Perioperative insulin and glucose infusion maintains normal insulin sensitivity after surgery

JONAS O. NYGREN,1 ANDERS THORELL,1 MATTIAS SOOP,1 SUAD EFENDIC,2 KERSTIN BRISMAR,2 FREDRIK KARPE,3 K. S. NAIR,4 AND OLLE LJUNGVIST1

Departments of 1Surgery and 2Endocrinology and Diabetes and 3Gustaf V Research Institute, Karolinska Hospital, S-171 76 Stockholm, Sweden; and 4Endocrine Research Unit, Mayo Clinic, Rochester, Minnesota 55905

Nygren, Jonas O., Anders Thorell, Mattias Soop, Suad Efendic, Kerstin Brismar, Fredrik Karpe, K. S. Nair, and Olle Ljungqvist. Perioperative insulin and glucose infusion maintains normal insulin sensitivity after surgery. Am. J. Physiol. 275 (Endocrinol. Metab. 38): E140–E148, 1998.—Elective surgery was performed after overnight fasting, a routine that may affect the metabolic response to surgery. We investigated the effects of insulin and glucose infusions before and during surgery on postoperative substrate utilization and insulin sensitivity. Seven patients were given insulin and glucose infusions 3 h before and during surgery (insulin group), and a control group of six patients underwent surgery after fasting overnight. Insulin sensitivity and glucose kinetics (0·[6,6-D2]glucose) were measured before and immediately after surgery using a hyperinsulinemic, normoglycemic clamp. Glucose infusion rates and whole body glucose disposal decreased after surgery in the control group. After surgery (insulin group), and a control group of six patients underwent surgery after fasting overnight. Insulin sensitivity and glucose kinetics (0·[6,6-D2]glucose) were measured before and immediately after surgery using a hyperinsulinemic, normoglycemic clamp. Glucose infusion rates and whole body glucose disposal decreased after surgery in the control group. After surgery, on body metabolism, insulin sensitivity, and endocrine responses immediately after a medium-sized elective operation. The insulin infusion was gauged to achieve a physiological elevation of insulin, whereas glucose was given to maintain normoglycemia.

METHODS

Subjects. Thirteen patients scheduled for total hip replacement were studied. We excluded patients >65 yr of age, with a personal or family history of diabetes mellitus or other metabolic diseases and on regular treatment with drugs known to affect glucose metabolism. The patients were randomized to either undergo surgery with (n = 7, insulin group, 2 males) or without (n = 6, control group, 5 males) hyperinsulinemic, normoglycemic clamp (see below). The age of the patients was 56 ± 5 and 59 ± 3 yr (means ± SE), and the body mass index (BMI) was 25.0 ± 1.0 and 26.5 ± 1.0 kg/m2 in the insulin and control groups, respectively. All subjects were informed orally and in writing about the purpose and nature of the study, and their informed consent was obtained before their participation. The protocol was approved by the institutional Ethics Committee.

The fact that the groups were not matched for gender differences is likely to have little influence on the postoperative (postop) change in insulin sensitivity found here (55). To assess the influence of this factor on the present measurements, 16 additional patients undergoing elective hip replacement were studied [age 62 ± 2 yr, BMI 25 ± 1 kg/m2, preoperative (preop) insulin sensitivity 3.65 ± 0.3 mg·kg−1·min−1, 5 males, 11 females] with the same protocol as for the control group in the present study. Insulin sensitivity was

given the widespread use of surgical treatment, it is important to minimize the negative side effects of the surgery, such as the catabolic response (22, 57). For about 150 years, elective surgery has been routinely performed after overnight fasting to ensure a healthy state. Recently, several countries have changed their recommendations for preoperative fasting to allow intake of clear fluids up to 2-3 h before surgery (51). Importantly, the fasting period before surgery is often long enough (10–16 h) to substantially deplete carbohydrate reserves and change the metabolic situation of the patient (48), and clear fluids have minimal effects on metabolism. The rationale for operating on patients in a fasted state instead of a fed state, normally occurring during the day, has not really been questioned.

