Preoperative oral carbohydrate treatment attenuates immediate postoperative insulin resistance

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Soop, Mattias, Jonas Nygren, Peter Myrenfors, Anders Thorell, and Olle Ljungqvist. Preoperative oral carbohydrate treatment attenuates immediate postoperative insulin resistance. Am J Physiol Endocrinol Metab 280: E576–E583, 2001.—Postoperative insulin resistance is a well-characterized metabolic state that has been shown to correlate with the length of postoperative stay in hospital. Preoperative intravenous or oral carbohydrate treatment has been shown to attenuate the development of postoperative insulin resistance measured 1 day after surgery. To study the effects of preoperative oral carbohydrate treatment on postoperative changes in insulin resistance and substrate utilization, in the absence of postoperative confounding factors, 15 patients were double-blindly treated with either a carbohydrate-rich beverage (12.5%) (n = 8) or placebo (n = 7) before undergoing total hip replacement surgery. Insulin sensitivity, endogenous glucose release, and substrate oxidation rates were measured before and immediately after surgery. Whole body insulin sensitivity decreased by 18% in the treatment group vs. 43% in the placebo group (P < 0.05, Student’s t-test for unpaired data). In both groups, the major mechanism of insulin resistance was an inhibition of insulin-induced nonoxidative glucose disposal after surgery. The better preservation of insulin sensitivity in the treatment group was attributable to a less reduced glucose disposal in peripheral tissues and increased glucose oxidation rates.

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Insulin sensitivity measured in the control situation varies considerably among well-matched nondiabetic subjects, as does the absolute decrease in insulin sensitivity after a given operation. However, the relative reduction in insulin sensitivity after a given operation is highly reproducible, and the degree of postoperative insulin resistance should therefore be expressed as the relative decrease in insulin sensitivity measured before and after surgery (32).

Elective surgery is usually performed after an overnight fast, often as long as 12–18 h. The metabolic state at the time of surgery has been shown to significantly influence the subsequent metabolic responses. A preoperative overnight treatment with intravenous infusion of glucose, rather than the conventional preoperative fast, attenuates the degree of insulin resistance after major abdominal surgery (20). If the absorptive state is mimicked by a preoperative infusion of insulin and glucose, insulin resistance after hip replacement surgery is completely abolished because of a maintained insulin-stimulated increase in whole body glucose disposal, and the endocrine response to surgery is also blunted (25).

To provide carbohydrates through a more physiological route of administration, a carbohydrate-rich beverage that can safely be given shortly before surgery was recently designed (23). Intake of 400 ml (50 g carbohydrate) stimulates a release of insulin similar to that seen after a mixed meal (plasma concentrations ~60 µU/ml) (21, 23). This amount of carbohydrate has been shown to convert the postabsorptive state into an absorptive state as effectively as a mixed meal (21). Osmolality is low (285 mosmol/kg), allowing a gastric transit time of ~90 min for 400 ml (23).

Treatment with this carbohydrate-rich beverage preoperatively attenuates the postoperative development of insulin resistance by 50% measured on the first postoperative day after major abdominal surgery (22). This was due to an attenuated reduction in whole body glucose disposal, whereas the postoperative reduction...
in insulin-stimulated nonoxidative glucose disposal was unaltered by treatment (22).

The hypocaloric nutrition and bed rest that are common during the postoperative period exacerbate the development of insulin resistance. Insulin sensitivity decreased by 22% in healthy volunteers treated with 24 h of hypocaloric nutrition (2 liters of glucose 25 mg/ml) and bed rest (24), a treatment similar to that given to the surgical patient on the day of, and often several days after, surgery.

The aim of the present study was to evaluate the effects of preoperative treatment with the carbohydrate-rich beverage on postoperative insulin resistance, in the absence of confounding factors such as hypocaloric nutrition and bed rest in the postoperative period. To avoid such confounding factors, postoperative insulin sensitivity was measured immediately after surgery, instead of on the first postoperative day as in our previous studies on preoperative carbohydrate treatment.

METHODS

Subjects. Nineteen patients undergoing elective total hip replacement at the study center and fulfilling the following criteria were studied: age between 18 and 80 yr; body mass index (BMI) between 18 and 28 kg/m²; not taking medication known to affect intermediary metabolism or gastric emptying; no symptoms or signs of metabolic, hepatic, renal, or gastric disease; and normal fasting circulating concentrations of glucose, C-reactive protein, liver function tests, and creatinine (Table 1).

