-determined hepatic insulin sensitivity index (HISI) in patients with preoperative type 2 diabetes (n = 10) and normal glucose tolerance (n = 10) 1 wk, 3 mo, and 1 yr postoperatively. Post-RYGB changes in inverse-HOMA-IR and HOMA2-%S did not correlate with changes in Rd at any visit, but were comparable to changes in HISI at 1 wk. Changes in QUICKI and revised-QUICKI correlated with Rd/I after surgery. Changes in the Matsuda and Gutt indices did not correlate with changes in Rd/I and Rd, respectively, whereas OGIS changes correlated with Rd changes at 1 yr post-RYGB. In conclusion, surrogate measures of insulin sensitivity may not reflect results obtained with gold standard methodology after RYGB, underscoring the importance of critical reflection when surrogate endpoints are used. Fasting surrogate indices may be particularly affected by post-RYGB changes in insulin clearance, whereas the validity of OGTT-derived surrogates may be compromised by surgical rearrangements of the gut.

Address for reprint requests and other correspondence: K. N. Bojesen-Møller, Dept. of Endocrinology, Hvidovre Hospital, Kettegaard Allé 30, DK-2650 Hvidovre, Denmark (e-mail: kirstine.bojesen-moeller@regionh.dk).

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derived) provide reliable estimates of postoperative changes in peripheral insulin sensitivity after RYGB. A secondary aim was to assess whether surrogate indices derived from fasting concentrations can be used to estimate changes in hepatic insulin sensitivity after RYGB.

Results from the HEC, including HGP and HISI, as well as data on weight loss, glycemic control, and gut hormones have been reported previously (4), but the surrogate indices of insulin sensitivity have not been previously published.

MATERIALS AND METHODS

Subjects

Ten obese patients with type 2 diabetes (T2D group: age 43.6 ± 3.4 yr, 4 men 6 women, BMI 38.9 ± 1.6 kg/m², HbA1c 7.0 ± 0.3%, diabetes duration 3.3 ± 1.0 yr; antidiabetic agents: diet alone [n = 2], metformin alone [n = 4], metformin/liraglutide [n = 2], metformin/NPH insulin [n = 2]) and 10 obese patients with normal glucose tolerance (NGT group: age 40.1 ± 2.8 yr, 3 men 7 women, BMI 40.2 ± 0.8 kg/m², HbA1c 5.4 ± 0.1%) scheduled for laparoscopic RYGB were included and investigated before (n = 20) and 1 wk (n = 16), 3 mo (n = 20), and 1 yr (n = 18) postoperatively, as described previously (4). Written informed consent was obtained from all participants and the study was approved by the Municipal Ethical Committee of Copenhagen in accordance with the Declaration of Helsinki and by the Danish Data Protection Agency and registered at www.ClinicalTrials.gov (NCT 01202526).

Study Design

Hyperinsulinemic-euglycemic clamps (HECs) including triple sampling during fasting and basal glucose tracer infusions were performed at all study visits, whereas oral glucose tolerance tests (OGTTs) and whole body dual energy X-ray absorptiometry (DEXA) scans (Discovery A, S/N 83487; Hologic, Bedford, MA) were performed on separate study days before and 3 mo and 1 yr after RYGB. Antidiabetic agents were discontinued ≥3 days before each study day, and participants were instructed to refrain from strenuous physical activity and alcohol for 3 days and to fast overnight (10–12 h) before all experiments. The timing of study days relative to surgery, and details of test procedures have been described previously (4). In short, for HECs, we applied a 4-h primed-continuous (40 μU·m²·min⁻¹) infusion of insulin (Actrapid; Novo Nordisk, Bagsværd, Denmark) combined with a variable infusion of 20% glucose enriched with [6,6-²H₂]-glucose (Cambridge Isotope Laboratories, Andover, MA) to maintain a target plasma glucose of 5.5 mmol/l during HECs (4), use of plasma glucose was kept stable at 5.5 mmol/l during HECs (4), use of glucose clearance will provide similar results as R₄ alone and was therefore not included in the present analysis. DEXA scans were not performed at 1 wk, and therefore, calculations of the 1-wk R₄ assumed no change in the relative contribution of ffm to total body weight from before to 1 wk after surgery. HISI was calculated from the tracer-determined basal rate of appearance (R₄) of glucose (in milligrams per minute) during the last 30 min of the basal [6,6-²H₂]-glucose infusion and from C-peptide concentrations: HISI (10⁰/[R₄ ⋅ C-peptide]) (4, 23).