The effect of changing the metabolic setting from an overnight fasted to a "fed state" before the trauma (i.e., surgery) on the subsequent development of the catabolic response has only recently been tested (38). Thus an overnight treatment with glucose infusions (5 mg·kg−1·min−1) before surgery substantially reduced the decrease in insulin sensitivity 24 h after uncomplicated abdominal surgery, compared with the levels in patients undergoing the same operation after overnight fasting. These findings suggest that fasting before surgery may contribute to the decline in insulin sensitivity that occurs with surgery. However, from that previous study (38), it was difficult to determine whether the large dose of carbohydrates (~300 g) given overnight or the accompanying elevation of insulin (~4 times above normal fasting levels, 45 µU/ml) was the key factor in the reported effects. In addition, a recent study shows that the common perioperative fluid regimen [2,000–3,000 ml of balanced electrolyte solutions containing a small amount of glucose (2.5%), accompanied by immobilization] has an impact on insulin sensitivity as early as after 24 h (42). To distinguish these influences from the outcome parameters, the effect of the treatments were studied immediately after the completion of surgery.

The aims of the present study were to investigate the effects of exogenous insulin and glucose infusion, begun shortly before surgery and continued throughout the surgery, on body metabolism, insulin sensitivity, and endocrine responses immediately after a medium-sized elective operation. The insulin infusion was gauged to achieve a physiological elevation of insulin, whereas glucose was given to maintain normoglycemia.
measured using a hyperinsulinemic (60 µU/ml), normoglycemic (4.5 mM) clamp 1 wk before surgery as well as immediately after the completion of surgery. These 16 patients were analyzed together with the 13 patients in the present study in a sequential multiple regression analysis model in which the effects of nutritional treatment, duration of surgery, and perioperative blood loss were accounted for. In this model, age, BMI, preop insulin sensitivity, and gender had no significant predictability regarding postop insulin resistance (n = 29). In addition, analysis of the data from 14 control patients (9 females) treated under the same protocol as the control group showed that gender had no effect on postop insulin resistance (P = 0.81). Furthermore, we have studied insulin sensitivity in >70 patients before and after elective orthopedic or abdominal surgery (Nygren, Thorrel, and Ljungqvist, unpublished data). Again, in this group of patients, no relationships were found among the relative change in insulin sensitivity after surgery and age, BMI, gender, or preop insulin sensitivity. These findings thus indicate that postop insulin resistance develops to a similar degree regardless of gender.

Anesthetics and perioperative and postop care. In all patients, surgery was commenced between 10:40 AM and 1:40 PM (no difference between groups). The same anesthetic procedures were employed in all patients. Premedication was provided by injection of morphine (Morfin Pharmacia, Pharmacía, Sweden; 5–15 mg im), according to body weight. Spinal anesthesia was induced with bupivacaine (Marcain Spinal, Astra, Södertälje, Sweden; 15–18 mg) immediately before surgery. All patients were fully anesthetized by the spinal anesthesia during the whole study (sensitivity to temperature and pain tested intermittently) (59), and no other anesthetics were used. Sedation was provided on demand with no difference between the groups, by the occasional use of midazolam (Dormicum, Roche, Basel, Switzerland; 1.25–2.5 mg) and/or piperazinylphenetazine (Esucos, UCB, Brussels, Belgium; 5 mg iv). Phylactic treatment to avoid postop thrombosis was given to all patients using a subcutaneous injection of 5,000 U of anti-Xa (Fragmin, Pharmacia-Upjohn, Stockholm, Sweden) the night before surgery. Total hip replacement was performed by use of the posterior approach with the patients lying on their side. The duration of surgery and perioperative blood loss was similar in both groups [124 ± 4 vs. 110 ± 6 min and 1,319 ± 165 vs. 1,316 ± 177 ml, P = not significant (NS), insulin and control groups, respectively]. The postop course was uneventful in all patients. The hospital stay was 4.4 ± 0.3 vs. 5.7 ± 0.6 days in insulin and control groups, respectively (P = 0.067).

Study design. The study was designed to investigate the effects of exogenous insulin and glucose infusions, given to achieve a physiological elevation of insulin (27) while maintaining normoglycemia before and during surgery, on postop insulin sensitivity, substrate oxidation, and endocrine responses.

On the morning of the surgery, patients in the insulin group were studied after fasting overnight. Insulin infusions were started at 8:00 AM after a basal study period of 30 min (Fig. 1). Insulin (Actrapid, Novo, Copenhagen, Denmark) was infused at a constant rate (0.8 mU·kg⁻¹·min⁻¹ iv), and a variable infusion of glucose (200 mg/ml iv) was given to maintain blood glucose at a constant level (4.5 mM). After steady-state conditions were maintained for 60 min, all patients underwent standardized anesthesia and surgical treatment (see above). The surgery began 290 ± 23 min after the start of the insulin infusion. At that time, the patients had received 1.1 ± 0.2 g glucose/kg. The hyperinsulinemic, normoglycemic clamp was then maintained during surgery and was continued for a further 3–4 h after surgery. The period of time from the initiation of insulin infusion to the end of the postop clamp was 488 ± 40 min.