Informed consent was obtained from each subject. The protocol was approved by the Institutional Ethics Committee at the Karolinska Hospital and was carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association.

Four patients were excluded from the study after inclusion. One patient suffered from irritable bowel syndrome and could not complete the metabolic studies because of severe symptoms. General anesthesia was required for one patient because of poor function of spinal-epidural analgesia. One patient became severely insulin resistant after surgery, and on review of her medical records a prior diagnosis of gestational diabetes mellitus was unsealed, not known to the investigators at the time of inclusion. One patient was excluded because of technical difficulties during the postoperative clamp, such that a steady state was not reached during that clamp.

**Table 1. Patient characteristics and perioperative data**

<table>
<thead>
<tr>
<th>Carbohydrate</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>8</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>1/7</td>
</tr>
<tr>
<td>Age, yr</td>
<td>66 ± 3</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25 ± 1</td>
</tr>
<tr>
<td>Duration of surgery, min</td>
<td>107 ± 9</td>
</tr>
<tr>
<td>Intraoperative blood loss, ml</td>
<td>769 ± 118</td>
</tr>
<tr>
<td>Length of postoperative hospital stay, days</td>
<td>5.5 ± 0.5</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no./group. BMI, body mass index. No significant differences were noted between carbohydrate and placebo groups.

**Anesthesia and surgery.** Total hip replacement surgery was performed using the posterior approach with the patient in the lateral position. Duration of surgery and perioperative blood loss did not differ significantly between groups (Table 1).

Premedication with midazolam (2 mg iv Dormicum; Roche, Stockholm, Sweden) was given as required 2 h after ingestion of the preoperative beverage (see Study design). Immediately after premedication, an epidural catheter was inserted at L₅-L₆. Perioperative and postoperative epidural anesthesia was provided with 2.5 mg/ml bupivacaine and 5 µg/ml epinephrine (Marcain Adrenalin; Astra, Södertälje, Sweden). Because of insufficient motor blockade, spinal anesthesia was added to the protocol after the first patient was studied. This patient, who was in the treatment group, did not differ in her response to surgery from the other patients in that group. Sedation was given as needed with midazolam (Dormicum), dixyrazin (Esucos; UCB, Malmö, Sweden), and/or propofol (Diprivan; Zeneca, Göteborg, Sweden). There was no difference between the groups in the use of perioperative medication.

Prophylactic treatment against deep venous thrombosis was given using a subcutaneous injection of 40 mg sodium enoxaparin (Klexane; Rhône-Poulenc, Helsingborg, Sweden) once daily from the evening before surgery until discharge or 10 days postoperatively. Prophylactic antibiotics were provided as a single-dose intravenous injection of 2 g flucloxacillin (Ekvacillin; Astra, Södertälje, Sweden) given at the start of the operation.

One patient in the treatment group had a deep venous thrombosis in the calf after discharge from the hospital. She recovered uneventfully. Apart from this complication, there were no early postoperative complications. The length of postoperative stay in hospital was not different between the groups (Table 1).

**Study design.** The study was randomized and double blinded. The patients were treated before surgery with either a carbohydrate-rich beverage (12.5 g/100 ml carbohydrate, 12% monosaccharides, 12% disaccharides, 76% polysaccharides, 285 mosmol/kg; Nutricia Preop; Numico, Zoetermeer, The Netherlands) (carbohydrate group) (n = 8) or a placebo beverage (acesulfame-K, 0.64 g/100 ml citrate, 107 mosmol/kg) (placebo group) (n = 7) consisting of sweetened water with an appearance indistinguishable from the carbohydrate-rich beverage. The two beverages were supplied by the manufacturer in random order in coded lots. These were given in consecutive order to patients enrolled in the study. Eight hundred milliliters of beverage were ingested between 1900 and 2400 on the evening before surgery. The last meal before the operation was served at 1700 on the evening before surgery, and after this meal patients were not allowed to eat or drink anything except the carbohydrate-rich beverage or the placebo beverage. Four hundred milliliters were ingested within 10 min on the morning of the day of operation 2 h before the estimated time of insertion of the epidural catheter (Fig. 1) and 2.5 h before the estimated time of surgery.