The choice of surrogate indices of insulin sensitivity was based on a recent meta-analysis of 120 studies in unoperated subjects (25) by selecting the indices with strongest, pooled correlations to the HEC. Based on fasting concentrations (mean of three samples) of glucose (G₀), insulin (I₀), and fatty acids (FA₀), we evaluated the following surrogate indices of insulin sensitivity: HOMA-IR (24) (expressed as inverse-HOMA-IR = 1/HOMA-IR to estimate insulin sensitivity rather than resistance), the computer-generated HOMA of insulin sensitivity (HOMA-%S) (18), QUICKI (16), and revised-QUICKI (26).

The OGTT-derived surrogate indices of insulin sensitivity evaluated included those described by Matsuda and DeFronzo (Matsuda index) (23) and Gutt et al. (Gutt index) (12), the oral glucose insulin sensitivity (OGIS) (21), Stumvoll metabolic clearance rate (MCR), and the Stumvoll insulin sensitivity index (ISI) (31). The two Stumvoll indices resulted in negative values in four subjects (one glucose-tolerant subject and three with type 2 diabetes) before surgery (data not shown), and those indices were therefore not further evaluated. Formulas for calculation of the remaining seven indices are listed in Table 1.

### Table 1. Formulas for calculating indices

<table>
<thead>
<tr>
<th>Surrogate Index</th>
<th>Formula/Calculation</th>
<th>Originally Validated Against HEC With Correction for Clamp Insulin (Reference)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fasting Surrogates</strong></td>
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<td></td>
</tr>
<tr>
<td>Inverse-HOMA-IR</td>
<td>22.5/(G₀ × I₀)</td>
<td>No (24)</td>
</tr>
<tr>
<td>HOMA-%S</td>
<td><a href="https://www.dtu.ox.ac.uk/homacalculator/">https://www.dtu.ox.ac.uk/homacalculator/</a></td>
<td>No (18)</td>
</tr>
<tr>
<td>QUICKI</td>
<td>1/(log G₀ + log I₀)</td>
<td>Yes (16)</td>
</tr>
<tr>
<td>Revised-QUICKI</td>
<td>1/(log G₀ + log I₀ + log FA₀)</td>
<td>Yes (26)</td>
</tr>
<tr>
<td><strong>OGTT Surrogates</strong></td>
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<td></td>
</tr>
<tr>
<td>Matsuda</td>
<td><a href="http://mmatsuda.diabetes-smc.jp/english.html">http://mmatsuda.diabetes-smc.jp/english.html</a></td>
<td>Yes (23)</td>
</tr>
<tr>
<td>Gutt</td>
<td>[75,000 + (G₀–G₁₂₀) × 0.19 × BW]/(120 × log ([I₀ + I₁₂₀]/2) × ([G₀ + G₁₂₀]/2))</td>
<td>No (12)</td>
</tr>
<tr>
<td>OGIS</td>
<td><a href="http://webmet.pcnr.it/ogis">http://webmet.pcnr.it/ogis</a></td>
<td>No (21)</td>
</tr>
</tbody>
</table>

HEC, hyperinsulinemic-euglycemic clamp; G₀, I₀, FA₀, fasting concentrations of glucose, insulin, and fatty acids, respectively. Log is the logarithm to the base of 10. G₁₂₀, I₁₂₀, concentrations of glucose and insulin, respectively, at 120 min during the OGTT. BW, body weight in kilograms.
Postoperative changes in absolute values of each index were evaluated with ANOVA in a linear mixed-effects model using time from surgery and group as fixed categorical effects and individual subjects as random effect. Logarithmic transformation was used in case of skewed distributions.