The controls were studied 7 ± 1 days before surgery with the use of the same protocol as for the preop situation (basally and during preop clamp; Fig. 1). The preop clamp measurement was performed at a similar point in time as in the insulin group. At 8:00 AM on the morning before surgery, after overnight fasting, the patients were studied in the basal condition and before and during surgery (Fig. 1). Saline was given during surgery. Immediately after surgery, an infusion of insulin was initiated (0.8 mU·kg⁻¹·min⁻¹), and a postop hyperinsulinemic, normoglycemic (4.5 mM) clamp (postop) was performed.

Fig. 1. Insulin sensitivity, glucose turnover ([6,6-2H2]glucose), and substrate oxidation [indirect calorimetry (ind cal)] were measured in patients undergoing total hip replacement. Insulin sensitivity was measured by using a hyperinsulinemic, normoglycemic clamp. Measurements were done before, during, and immediately after surgery. Insulin group received infusions of insulin (0.8 mU·kg⁻¹·min⁻¹) and glucose (to maintain normoglycemia, 4.5 mM = clamp) before and during surgery, whereas control group underwent surgery after fasting overnight. In these patients, preoperative clamp was performed 1 wk before surgery, and postoperative clamp was performed immediately after surgery. Basal, measurements before insulin and glucose infusions; preop, preoperative clamp measurement; early/late, measurements during early and late part of operation; postop, postoperative clamp measurement. Arrows, commencement of a 30-min period of ind cal. For further details, see text.
The data will be presented according to the following nomenclature (Fig. 1): basal (last 30 min before start of surgery), preop clamp (steady-state hyperinsulinemic, normoglycemic clamp for 60 min performed before surgery), early op (from 10 to 40 min after initiation of surgery), late op (last 30 min of surgery), and postop clamp (steady-state hyperinsulinemic, normoglycemic clamp for 60 min performed as soon as possible after the surgery was completed, starting 67 ± 17 min after completion, no difference between groups) in all but three patients in the insulin group, who were studied for 30 min.

Glucose turnover measurements and indirect calorimetry. Primed (3 mg/kg), continuous (1.8 mg·kg⁻¹·h⁻¹) infusions of [6,6-²H₂]glucose (Isotec, Miamisburg, OH) were given for 120 min before the basal period as well as throughout the hyperinsulinemic, normoglycemic clamp studies. The d-[6,6-²H₂]glucose was sterile and nonpyrogenic and proved to be >96% pure by HPLC. The infusions were performed with a syringe pump (Perfusor-Secura, Braun, Melsungen, Germany). To minimize changes in plasma d-[6,6-²H₂]glucose enrichment during the clamp, d-[6,6-²H₂]glucose was added to the glucose infusate (19, 20). Glucose disappearance was calculated using a modified Steele equation, taking into account the varying tracer infusion rates (13, 19, 20). The glucose volume of distribution was estimated to be 250 ml/kg and the pool correction factor 0.65. Endogenous glucose production (EGP) was calculated by subtracting the glucose infusion rate from the tracer-determined rate of appearance (19, 20).

In all patients, indirect calorimetry (Deltatrac, Dansjöö, Sweden) (21, 52) was performed during 30-min periods at basal, twice during surgery (early op and late op), and during the last 30 min of the preop and postop clamps. Timed sampling of urine for analysis of urinary urea excretion was performed after correction for changes in the urea pool size (53), energy expenditure (EE) and substrate oxidation rates were calculated.

Sampling and analysis. All blood was sampled in a standardized way in conformity with the study protocol. Arterialized blood samples were collected from a heated hand vein (10). Blood glucose was sampled at least every 10 min during the study and was analyzed immediately after collection by use of the glucose oxidase method (Yellow Springs Instruments, Yellow Springs, OH) (31). Plasma samples for the determination of isotope enrichment levels were collected before the infusion and every 10 min during the study periods. The glucose infusion rate (GIR) during each 10-min interval was recorded repeatedly, and the calculations were performed during each study period as indicated in the study design (see above). EGP and whole body glucose disposal (WGD) were calculated from the GIR and enrichment levels. Trimethylsilyl-O-methyloxime derivative of plasma glucose was analyzed in a gas chromatography-mass spectrometer to measure d-[6,6-²H₂]glucose isotopic enrichment in the tracer, glucoses, and plasma samples (34). Serum insulin was sampled every 30 min during the study and analyzed by RIA using an antibody developed in our laboratory (26). The following substrates and hormones were measured once at the end of four of the study periods (basal, preop, late op, and postop) as well as 10 min after the initiation of surgery (early op). Plasma lactate was measured by use of the lactate oxidase method. Serum C-peptide (Novo Research, Bagsvaerd, Denmark), serum cortisol (60), serum insulin-like growth factor I (IGF-I) (2), serum IGF-binding protein-1 (IGFBP-1) (43), and plasma glucose (Euro-Diagnostica, Malmö, Sweden) (17) were analyzed by using RIA methods. Free fatty acids (FFA) were determined after lipid extraction of plasma (15) according to Ho (30). Serum samples were permitted to clot, whereas plasma samples were immediately centrifuged at 4 and 3,000 rpm for 10 min and stored at −20°C for later batch analyses. Urinary urea was analyzed by an AutoAnalyzer (Ektachem 700 XR, Eastman Kodak, Rochester, NY).