Insulin sensitivity was measured by the hyperinsulinemic-euglycemic clamp technique (see the next section) ~1 wk before surgery at noon (control clamp) and 40–60 min after surgery at ~1330 (postop clamp) (Fig. 1). Patients followed a diet prescribed by a dietician to standardize caloric and protein intake 4 days before the control study, which was carried out in the basal state, i.e., patients fasted overnight and rested for ≥2 h before any measurements.

**Hyperinsulinemic-euglycemic clamp studies, tracer methodology, and indirect calorimetry.** Insulin (Actrapid; Novo Nordisk, Copenhagen, Denmark) was infused intravenously at 0.8 mU·kg⁻¹·min⁻¹ for 120 min. Glucose (200 mg/ml...
Glucos Pharmacia; Pharmacia & Upjohn, Stockholm, Sweden) was simultaneously infused intravenously at a variable rate to maintain the blood glucose concentration at 4.5 mmol/l. Insulin sensitivity was expressed as the mean glucose infusion rate (GIR) during a steady-state period during the last 60 min of the clamps.

A stable isotopomer of glucose, d-[6,6-2H2]glucose (Isotec, Miamisburg, OH), was given as a primed (3 mg/kg)-continuous (2.4 mg·kg⁻¹·h⁻¹) infusion that started 150 min before and continued during the clamps. All glucose infusates were enriched with the same isotopomer (molar excess 1.27% in the control measurements and 0.85% on the day of surgery) to minimize fluctuations in plasma tracer enrichment during clamps (8, 24). Whole body glucose disposal rates (WGD) and endogenous glucose release rates (EGR) were calculated using a modified Steele’s equation, taking into account the varying tracer infusion rates (8). WGD values were corrected to take into account any difference in the glucose concentration between the commencement and the end of the steady-state period (glucose pool assumed to be 250 ml/kg body wt with a pool correction factor of 65%) (8). Nonoxidative glucose disposal was calculated by subtracting the glucose oxidation rate from WGD.

Substrate oxidation rates were measured by indirect calorimetry (Deltatrac, Dansjöö, Stockholm, Sweden) performed during 30-min periods (Fig. 1). Patients breathed ambient room air during indirect calorimetry. Urine was sampled for measurement of urinary urea excretion before and during clamps. Energy expenditure (EE), nonprotein respiratory quotients (npRQ), and substrate oxidation rates were calculated (9) after correction for changes in urea pool size (29).

Sampling and chemical analysis. Circulating glucose, lactate, and d-[6,6-2H2]glucose concentrations were determined every 10 min during the following time periods: insulin, every 30 min; glucagon, cortisol, glycerol, and nonesterified fatty acids (NEFA), once in the middle of each time period. Averages are presented for each time period. The time periods of data collection were control basal: a 30-min period immediately before the start of the insulin infusion of the control clamp; control clamp: the last 30 min of the 120-min control clamp; preop basal: a 30-min period immediately before the ingestion of the preoperative beverage on the morning of surgery; preop drink: a 30-min period starting 40 min after ingestion of the preoperative beverage; intraop: a 70-min period starting 10 min after the start of operation; postop basal: a 30-min period starting ~15 min after the end of the operation and immediately followed by the start of insulin infusion of the postoperative clamp; and postop clamp: a 30-min period at the end of the 120-min postoperative clamp.

The forearm venous blood was arterialized with a heater sleeve set at 50°C (Kan Med; Stockholm, Sweden) and sampled through an intravenous catheter (Venflon; Viggo, Helsingborg, Sweden) in an antecubital vein. All infusions were given in the contralateral arm. Blood glucose and plasma 1-lactate concentrations were determined immediately upon collection by use of the glucose and lactate oxidase methods (Yellow Springs Instruments, Yellow Springs, OH) (16). Plasma was sampled every 10 min during 30-min steady-state periods for determination of [6,6-2H2]glucose enrichment. The trimethylsilyl-O-methylxime derivative of plasma and infused glucose was measured in a gas chromatography-mass spectrometer (18). Serum insulin (11), serum C-peptide (Novo Research, Bagsværd, Denmark), serum cortisol (34), and plasma glucagon (Euro-Diagnostica, Malmö, Sweden) (12) concentrations were measured using RIA methods. Plasma glycerol concentrations were measured by luminometric kinetic assay (14). Plasma NEFA concentrations were measured after lipid extraction of plasma (15). All serum samples were permitted to clot while plasma samples were immediately centrifuged at 4°C at 2,010 g for 10 min. All samples were stored in a −20°C freezer for later batch analysis.