Each surrogate index was evaluated against the HEC-estimated $R_d$ either with or without correction for clamp insulin concentration depending on how the index was originally validated (listed in Table 1), whereas only the fasting surrogates were tested against HISI. This was performed in two ways: 1) evaluation of the correlations between the absolute surrogate index and the HEC estimate or HISI by Pearson’s test before and at every postoperative visit; and 2) evaluation of the correlations between the changes ($\Delta$ post-preoperative) in surrogates and HEC estimates or HISI by Pearson’s test. Finally, repeated-measures ANOVA was used to compare the trajectories of each individual surrogate index with trajectories in the HEC estimate or HISI after log-transformation in a linear mixed-effects model using time from surgery (time), the index of insulin sensitivity (index), and the time × index interaction as fixed categorical effects and individual subjects as random effect and with time × index (T × I) as the primary read-out.

Statistical analyses were performed in R version 2.11.1 (www.R-project.org) with $P < 0.05$ as the level of significance. No adjustments for multiple comparisons were made. Data are expressed as means ± SE if normally distributed. In case of skewed distributions, data are expressed as medians (IQR).

RESULTS

Weight Loss and Glycemic Control after RYGB

Weight loss was minimal by 1 wk (% of total preoperative weight: T2D, $-4.1 \pm 0.4\%$; NGT, $-4.1 \pm 0.6\%$; $P = NS$ for comparison between groups), had increased substantially by 3 mo (T2D, $-15 \pm 1\%$; NGT, $-17 \pm 2\%$; $P = NS$), and was highest in the NGT group by 1 yr (T2D, $-22 \pm 2\%$; NGT, $-28 \pm 3\%$; $P < 0.05$). HbA1c declined after surgery in the T2D group (pre, $7.0 \pm 0.1\%$; 1 yr, $5.3 \pm 0.2\%$; $P < 0.05$), but was unchanged in the NGT group by 1 yr ($P = NS$) (4).

Peripheral and Hepatic Insulin Sensitivity after RYGB

At 1 wk after RYGB, peripheral insulin sensitivity ($R_d$ and $R_d/I$) was unchanged in the T2D group, whereas in the NGT group, $R_d$ was decreased and $R_d/I$ was unchanged (Table 2, Fig. 1A). After 3 mo and 1 yr after RYGB, improvements in peripheral insulin sensitivity were observed in both groups (Table 2, Fig. 1A).

In contrast, HISI had increased by ~60% from preoperative values in both groups at 1 wk, by ~100% at 3 mo, and remained stable at twice the preoperative value by 1 yr after RYGB (Table 2, Fig. 1A).

Fasting Surrogate Indices of Insulin Sensitivity

**HOMA vs. peripheral insulin sensitivity ($R_d$).** At 1 wk after RYGB, both inverse-HOMA-IR and HOMA-%S were increased by 45–65% with further increases at 3 mo and 1 yr, resulting in >200% and >150% change from preoperative values for inverse-HOMA-IR and HOMA-%S, respectively (Table 2, Fig. 1B).

The absolute values of inverse-HOMA-IR and HOMA-%S correlated with $R_d$ both before and after RYGB with correla-
tion coefficients of 0.6–0.8 (all \( P < 0.05 \), Table 3), with almost similar results for inverse-HOMA-IR and HOMA-%S. However, the postoperative changes did not correlate with changes in \( R_d \) at any postoperative visit (Fig. 2, A–C) and postoperative trajectories also differed (ANOVA \( T \times I: P < 0.01 \) for both indices vs. \( R_d \), Fig. 1).