Control study in healthy subjects not undergoing surgery. To evaluate the effect of the prolonged hyperinsulinemic, normoglycemic clamp in the insulin group, a separate group of healthy subjects (n = 5, 4 males, age 38 ± 7 yr, BMI 24 ± 1 kg/m²) was studied after overnight fasting, during an 8-h hyperinsulinemic (0.8 mU·kg⁻¹·min⁻¹), normoglycemic (4.5 mM) clamp. Substrate oxidation was measured by indirect calorimetry (see above), and levels of glucose, FFA, insulin, glucagon, cortisol, IGF-I, and IGFBP-1 were analyzed. The relative change in these parameters during the 8th h of clamp (corresponding to postop clamp in insulin group) was compared with levels found during the 2nd h of clamp (corresponding to preop clamp in insulin group).

Statistics. All values are given as individual values or means ± SE. Samples taken repeatedly during the five study periods (i.e., glucose, insulin, GIR, EGP, and WGD) are given as mean values during each study period (see above). Statistical significance was accepted at P < 0.05 by Wilcoxon’s signed-rank test and the Mann-Whitney U-test for paired and unpaired data, respectively. A two-way ANOVA for repeated measures was used to assess changes related to the three study periods during and after surgery (early op, late op, and postop clamp). Correlations were tested by multiple or simple regression.

RESULTS

Blood glucose and plasma lactate. Fasting glucose levels were not significantly different between the insulin and control groups at any point in time during the study (Table 1). During preop and postop clamps, the mean intraindividual coefficient of variation (CV) for glucose was 4.6% in the control group and 6.2% in the insulin group. Plasma lactate (Table 1) levels were lower (P < 0.05 vs. insulin) in the control group during the preop clamp as well as during surgery. However, plasma lactate levels did not change significantly after surgery in any of the groups compared with preop levels. When the results during and after surgery were analyzed, no difference was found regarding blood glucose levels, whereas significantly lower lactate levels were found in the control group (P < 0.05 vs. insulin, ANOVA).

FFA levels. Plasma FFA levels did not differ significantly between the groups before surgery. During surgery as well as during the postop clamp, levels of FFA were higher in the control group than in the insulin group (P < 0.0001, ANOVA).

Insulin and C-peptide levels. Serum insulin (Table 1) in the control group was unchanged compared with basal levels and was lower than in the insulin group (P < 0.01) during surgery. Insulin levels during preop and postop clamps were similar in the groups (Table 1). C-peptide levels (Table 1) were similar in the groups before surgery. During surgery (i.e., early op), higher levels were found in the control group (P < 0.05). Levels of C-peptide did not change at the postop clamp compared with the preop clamp in any group.
IGF-I and IGFBP-1. Serum IGF-I (Table 1) did not differ between the groups at any time point. During the postop clamp, IGF-I decreased (P < 0.05) in both groups compared with the preop clamp. Serum IGFBP-1 did not differ between the groups before surgery. During surgery, significantly higher levels were found in the control group than in the insulin group. During the postop clamp, IGFBP-1 decreased in the insulin group (P < 0.05), whereas increased levels (P < 0.05) were found in the control group compared with the preop clamp (Fig. 2). Levels of IGFBP-1 were higher (P < 0.05) in the control group than in the insulin group at the postop clamp. An analysis of changes during and after surgery showed that levels of IGF-I fell significantly in both groups during this period (P < 0.01, ANOVA), the fall being greater in the controls than in the insulin group (P < 0.05). In addition, levels of IGFBP-1 were lower in the insulin group than in the controls during and after surgery (P < 0.05, ANOVA).