Statistics. All values are means ± SE. Two-way ANOVA for repeated measures was used when appropriate (Statistica 4.1 for Mac OS, StatSoft). Post hoc analysis and other comparisons were performed using Student’s t-test for paired and unpaired data. Statistical significance was accepted at P < 0.05.

Fig. 1. Study protocol. Clamp, hyperinsulinemic-euglycemic clamp; tracer infusion, primed-continuous infusion of [6,6-2H2]glucose; Op, operation; EDA, epidural anesthesia; EGR, determination of endogenous glucose release; Calorimetry, indirect calorimetry; Blood, blood sampling. Patients ingested 400 ml of a carbohydrate-rich beverage or a placebo at ~4.5 h (~2.5 h before surgery) and 800 ml the evening before surgery (not shown).
Table 2. Circulating substrates and hormones

<table>
<thead>
<tr>
<th>Data Collection Periods</th>
<th>Control basal</th>
<th>Control clamp</th>
<th>Preop basal</th>
<th>Preop drink</th>
<th>Intraop</th>
<th>Postop basal</th>
<th>Postop clamp</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group</strong></td>
<td>Control basal</td>
<td>Control clamp</td>
<td>Preop basal</td>
<td>Preop drink</td>
<td>Intraop</td>
<td>Postop basal</td>
<td>Postop clamp</td>
</tr>
<tr>
<td>Glucose, mmol/l Placebo</td>
<td>4.7 ± 0.1</td>
<td>4.5 ± 0</td>
<td>4.9 ± 0.1</td>
<td>7.5 ± 0.9‡‡‡</td>
<td>5.6 ± 0.4</td>
<td>6.3 ± 0.4‡</td>
<td>4.4 ± 0.1</td>
</tr>
<tr>
<td>Lactate, mmol/l Placebo</td>
<td>4.4 ± 0.1</td>
<td>4.5 ± 0.1</td>
<td>4.5 ± 0.1</td>
<td>4.5 ± 0.1</td>
<td>4.5 ± 0.1</td>
<td>6.3 ± 0.2††</td>
<td>6.5 ± 0.3‡†</td>
</tr>
<tr>
<td>NEFA, µmol/l Placebo</td>
<td>83.8 ± 66</td>
<td>27.3 ± 3.1‡‡‡</td>
<td>71.6 ± 8.9</td>
<td>61.1 ± 12.2</td>
<td>78.2 ± 16.0</td>
<td>117 ± 40.2</td>
<td>42.8 ± 5.8‡§</td>
</tr>
<tr>
<td>Insulin, µU/ml Placebo</td>
<td>13 ± 1</td>
<td>63 ± 11†††</td>
<td>13 ± 2</td>
<td>69 ± 6*†††</td>
<td>24 ± 3††</td>
<td>20 ± 5†</td>
<td>60 ± 4</td>
</tr>
<tr>
<td>C-peptide, µmol/l Placebo</td>
<td>0.63 ± 0.07</td>
<td>0.84 ± 0.07††</td>
<td>1.35 ± 0.08‡</td>
<td>0.72 ± 0.31</td>
<td>1.13 ± 0.15†</td>
<td>1.13 ± 0.15†</td>
<td></td>
</tr>
<tr>
<td>Glucagon, pg/ml Placebo</td>
<td>74 ± 9</td>
<td>82 ± 10*</td>
<td>62 ± 7††</td>
<td>65 ± 6*</td>
<td>65 ± 6*</td>
<td>65 ± 6*</td>
<td>65 ± 6*</td>
</tr>
<tr>
<td>NEFA, µmol/l Placebo</td>
<td>66 ± 3</td>
<td>67 ± 3</td>
<td>55 ± 4</td>
<td>46 ± 2††</td>
<td>46 ± 2††</td>
<td>46 ± 2††</td>
<td>46 ± 2††</td>
</tr>
<tr>
<td>Cortisol, µmol/l Placebo</td>
<td>147 ± 19</td>
<td>233 ± 19†††</td>
<td>402 ± 54†</td>
<td>294 ± 32</td>
<td>244 ± 51†</td>
<td>231 ± 63</td>
<td>455 ± 53§§§</td>
</tr>
</tbody>
</table>

Values are means ± SE. NEFA, nonesterified fatty acids. Significant differences (by two-way ANOVA and Student’s t-tests for paired and unpaired data): *vs. placebo; †vs. control basal; ‡vs. preop basal; §§vs. control clamp. One symbol, P < 0.05; 2 symbols, P < 0.01; 3 symbols, P < 0.001.