**HOMA vs. hepatic insulin sensitivity.** Inverse-HOMA-IR and HOMA-%S correlated with HISI before and after RYGB with correlation coefficients of 0.7–0.9, highest for HOMA-%S (all \( P < 0.01 \), Table 3). The \( \Delta \)-changes in inverse-HOMA-IR and HOMA-%S also correlated with \( \Delta \)-changes in HISI (1 wk, \( r = 0.83 \) and 0.84; 3 mo, \( r = 0.68 \) and 0.69; 1 yr, \( r = 0.79 \) and 0.78, all \( P < 0.01 \) for inverse-HOMA-IR and HOMA-%S, respectively, plots not shown). However, the postoperative trajectories differed (ANOVA \( T \times I: P < 0.01 \) for both indices vs. HISI, Fig. 1). Notably, this was driven by a difference in the magnitude of the relative changes at 3 mo and 1 yr (\( P < 0.01 \) for inverse-HOMA-IR vs. HISI, \( P < 0.05 \) for HOMA-%S vs HISI), whereas the magnitude of the relative changes in both indices were comparable to relative changes in HISI at 1 wk after surgery (\( P = 0.9 \) and \( P = 0.4 \), respectively).

**QUICKI vs. peripheral insulin sensitivity (\( R_d/I \)).** By 1 wk after RYGB, QUICKI was slightly increased and revised-QUICKI was unchanged, whereas both indices improved at later postoperative visits with revised-QUICKI increasing slightly more than QUICKI at 1 yr (Table 2, Fig. 1B).

The absolute values of QUICKI and revised-QUICKI correlated with \( R_d/I \) both before and after RYGB with correlation coefficients of 0.5–0.8, highest for QUICKI (all \( P < 0.05 \), Table 3). In addition, changes in QUICKI and revised-QUICKI both correlated with changes in \( R_d/I \) at all visits after RYGB (Fig. 3, A–C). However, the overall trajectories of relative changes in QUICKI and revised-QUICKI differed from the \( R_d/I \) trajectory (ANOVA \( T \times I: P < 0.01 \) for both, Fig. 1). This was driven by differences in the magnitude of relative change.

**Table 3. Correlation coefficients**

<table>
<thead>
<tr>
<th>Surrogate Index</th>
<th>( R_d ) Before</th>
<th>( R_d ) 1 Wk</th>
<th>( R_d ) 3 Mo</th>
<th>( R_d ) 1 Yr</th>
<th>( R_d/I ) Before</th>
<th>( R_d/I ) 1 Wk</th>
<th>( R_d/I ) 3 Mo</th>
<th>( R_d/I ) 1 Yr</th>
<th>HISI Before</th>
<th>( R_d/I ) Before</th>
<th>( R_d/I ) 1 Wk</th>
<th>( R_d/I ) 3 Mo</th>
<th>( R_d/I ) 1 Yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting Surrogates</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
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<td>NA</td>
<td>NA</td>
<td>NA</td>
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<td>0.83#</td>
<td>0.73#</td>
<td>0.85#</td>
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<tr>
<td>HOMA-%S</td>
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<td>0.78#</td>
<td>0.65#</td>
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<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.85#</td>
<td>0.90#</td>
<td>0.77#</td>
<td>0.87#</td>
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<td>Revised-QUICKI</td>
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<td>NA</td>
<td>NA</td>
<td>0.67#</td>
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<td>0.73#</td>
<td>0.74#</td>
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<td>0.74#</td>
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<tr>
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\( R_d \), rate of glucose disappearance (in mg·min\(^{-1}\)·kg of fat-free mass\(^{-1}\)); \( R_d/I \), rate of glucose disappearance (in \( \mu \)g·min\(^{-1}\)·kg of fat-free mass\(^{-1}\)·pmol/l of insulin concentration\(^{-1}\)); HISI, hepatic insulin sensitivity index based on basal \( R_d \) (rate of glucose appearance in mg/min) and C-peptide concentrations (pmol/l) (HISI = 10\(^2\)/(\( R_d \) × C-peptide)); NA, not assessed. *Exclusion of one extreme outlier. †\( P < 0.01 \); ‡\( P < 0.05 \) for the correlation between the absolute measures evaluated by Pearson’s test.
at 3 mo and 1 yr (P < 0.01 for both QUICKI and revised-
QUICKI vs Rd/I), whereas relative changes did not differ
significantly at 1 wk (P = 0.7 and P = 0.9 for QUICKI and
revised-QUICKI, respectively).