Cortisol and glucagon levels. Plasma glucagon levels were lower (P < 0.01) in the control group during the preop clamp. In both groups, glucagon levels decreased (P < 0.05) after surgery (Table 1). Serum cortisol levels did not differ significantly between the groups at any time. However, during the postop clamp, cortisol levels decreased by 65% in the insulin group (P < 0.05 vs. preop clamp), whereas no significant difference was found in the control group (P = 0.1). The relative changes in levels of cortisol and glucagon at the postop clamp (vs. preop clamp) were significantly different in the control and insulin groups (Fig. 2). During and after surgery, glucagon decreased (P < 0.01, ANOVA), whereas no difference was found between the groups. Furthermore, the change in the cortisol levels during this period of time (P < 0.01, ANOVA) was different in the two groups (P < 0.0001, ANOVA).

Glucose kinetics. Plasma isotope enrichment levels (specific activities) were stable during all measurements, with mean intrasubject CVs of 4.2 ± 0.5 and

Table 1. Levels of substrates and hormones in patients undergoing total hip replacement after fasting overnight or 4 h of physiological hyperinsulinemia

<table>
<thead>
<tr>
<th>Group</th>
<th>Basal</th>
<th>Preop</th>
<th>Early Op</th>
<th>Late Op</th>
<th>Postop</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood glucose, mM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>5.0 ± 0.2</td>
<td>4.5 ± 0.1</td>
<td>4.4 ± 0.2</td>
<td>4.9 ± 0.2</td>
<td>4.5 ± 0.1</td>
</tr>
<tr>
<td>Control</td>
<td>5.0 ± 0.2</td>
<td>4.4 ± 0.1</td>
<td>5.0 ± 0.3</td>
<td>5.0 ± 0.3</td>
<td>4.4 ± 0.0</td>
</tr>
<tr>
<td>Plasma lactate, mM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>1.31 ± 0.21</td>
<td>1.83 ± 0.25</td>
<td>1.69 ± 0.09</td>
<td>2.02 ± 0.21</td>
<td>1.91 ± 0.20</td>
</tr>
<tr>
<td>Control</td>
<td>1.09 ± 0.08</td>
<td>1.27 ± 0.12*</td>
<td>1.12 ± 0.12*</td>
<td>1.20 ± 0.19*</td>
<td>1.42 ± 0.22</td>
</tr>
<tr>
<td>Plasma FFA, µM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>799 ± 170</td>
<td>227 ± 39</td>
<td>141 ± 23</td>
<td>154 ± 52</td>
<td>147 ± 28</td>
</tr>
<tr>
<td>Control</td>
<td>886 ± 112</td>
<td>251 ± 72</td>
<td>596 ± 48†</td>
<td>658 ± 97†</td>
<td>253 ± 36*</td>
</tr>
<tr>
<td>Serum insulin, µM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>17 ± 5</td>
<td>64 ± 4</td>
<td>50 ± 3</td>
<td>69 ± 5</td>
<td>65 ± 3</td>
</tr>
<tr>
<td>Control</td>
<td>16 ± 2</td>
<td>62 ± 7</td>
<td>16 ± 2†</td>
<td>14 ± 2†</td>
<td>55 ± 4</td>
</tr>
<tr>
<td>Serum C-peptide, nM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>0.68 ± 0.09</td>
<td>0.45 ± 0.05</td>
<td>0.42 ± 0.06</td>
<td>0.55 ± 0.12</td>
<td>0.55 ± 0.14</td>
</tr>
<tr>
<td>Control</td>
<td>0.68 ± 0.08</td>
<td>0.41 ± 0.09</td>
<td>0.70 ± 0.11*</td>
<td>0.70 ± 0.12</td>
<td>0.32 ± 0.08</td>
</tr>
<tr>
<td>Serum IGF-I, µg/l</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>149 ± 19</td>
<td>143 ± 17</td>
<td>116 ± 15</td>
<td>106 ± 15</td>
<td>111 ± 16†</td>
</tr>
<tr>
<td>Control</td>
<td>140 ± 8</td>
<td>144 ± 8</td>
<td>126 ± 10</td>
<td>113 ± 5</td>
<td>101 ± 8†</td>
</tr>
<tr>
<td>Serum IGFBP-1, µg/l</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>55 ± 10</td>
<td>35 ± 5</td>
<td>25 ± 3</td>
<td>28 ± 4</td>
<td>25 ± 2†</td>
</tr>
<tr>
<td>Control</td>
<td>33 ± 4</td>
<td>30 ± 3</td>
<td>45 ± 4†</td>
<td>55 ± 7*</td>
<td>83 ± 31†</td>
</tr>
<tr>
<td>Plasma glucagon, pM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>58 ± 7</td>
<td>52 ± 3</td>
<td>40 ± 3</td>
<td>35 ± 4</td>
<td>33 ± 4‡</td>
</tr>
<tr>
<td>Control</td>
<td>48 ± 2</td>
<td>42 ± 1†</td>
<td>43 ± 3</td>
<td>41 ± 3</td>
<td>37 ± 2‡</td>
</tr>
<tr>
<td>Serum cortisol, nM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>171 ± 41</td>
<td>266 ± 35</td>
<td>234 ± 46</td>
<td>212 ± 44</td>
<td>180 ± 41‡</td>
</tr>
<tr>
<td>Control</td>
<td>229 ± 39</td>
<td>238 ± 21</td>
<td>154 ± 63</td>
<td>116 ± 43</td>
<td>366 ± 83</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 6 (control) and 7 (insulin). FFA, free fatty acids; IGF-I, insulin-like growth factor I; IGFBP-1, IGF-binding protein-1; preop, before surgery; early and late op, early and late part of operation, respectively; postop, after surgery. *P < 0.05 vs. insulin, Mann-Whitney U-test. †P < 0.01 vs. insulin, Mann-Whitney U-test. ‡P < 0.05 vs. preop, Wilcoxon's signed-rank test.
5.2 ± 0.4% in the control and insulin groups, respectively. Mean levels of plasma enrichments were 1.8 ± 0.0% molar excess. Basal levels of EGP and WGD were higher (P < 0.05) in the control group than in the insulin group. During preop clamps, GIRs required to maintain normoglycemia and WGD (Table 2) did not differ significantly between the two groups. GIRs were lower in the control group during the postop clamp than during the preop clamp (−40 ± 5%, P < 0.05), whereas no significant change was found in the insulin group (+16 ± 20%, P = NS). In addition, WGD was lower in the control group during the postop clamp than during the preop clamp (−29 ± 6%, P < 0.05), whereas no significant change was found in the insulin group (+25 ± 11%, P = NS). During the postop clamp, levels of GIR (P = 0.01) and WGD (P < 0.05) were lower in the control group than in the insulin group. Furthermore, the relative change in GIR (P = 0.01, Fig. 3) and WGD (P < 0.005) during the postop clamp, compared with the preop clamp, differed between the insulin and control groups. EGP (Table 2) was almost totally suppressed during both preop and postop clamps in both groups, although a small but significant increase in EGP was noted during the postop clamp compared with the preop clamp (P < 0.05) in the insulin group. During and after surgery, levels of EGP were higher (P < 0.0001, ANOVA) but WGD was lower (P < 0.05, ANOVA) in the controls than in the insulin-treated patients.