RESULTS

Glucose, lactate, and insulin concentrations. Circulating glucose and insulin concentrations were not different between groups during basal and clamp periods (Table 2). Glucose and insulin concentrations and [6,6-2H2]glucose enrichments were stable during clamps. The mean intraindividual coefficient of variation of blood glucose concentrations at steady state during the glucose clamps was 4.2 ± 0.4 and 3.9 ± 1.0% in the carbohydrate and the placebo groups, respectively. The corresponding values for plasma [6,6-2H2]glucose enrichments were 3.6 ± 0.3 and 2.8 ± 0.4%.

After ingestion of the beverage on the morning of the day of surgery, glucose, lactate, and insulin concentrations increased in the carbohydrate group (preop drink data).

During the intraop period, glucose concentrations increased from control basal concentrations in the placebo group but not in the carbohydrate group. Surgery was associated with a slight increase of circulating insulin concentrations in both groups.

During the postop basal period, glucose, lactate, and insulin concentrations were similarly elevated in both groups compared with control basal concentrations.

Glycerol, NEFA, and glucoregulatory hormone concentrations. Carbohydrate ingestion caused a marked decrease in circulating concentrations of glycerol and NEFA during the preop drink period. In the postop basal and postop clamp periods, these concentrations were similar again in both groups.

Glucagon concentrations in the postop basal period were lower in the placebo group than in the carbohydrate group. Cortisol concentrations increased in response to surgery, but there were no differences between groups in cortisol concentrations during any time period.

C-peptide concentrations were elevated from control basal concentrations during the preop basal period in the carbohydrate group and further increased during the postop basal period. There was a smaller increase during this period also in the placebo group.

Glucose kinetics and substrate utilization. At the control study, GIR, WGD, EGR, substrate oxidation rates, and EE did not differ between groups (Table 3). After surgery, there were no differences in GIR, WGD, or EGR between the groups. However, GIR decreased in both groups, but less in the carbohydrate group than in the placebo group (−18 ± 6 vs. −43 ± 9%, P < 0.05; Fig. 2). Likewise, WGD during clamps decreased in both groups after surgery, but less in the carbohydrate group than in the placebo group (−19 ± 5 vs. −37 ± 7%, P < 0.05; Fig. 2). EGR suppression by insulin was unaffected by surgery in either group.

Glucose oxidation rates (GOX) were significantly increased in the carbohydrate group during the preop basal period. Ingestion of the preoperative carbohydrate-rich beverage on the day of surgery caused a further increase in GOX and a complete suppression of fat oxidation during the preop drink period. GOX were still increased immediately after surgery (postop basal) in the carbohydrate group.

In response to insulin infusion during the postop clamp, carbohydrate oxidation rates in the carbohydrate group increased further to exceed control clamp rates, whereas carbohydrate oxidation rates in the placebo group did not reach control clamp rates (+42 ± 6 vs. −6 ± 11%, P < 0.01; Fig. 2). Postoperatively, fat oxidation rates were markedly depressed in the carbohydrate group both at basal state and during insulin infusion. Nonoxidative glucose disposal did not increase in response to insulin infusion during the postop clamp in any group (Table 3).

DISCUSSION

Oral carbohydrate treatment shortly before surgery attenuated the decrease in whole body insulin sensitivity immediately after total hip replacement surgery. In contrast to our previous study of preoperative oral
carbohydrate treatment (22), confounding effects of postoperative management, such as hypocaloric nutrition and bed rest (24), were avoided, and a different model of surgical trauma, total hip replacement instead of major abdominal surgery, was studied. The present data show that this simple preparation allows the patient to finish major surgery with only a minimal degree of insulin resistance.

The clinical significance of insulin resistance is illustrated by a recent pooled analysis of 60 patients participating in previous studies of preoperative carbohydrate administration. The degree of postoperative insulin resistance was found to be an independent factor determining the variation in the length of postoperative hospital stay (LOS) (32). In these studies, there was a high pressure for patient beds, and there was no incentive to keep patients hospitalized longer than necessary, and LOS is therefore considered a measure of speed of postoperative recovery of functions of daily living. In a further pooled analysis, preoperative carbohydrate treatment was shown to reduce the hospital stay after elective surgery (19).