QUICKI vs. hepatic insulin sensitivity. QUICKI and revised-
QUICKI correlated with HISI before and after RYGB with
correlation coefficients of 0.6–0.9 (all P < 0.01, Table 3).
Post-RYGB Δ-changes in QUICKI and revised-QUICKI cor-
related with Δ-changes in HISI (r values of 0.5–0.7, all P <
0.05, except for revised-QUICKI at 3 mo, r = 0.32, P = ns,
plots not shown), but the postoperative trajectories differed
significantly from HISI at all study visits (ANOVA T × I: P <
0.01 for both indices vs. HISI, Fig. 1).

OGTT-Derived Surrogate Indices of Insulin Sensitivity

All OGTT-derived surrogate indices of insulin sensitivity
increased significantly 3 mo after RYGB and further after 1 yr
(Table 2, Fig. 1C).

Matsuda vs. peripheral insulin sensitivity (Rd/I). The Mat-
suda index increased from preoperative values both at 3 mo
(~90%) and at 1 yr (~160%) after RYGB (Table 2, Fig. 1C).

Fig. 2. The surrogate indices of inverse-HOMA-IR and HOMA-%S after Roux-en-Y gastric bypass. Correlations between changes (Δ from preoperative value) in inverse-HOMA-IR vs. peripheral insulin sensitivity (Rd/I) derived from the HEC in the group (n = 20) of patients with preoperative type 2 diabetes (triangles) and normal glucose tolerance (NGT; circles) at 1 wk (A), 3 mo (B), and 1 yr (C). Similar results for ΔHOMA-%S vs. ΔRd: 1 wk r = 0.17; 3 mo r = -0.003; 1 yr r = 0.41, all P = ns.

Fig. 3. The surrogate indices of QUICKI and revised QUICKI after Roux-en-Y gastric bypass. Correlations between changes (Δ from preoperative value) in QUICKI vs. peripheral insulin sensitivity (Rd/I) derived from the HEC in the group (n = 20) of patients with preoperative type 2 diabetes (triangles) and NGT (circles) at 1 wk (A), 3 mo (B), and 1 yr (C). Similar results for Δrevised-QUICKI vs. ΔRd/I: 1 wk r = 0.77, P < 0.01, 3 mo r = 0.60, P < 0.01, 1 yr r = 0.51, P < 0.05. For the 1-yr correlations, an extreme outlier (ΔRd/I: 49, ΔQUICKI: 0.10, Δrev.QUICKI: 0.17) was removed from the data set.
Absolute values of the Matsuda index correlated significantly with $R_d/I$ both before and after RYGB with correlation coefficients ($r$ values) of 0.6–0.7 (all $P < 0.01$, Table 3). In contrast, the changes in Matsuda index did not correlate with changes in $R_d/I$ either at 3 mo or at 1 yr (Fig. 4, A and B), whereas postoperative trajectories did not differ significantly (ANOVA $T \times I: P = 0.44$, Fig. 1).