Indirect calorimetry. Substrate oxidation rates (Table 2) did not differ between the groups in the preop situation. During surgery, fat oxidation was higher (P < 0.05) and glucose oxidation rates were lower (P < 0.05) in the control group than in the insulin group. No significant differences in substrate oxidation rates were found during the postop clamp compared with the preop clamp in any group. However, higher fat oxidation rates (P < 0.05) were found in the control group compared with the insulin group during the postop clamp.

![Fig. 3. Relative change (postop vs. preop clamp) in glucose infusion rate (GIR) and glucose (gox) and fat oxidation (fox) rates during hyperinsulinemic, normoglycemic clamps in 7 patients treated with insulin and glucose infusions before and during surgery (insulin group) and patients undergoing surgery after an overnight fast (control group). Relative change in GIR between 2nd and 8th hours of a similar glucose clamp in 5 healthy subjects not undergoing surgery is also shown. *P < 0.05 vs. preop clamp; †P < 0.05 vs. change (%) in insulin group.](http://ajpendo.physiology.org/)

Values are means ± SE; n = 6 (control) and 7 (insulin). GIR, glucose infusion rate; EGP, endogenous glucose production; WGD, whole body glucose disposal; EE, energy expenditure. *P < 0.05 vs. insulin, Mann-Whitney U-test. †P < 0.01 vs. insulin, Mann-Whitney U-test. ‡P < 0.05 vs. preop, Wilcoxon's signed-rank test.
Glucose utilization (percent oxidized of WGD) did not differ between the groups at any time. No significant change was found in glucose utilization after surgery in any group.

Resting EE in the basal state was higher in the control group than in the insulin group before surgery. EE did not change significantly in the insulin group after surgery, whereas a significant decrease (P < 0.05) was found in the control group.