This study was performed in a small group of patients, and we were unable to detect any difference in LOS between the groups. The groups are comparable, because neither of the factors shown to influence the degree of postoperative insulin resistance was different between the groups: duration of surgery (22) or perioperative blood loss (32). Uneven distributions in gender or age (no statistically significant differences between groups in the current study) are unlikely to affect outcome, because these variables have been shown not to affect the development of postoperative insulin resistance (32).

Insulin sensitivity in the control situation has been shown to vary considerably among well-matched non-diabetic subjects, in our hands seven-fold (32) (presently based on studies of >120 subjects). However, the relative reduction in insulin sensitivity after a given operation is highly reproducible, with a coefficient of variation of ≤12.3% (32). When multiple regression analysis has been used, the relative reduction in insulin sensitivity has been shown to be an independent factor predicting the variation in length of postoperative hospital stay, whereas no such correlation was found regarding the absolute values of preoperative or postoperative insulin sensitivity or the absolute reduction of insulin sensitivity (32). Therefore, to yield the best estimate of postoperative insulin resistance, the relative rather than the absolute values should be used. The variability of the clamp method has been shown not to affect the development of postoperative insulin resistance (32).

Table 3. Glucose kinetics and substrate utilization

<table>
<thead>
<tr>
<th>Group</th>
<th>Control basal</th>
<th>Control clamp</th>
<th>Preop basal</th>
<th>Preop drink</th>
<th>Postop basal</th>
<th>Postop clamp</th>
</tr>
</thead>
<tbody>
<tr>
<td>GIR Carbohydrate</td>
<td>0 ± 0.12</td>
<td>0 ± 0.12</td>
<td>0 ± 0.12</td>
<td>0 ± 0.12</td>
<td>0 ± 0.12</td>
<td>0 ± 0.12</td>
</tr>
<tr>
<td>Placebo</td>
<td>0 ± 0.12</td>
<td>0 ± 0.12</td>
<td>0 ± 0.12</td>
<td>0 ± 0.12</td>
<td>0 ± 0.12</td>
<td>0 ± 0.12</td>
</tr>
<tr>
<td>WGD Carbohydrate</td>
<td>2.08 ± 0.08</td>
<td>2.08 ± 0.08</td>
<td>2.08 ± 0.08</td>
<td>2.08 ± 0.08</td>
<td>2.08 ± 0.08</td>
<td>2.08 ± 0.08</td>
</tr>
<tr>
<td>Placebo</td>
<td>2.08 ± 0.08</td>
<td>2.08 ± 0.08</td>
<td>2.08 ± 0.08</td>
<td>2.08 ± 0.08</td>
<td>2.08 ± 0.08</td>
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</tr>
<tr>
<td>EGR Carbohydrate</td>
<td>1.27 ± 0.17</td>
<td>1.27 ± 0.17</td>
<td>1.27 ± 0.17</td>
<td>1.27 ± 0.17</td>
<td>1.27 ± 0.17</td>
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<tr>
<td>Placebo</td>
<td>1.27 ± 0.17</td>
<td>1.27 ± 0.17</td>
<td>1.27 ± 0.17</td>
<td>1.27 ± 0.17</td>
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</tr>
<tr>
<td>FOX Carbohydrate</td>
<td>2.23 ± 0.09</td>
<td>2.23 ± 0.09</td>
<td>2.23 ± 0.09</td>
<td>2.23 ± 0.09</td>
<td>2.23 ± 0.09</td>
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<tr>
<td>Placebo</td>
<td>2.23 ± 0.09</td>
<td>2.23 ± 0.09</td>
<td>2.23 ± 0.09</td>
<td>2.23 ± 0.09</td>
<td>2.23 ± 0.09</td>
<td>2.23 ± 0.09</td>
</tr>
</tbody>
</table>

Values are means ± SE expressed in mg·kg⁻¹·min⁻¹ (except for EE, in kcal·kg⁻¹·24 h⁻¹). GIR, glucose infusion rate; WGD, whole body glucose disposal; EGR, endogenous glucose release; GOX, glucose oxidation rate; NGD, nonoxidative glucose disposal rate; FOX, fat oxidation rate; EE, energy expenditure. Significant differences (by two-way ANOVA and Student’s t-tests for paired and unpaired data): * vs. placebo; † vs. control basal; ‡ vs. preop basal; § vs. control clamp. One symbol, P < 0.05; 2 symbols, P < 0.01; 3 symbols, P < 0.001.