**Gutt vs. peripheral insulin sensitivity ($R_d$).** The Gutt index displayed similar postoperative changes as the Matsuda index with increases of ~90% at 3 mo and ~150% after 1 yr (Table 2, Fig. 1C). The Gutt index correlated with $R_d$ before ($r = 0.6, P < 0.05$), but neither the absolute index nor the $\Delta$-changes correlated at 3 mo or at 1 yr (plots not shown), and postoperative trajectories differed significantly (ANOVA $T \times I: P < 0.01$, Fig. 1).

**OGIS vs. peripheral insulin sensitivity ($R_d$).** OGIS increased by ~30% at 3 mo and ~50% at 1 yr (Table 2, Fig. 1C). The absolute values of OGIS correlated significantly with $R_d$ before ($r = 0.6, P < 0.01$) and 1 yr after RYGB ($r = 0.5, P < 0.05$), but only tended to correlate at 3 mo ($r = 0.4, P < 0.10$) (Table 3). Similarly, the postoperative changes in OGIS correlated significantly at 1 yr, but not at 3 mo (Fig. 5, A and B), whereas postoperative trajectories were comparable both at 3 mo and at 1 yr (ANOVA $T \times I: P = 0.9$ for OGIS vs. $R_d$, Fig. 1).

**DISCUSSION**

In this study, post-RYGB changes in surrogate measures of insulin sensitivity were compared with changes in peripheral insulin sensitivity obtained with the HEC and changes in hepatic insulin sensitivity estimated from a basal glucose tracer infusion. Comparisons were performed from 1 wk postoperatively and throughout the first postoperative year in a group of obese subjects, including both patients with preoperative type 2 diabetes and normal glucose tolerance. Four surrogate indices based on fasting measurements (HOMA-IR, HOMA-%S, QUICKI, and revised-QUICKI) as well as three OGTT-derived indices (Matsuda, Gutt, and OGIS) were selected for evaluation because they had demonstrated the strongest correlations to the HEC in unoperated subjects in a recent meta-analysis of...
120 studies (25). The Stumvoll indices were not evaluated, because negative values were obtained in 20% \( (n = 4) \) of subjects preoperatively and mainly \( (n = 3) \) in patients with type 2 diabetes, which may reflect a nonlinear relationship with the HEC in patients with high BMI (19) or the lack of validation of the indices in patients with type 2 diabetes (31). Peripheral insulin sensitivity was estimated as the HEC-derived rate of disappearance of glucose with or without correction for insulin concentration \( (R_d/I) \) or \( R_d \), respectively. Whether corrections for clamp insulin concentration should be performed has been a matter of debate, because the correction introduces more variation (2), assumes linearity between glucose disposal and insulin concentration, but may be of particular importance when insulin clearance differs, as observed after RYGB (3). In the present study, each surrogate index was evaluated against \( R_d \) with or without correction for clamp insulin concentration depending on how the index was originally validated (Table 1) to investigate whether the surrogate index of insulin sensitivity retained its original validity after RYGB. Because plasma glucose was kept stable at 5.5 mmol/l during all HECs in this study (4), corrections for clamp glucose concentrations (i.e., clamp glucose clearance rate) provided similar results as \( R_d \) alone (data not shown).

The primary aim of our study was to evaluate whether the surrogate indices of insulin sensitivity (fasting or OGTT-derived) can be used to assess postoperative changes in peripheral insulin sensitivity after RYGB. This has not been previously investigated, although an acceptable correlation between changes in OGTT and the HEC has been demonstrated in subjects after biliopancreatic diversion, a less frequently used but more extensive bariatric operation compared with RYGB (20). A secondary aim was to assess whether fasting surrogate indices can be used to estimate changes in hepatic insulin sensitivity after RYGB. Hepatic insulin sensitivity was calculated as the \( R_d \) of glucose in the fasting state with correction for peripheral C-peptide concentrations, which reflect prehepatic insulin to a larger extent than peripheral insulin concentrations. The correlations between OGTT-derived surrogates and HISI were not assessed to avoid comparing postprandial with fasting estimates of hepatic insulin sensitivity.