During and after surgery, levels of glucose oxidation were lower (P < 0.01, ANOVA) and fat oxidation was higher (P < 0.001, ANOVA) in the controls than in the insulin-treated patients. Furthermore, glucose utilization increased similarly in the two groups (P < 0.05, ANOVA) but remained higher in the control group (P < 0.01, ANOVA) than in the insulin group during and after surgery. EE increased (P < 0.01, ANOVA) during this period of time but did not differ between the groups.

Healthy subjects not undergoing surgery. The mean blood glucose levels during clampings were 4.5 ± 0.0 mM with a mean intraindividual CV of glucose of 7.2 ± 1.0%. Mean serum levels of insulin during the two clamp periods (59 ± 2 and 57 ± 2 µU/ml) did not differ from those found in the insulin group. The relative change in the GIR during the 8th h of clamp (corresponding to postop clamp in insulin group) compared with the 2nd h of clamp (corresponding to preop clamp in insulin group) was similar to what was found in the insulin group (+16 ± 10%, P > 0.05, Fig. 3). The same trends were found regarding the change in fat (4 ± 12%, Fig. 3) and glucose (0 ± 4%, Fig. 3) oxidation rates, levels of FFA (−29 ± 13%), cortisol (−16 ± 37%, Fig. 2), and IGF-I, have been in the spotlight during the last few years (64), less attention has been paid to insulin. However, some early studies have shown reduced nitrogen losses after treatment with insulin in catabolic traumatized patients (9, 29, 63). A recent study demonstrates a significant anabolic effect on protein metabolism in catabolic burned patients by use of pharmacological infusions of insulin and glucose over several days (50). Yet another study shows that the decreased glucose uptake in the postop state can be overcome by insulin treatment (6), and this treatment also normalized substrate oxidation and improved nitrogen balance. Even though benefits of insulin administration have been demonstrated in catabolic patients, only an attenuation of the catabolic response has been reported to be achieved even when large doses of insulin were used (50, 63). Such large doses of insulin require intensive and constant attention to avoid severe hypoglycemia, which makes this approach difficult in clinical practice.

A different approach to postop catabolism was employed in the present study. The hypothesis was that the postop overnight fast represents an additional stress which augments the development of postop catabolism. Therefore, the metabolic state was reversed to a fed state by an exogenous insulin infusion before the start of surgery. Starting the treatment before the surgery was intentional, since several animal studies have shown that coping with stress is much improved if the animals enter the trauma in a fed rather than fasted state (16, 35–37).

DISCUSSION

This study demonstrates for the first time that it is possible to maintain normal insulin sensitivity and substrate oxidation after a medium-sized operation by administering insulin and glucose infusions before and during surgery. Using this method, we observed a reduction in glucagon and cortisol levels but a normalization of the bioavailability of IGF-I, as measured by levels of IGFBP-1, in the immediate postop state. These changes were similar to what was found in healthy subjects during an equivalent period of insulin and glucose administration without the corresponding surgery. In contrast, patients subjected to the same surgical procedure after fasting overnight displayed the expected decrease in insulin sensitivity (7, 56–58) and reduction in IGF-I bioavailability (47) immediately after surgery.

The patients in this study were randomly assigned to receive one of the two treatments. As the randomization came out, there was an uneven gender distribution between the two groups. This could possibly be a factor affecting the outcome. However, when the issue of the effect of patient parameters on postop insulin sensitivity in a larger group of patients studied immediately after elective hip replacement was addressed, it could be seen that gender, age, BMI, and preop insulin sensitivity are all variables that do not affect the development of postop insulin resistance (55).

Another potential factor that may influence the comparison between the two groups is that the preop determination was made on the morning of surgery in the insulin group, whereas the corresponding determination was made 1 wk before surgery in the control group. The possibility of an effect from differences in anxiety, physical activity, dietary intake, or fatigue between the two groups cannot be ruled out. However, several factors suggest that the potential effect of these differences is not likely to be of great importance. In our own experience, we have found that repeated determinations of insulin sensitivity in the same individuals are very constant (CV ~5–8%; M. Soop, J. Nygren, A. Thorell, and O. Ljungqvist, unpublished observations), despite our impression that most subjects are more anxious during their first clamp study than during any subsequent study. Also, there were no major differences in the basal measurements between the two groups to indicate marked differences at the time of the determinations. Although any potential effect of the above factors cannot be ruled out, it is reasonable to assume that they had little impact on the outcome of the present data.