Fig. 2. Relative change (postop vs. control clamp) in glucose infusion rates (GIR), whole body glucose disposal rates (WGD), and glucose oxidation rates (GOX) in patients undergoing total hip replacement surgery pretreated with a carbohydrate-rich beverage (n = 8) (carbohydrate) or placebo (n = 7) (placebo). *P < 0.05; **P < 0.01 vs. placebo.
WGD after surgery, although the control GIR tended to be higher in the placebo group \( (P = 0.25) \).

The rationale for measuring postoperative insulin resistance immediately after surgery was to avoid, as far as possible, confounding factors that are known to influence insulin sensitivity, such as hypocaloric nutrition and immobilization in the postoperative period \( (24) \). Hypothetically, postoperative insulin sensitivity may decrease further after the immediate postoperative period also because of the possible appearance of stress endocrine and paracrine mediators. However, we have previously \( (25) \) and presently shown that a significant degree of insulin resistance is present immediately after hip replacement surgery.

The present data are in agreement with the findings in our previous study of preoperative oral carbohydrate treatment \( (22) \). In that study, GIR decreased after surgery by 48 and 68% in the treatment group and the placebo group, respectively. WGD decreased by 26 vs. 49%, respectively. The postoperative clamp was performed on the day after surgery. The more pronounced insulin resistance compared with the present data may be caused by postoperative hypocaloric nutrition \( (24) \) or the greater magnitude of operation in that study (major abdominal surgery under general and epidural anesthesia lasting \( \sim \)220 min) \( (32) \).

The concept of preoperative carbohydrate treatment to attenuate postoperative insulin resistance was first investigated using an overnight intravenous infusion of glucose \( (5 \text{ mg·kg}^{-1}·\text{min}^{-1}) \) in patients undergoing elective open cholecystectomy \( (20) \). GIR during clamps performed on the day after surgery decreased less in the treated group than in the untreated group \( (32 \text{ vs.} \ 55\%) \). The more pronounced insulin resistance seen in this study may again be due to postoperative hypocaloric nutrition and/or a larger magnitude of operation. Furthermore, epidural anesthesia was not used in this study, which may also contribute to the differences in postoperative insulin resistance \( (33) \).

The effect of hyperinsulinemia in combination with glucose infusion during surgery in attenuating insulin resistance was investigated in patients undergoing total hip replacement surgery \( (25) \). Patients were treated with a perioperative insulin-glucose or saline infusion. GIR was unaffected immediately after surgery in insulin-treated patients, whereas a 40% decrease in GIR was found in control patients. The latter is very similar to the reduction in insulin sensitivity seen in the placebo group in the present study. Perioperative insulin concentrations in the treatment group in that study were 58–69 µU/ml. This sustained hyperinsulinemia during surgery may account for the more potent effect of perioperative insulin infusion in abolishing postoperative insulin resistance.

Postoperative insulin resistance may be due to multiple factors present during the day of surgery and not exclusively to the surgical trauma during operation. The day of surgery is also associated with a preoperative and perioperative period of fasting and immobilization that may contribute to postoperative insulin resistance \( (24) \). Furthermore, recent preliminary data suggest that pain can induce a significant degree of insulin resistance \( (10) \). The present data cannot prove that preoperative carbohydrate treatment specifically blunts surgery-induced insulin resistance, but the effects seen may in fact be nonspecific. Nevertheless, the protocol including preoperative carbohydrates resulted in improved postoperative insulin sensitivity, and this is likely to be of importance \( (32) \).

During surgery, insulin concentrations in carbohydrate and placebo groups were similar. Nevertheless, glucose concentrations increased from basal concentrations in the placebo group but not in the carbohydrate group. Calculation of a glucose-to-insulin ratio \( (7) \) \( (0.39 \pm 0.08 \text{ vs.} \ 0.25 \pm 0.08 \text{ mmol}·\text{mU}^{-1}) \) placebo vs. carbohydrate, \( P < 0.01 \) suggests a more pronounced development of insulin resistance early during surgery in the placebo group compared with the carbohydrate group.