After RYGB, changes in fasting surrogate indices were in general not comparable to changes in peripheral insulin sensitivity, especially in the early postoperative period. At 1 wk after RYGB, peripheral insulin sensitivity estimated by the HEC \( (R_d) \) was not improved, whereas all fasting surrogates, except for revised-QUICKI, were increased. This discrepancy between fasting surrogate indices and peripheral insulin sensitivity might be expected given that fasting indices are reflections of hepatic insulin sensitivity, which improves faster than peripheral insulin sensitivity in response to post-RYGB calorie restriction (4). Along with improved hepatic insulin sensitivity (3, 4, 32), hepatic insulin clearance increases early after RYGB (3), whereby the decrease in fasting peripheral insulin concentrations is exacerbated. Indices relying strongly on fasting insulin concentrations (i.e., the fasting surrogates) may therefore not reflect changes in peripheral glucose disposal after RYGB, as observed by the lack of correlation between changes in the HOMA indices and \( R_d \) (Fig. 2). Adjusting glucose disposal for clamp insulin concentration \( (R_d/I) \) introduces adjustment for changes in insulin clearance and thereby improves the correlations between the HEC estimates and the fasting surrogates (i.e., the significant correlations between changes in \( R_d/I \) and the QUICKI indices, Fig. 3). Whether peripheral C-peptide concentrations should be used instead for calculation of the fasting surrogates is not clear (33), but may be more appropriate when insulin clearance changes as seen after RYGB (3). Logarithmic transformation of peripheral insulin concentrations as applied in the QUICKI and revised-QUICKI indices has also been previously recommended, but this procedure also introduces a different “calibration” of the indices, which complicates direct comparison with other indices of insulin sensitivity, especially when evaluating relative changes (Fig. 1). For hepatic insulin sensitivity, only 1-wk changes in inverse-HOMA-IR and HOMA-%S were comparable to changes in HISI, whereas changes seem to be overestimated at later time points, which again, potentially could be attributed to the use of insulin vs. C-peptide concentrations.

Thus the use of fasting surrogate indices to estimate changes in peripheral insulin sensitivity may not be accurate after RYGB, since fasting surrogates may be particularly affected by post-RYGB changes in insulin clearance, and therefore will not reflect insulin-mediated peripheral glucose disposal.

Postoperative changes in the OGTT-derived surrogates of the Matsuda and Gutt indices did not correlate with changes in \( R_d/I \) and \( R_d \), respectively, whereas OGIS changes correlated with \( R_d \) changes at 1 yr after RYGB. The Matsuda and Gutt indices are based on calculation applying the concentrations of glucose and insulin at 0, 30, 60, 90, and 120 min relative to ingestion of the glucose drink for the Matsuda index (23) and at 0 and 120 min combined with body weight for Gutt index (12). In contrast, OGTT is a model-based approach that estimates clearance of the glucose load adjusted for body surface area and is based on the concentrations of glucose at 0, 90, and 120 min and of insulin at 0 and 90 min (21). Adjustment to body surface area instead of body weight is often recommended and may be particularly important for insulin-mediated glucose clearance in severely obese patients given the large proportion of adipose tissue with lower glucose uptake relative to skeletal muscle (7, 29).

After RYGB, the upper gastrointestinal tract is surgically rearranged, resulting in an accelerated rate of systemic glucose appearance (5, 6, 13, 27) with leftward shifting of the postprandial glucose concentration profile (4, 22). Postprandial glucose kinetics are thus completely altered after RYGB, which may question the validity of OGTT-derived surrogate indices of insulin sensitivity. In particular, if concentrations obtained within the first postprandial hour are applied, when post-RYGB changes are largest and not reflecting changes in peripheral insulin sensitivity (1), but more likely rates of intestinal glucose absorption. Moreover, glucose ingestion in RYGB-operated subjects may induce postprandial reactive hypoglycemia caused by excessive insulin secretion due to changes in glucose absorption kinetics and increased GLP-1 secretion (10, 28). Because hypoglycemia may release counterregulatory responses, this may also compromise the validity of the OGTT-derived indices of insulin sensitivity.