It is well known that an oral glucose load increases glucose disposal, glucose oxidation, and nonoxidative glucose disposal \( (21) \). Presently, we noted a significant increase in GOX in the \( \text{goop basal} \) from \( \text{control basal} \) values, \( \sim 6–8 \text{ h after the carbohydrate load on the evening before surgery, and an almost} 100\% \text{ increase in glucose oxidation in response to the oral carbohydrate load on the morning before the operation. Even after the operation, glucose oxidation was still elevated compared with} \text{proop basal} \text{ values. When insulin was given, GOX were further enhanced. The immediate postoperative glucose metabolism in patients given a single preoperative carbohydrate load has not previously been studied. The present data suggest that the observed maintenance of glucose oxidation is a key factor in maintaining glucose uptake in the immediate postoperative situation. The relative increase in glucose oxidation in response to insulin was similar in the two groups postoperatively. However, because the carbohydrate group had a higher GOX before the postoperative clamp, the insulin-stimulated glucose oxidation was higher. Similarly increased GOX were seen on the day after surgery in our previous study of preoperative carbohydrate treatment \( (22) \) (see further in DISCUSSION). The stimulus of the high GOX seen is unclear. Insulin concentrations were not increased during these time periods. The greater increase in C-peptide concentrations seen in the carbohydrate group may play a role in elevating GOX \( (17) \).

Nonoxidative glucose disposal rates failed to increase in response to insulin infusion during the \( \text{postop clamp} \) in both groups. Muscle glycogen synthesis accounts for most of the entire nonoxidative glucose disposal during hyperinsulinemia in health \( (3, 27) \). Thus the present data suggest that postoperative insulin resistance is associated with a dysfunction in insulin-induced glycogen synthesis. Carbohydrate treatment before surgery does not seem to affect the dysfunction of insulin-induced glycogen synthesis postoperatively, but it attenuates the reduction in insulin-stimulated glucose uptake and significantly increases glucose oxidation. The same pattern was seen on the day after surgery in our previous study of preoperative carbohy-
Preoperative oral carbohydrate treatment (22), where the higher GIR in the treatment group was associated with higher glucose disposal and glucose oxidation, whereas the dysfunction of insulin-induced nonoxidative glucose disposal was similar to that in the placebo group. The only postoperative hormonal difference between patients treated with oral carbohydrates or fasted overnight was an increase in proteolysis of insulin-like growth factor (IGF) binding protein-3, indicating increased IGF-I activity (1), which may contribute to increased GOX. When exogenous insulin was given intraoperatively during hip replacement surgery, postoperative basal and insulin-stimulated nonoxidative glucose disposal rates were higher than preoperative levels (25).

Because suppression of EGR by insulin was unaffected by surgery in both groups, it can be concluded that preoperative carbohydrate treatment blunted development of insulin resistance in peripheral tissues.

Lower circulating concentrations of NEFA and a lower rate of fat oxidation perioperatively in the carbohydrate group compared with the placebo group (Tables 1 and 2) may have contributed to an attenuation of insulin resistance, because intravenous infusion of lipids has been shown to inhibit subsequent insulin-induced glucose oxidation and nonoxidative glucose disposal in healthy subjects (4).

In routine practice, surgery thus causes a state not unlike non-insulin-dependent diabetes mellitus (NIDDM). A consistent finding in the present and previous data (22) is a blunted stimulation of nonoxidative glucose disposal by insulin as the main defect in glucose handling in postoperative insulin resistance. This defect, associated with an impaired glycogen synthase activity and GLUT-4-mediated glucose transport in skeletal muscle (31), is very similar to the pathophysiology in NIDDM (27) as well as other insulin-resistant states such as obesity (26). This diabetic state induced by surgery is rarely treated in routine practice, even when patients resume an oral diet. Postoperative hyperglycemia and defective handling of substrates may thus complicate nutrition in the insulin-resistant state after surgery. Preoperative carbohydrate treatment largely attenuates the postoperative diabetic state. Postoperative nutrition in this less affected metabolic state might be better tolerated and better utilized than when given to routinely treated postoperative patients. This may be a contributing factor to quicker recovery, as demonstrated in larger pooled data (19), and to less discomfort after elective surgery (13).

To conclude, preoperative oral carbohydrate treatment attenuated the development of immediate postoperative insulin resistance, in accord with previous studies that used preoperative carbohydrate administration (19, 22). In these studies, as in the present data, the differences in relative insulin resistance between treatment and control groups have been very similar (23, 20, and 25%, respectively). We observed a less reduced glucose uptake in peripheral tissues and maintained GOX in the treatment group, whereas no effect was seen on the reduction of nonoxidative glucose disposal. Further studies are needed to investigate the potential benefits of a combination of this treatment with immediate isocaloric postoperative nutrition.

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