Thus surrogate indices of insulin sensitivity obtained from oral tests may be inaccurate after RYGB. When compared with the HEC clamp, OGTT seems to perform better than the Matsuda or Gutt indices in assessing changes in peripheral insulin sensitivity within the first year after RYGB.
The study is limited by the number of subjects, which makes adjustment for preoperative glucose tolerance or other potential confounders difficult. Also, adjustments for multiple corrections have not been performed, and therefore, conclusions based on single $P$ values should be drawn with caution. The strengths of the study are the comprehensive longitudinal assessment of insulin sensitivity at several time points early, medium-, and long-term after RYGB by use of fasting surrogate indices, OGTT-derived surrogate indices, and gold standard estimation of both the peripheral insulin sensitivity by use of the HEC and hepatic insulin sensitivity obtained from glucose tracer infusion. Furthermore, the post-RYGB setting is interesting for evaluation of the surrogate measures of insulin sensitivity, since both hepatic and peripheral insulin sensitivity change markedly after surgery but with different rates of improvement.

In conclusion, throughout the first year after RYGB, changes in surrogate measures of insulin sensitivity were in general not reflecting results obtained with gold standard methodology (i.e., HECs and tracer-determined hepatic insulin sensitivity). Fasting surrogate indices may be particularly affected by post-RYGB changes in insulin clearance, and indices based on the homeostatic model assessment (HOMA) can therefore not be used to estimate changes in peripheral glucose disposal. The validity of oral tests may be compromised by the surgical rearrangements of the gut inducing marked changes in glucose and insulin metabolism, and OGTT-derived surrogates should be used with caution after RYGB, although OGIS seems to perform better than the Matsuda and Gutt indices.

**Perspectives and Significance**

This study underscores the importance of critical reflection on the use of surrogate end points, and in particular, that method validation in the relevant study population is essential. Before widespread use of the surrogate indices of insulin sensitivity in bariatric populations, it is necessary to validate the indices against gold standard methods keeping in mind the extensive changes in gastrointestinal anatomy, glucose fluxes, gut hormone secretion, insulin secretion, insulin clearance, and body composition.

**ACKNOWLEDGMENTS**

We thank the participants for their willingness to participate in this study. This work would not have been possible without the professional help of D. B. Nielsen, S. Polmann, and A. S. Andersen (Hvidovre Hospital, Denmark) and G. van Hall (Clinical Metabolomics Core Facility, Rigshospitalet, Copenhagen, Denmark).

**GRANTS**

This work was carried out as a part of the program of the UNIK: Food, Fitness & Pharma for Health and Disease (see www.foodfitnesspharma.ku.dk). The UNIK project is supported by the Danish Ministry of Science, Technology and Innovation. K. N. Bojsen-Møller has a postdoc funded by the Danish Council for Independent Research Medical Sciences (FSS).

**DISCLOSURES**

K. N. Bojsen-Møller, C. Dirksen, M. S. Svane, N. B. Jørgensen, J. J. Holst, and S. Madsbad are affiliated with the Novo Nordisk Foundation Centre for Basic Metabolic Research, which is funded by the Novo Nordisk Foundation. E. A. Richter has nothing to disclose.

**AUTHOR CONTRIBUTIONS**

K.N.B.-M. and C.D. wrote the study protocol, identified eligible participants and conducted the study. K.N.B.-M. performed data analysis and wrote the manuscript. C.D., M.S.S., and N.B.J. contributed to data analysis and discussion and reviewed/editied the manuscript. E.A.R., J.J.H., and S.M. contributed to the design of the study protocol, data generation and analysis, discussion and reviewed/editied the manuscript. All authors approved the final version of the manuscript.

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