Although treatments of various catabolic conditions with anabolic hormones, such as growth hormone and IGF-I, have been in the spotlight during the last few years (64), less attention has been paid to insulin. However, some early studies have shown reduced nitrogen losses after treatment with insulin in catabolic traumatized patients (9, 29, 63). A recent study demonstrates a significant anabolic effect on protein metabolism in catabolic burned patients by use of pharmacological infusions of insulin and glucose over several days (50). Yet another study shows that the decreased glucose uptake in the postop state can be overcome by insulin treatment (6), and this treatment also normalized substrate oxidation and improved nitrogen balance. Even though benefits of insulin administration have been demonstrated in catabolic patients, only an attenuation of the catabolic response has been reported to be achieved even when large doses of insulin were used (50, 63). Such large doses of insulin require intensive and constant attention to avoid severe hypoglycemia, which makes this approach difficult in clinical practice.
Postop insulin sensitivity was determined immediately after surgery to minimize the effect of hypocaloric nutrition on insulin sensitivity (42). The insulin infusion rate was chosen to obtain physiological levels of insulin in the range found after a standard meal (27). At this rate of infusion, EGP was, as expected, almost completely suppressed during both the preop and postop clamps in both groups (32, 42). The prolonged insulin infusion in only one of the two groups could possibly have influenced the comparison between the two groups in the postop situation, since prolonged insulin infusions have been suggested to increase GIR (14). In the present study, we found a trend toward an increase in GIR during the 8-h clamp in the subjects not undergoing surgery. A very similar trend was also seen in the insulin group. This shows that the change in whole body insulin sensitivity (i.e., GIR) in the insulin group is what is to be expected in healthy subjects given this insulin and glucose treatment.

From this study, although conducted with a limited number of patients, it is clear that it is possible to perform surgery without any immediate stress response provided that the patient undergoes surgery during insulinization. The clinical relevance of these findings is supported by a study by Crowe et al. (11), in which they reported decreased urinary urea and 3-methylhistidine excretion in patients given high-dose glucose infusions (5 mg·kg\(^{-1}·\text{min}^{-1}\)) after abdominal surgery. Furthermore, patients given glucose infusions before surgery displayed a decrease in urinary urea excretion during the first 24 h after surgery compared with patients in whom glucose infusions were started after surgery (11), suggesting that the preop treatment may be more effective. A study in a larger number of patients would be required to determine whether our present findings may lead to shorter hospital stays or other clinical end points. However, it is interesting to note that the hospital stay in the insulin group tended to be shorter (4 vs. 6 days, P = 0.067) than in the control group.

Several factors known to trigger the metabolic response after trauma were affected by insulin and glucose infusions. Thus the stress hormone response was attenuated, the level of IGFBP-1 was decreased, and the level of FFA was maintained. All of this could help explain why the postop insulin sensitivity and substrate handling were virtually unaffected by surgery in this group.

The cortisol reduction found after surgery in the insulin group resembles the normal diurnal pattern. This was in contrast to that found in the control group (62). The differences found in glucocorticoid responses in the present study paralleled those in earlier animal studies (35). Although rats fasted 24 h before hemorrhagic stress showed a fourfold elevation in corticosterone during hemorrhage, this response was completely abolished in rats fed until the onset of stress. High cortisol levels are known to increase protein wasting by increasing protein breakdown and amino acid oxidation (3). Although less pronounced than the cortisol response, the glucagon levels were lower in the insulin group. Glucagon is a potent stimulator of gluconeogenesis, but its role in peripheral tissues is still a matter of controversy (40). Nevertheless, elevations of both these hormones are known to cause insulin resistance (1, 25, 39, 61), and the patterns presently found may contribute to the differences in postop metabolism seen in the two treatment groups.

Although the main focus in stress was on the catabolic hormones for a long time, the role of the anabolic hormones in trauma metabolism is receiving more and more attention. IGF-I levels have been shown to be markedly reduced after burn trauma (41), in critical illness (46), and after major surgical procedures (12). In the present study, IGF-I levels decreased in the control group in response to surgery, whereas levels of IGFBP-1 increased. Levels of IGFBP-1 are important, since this binding protein must be considered when assessing the biological significance of serum levels of IGF-I (28). IGFBP-1 has been shown to decrease IGF-I activity and receptor binding in different cell lines (45, 49). In addition, IGFBP-1 has been shown to be inversely proportional to levels of free IGF-I in obese insulin-resistant patients (23) as well as to IGF-I activity, as measured by bioassays in diabetic patients (54). In contrast to the finding in the control group, levels of IGFBP-1 decreased after surgery in the insulin group. This was probably mediated by insulin, since IGFBP-1 levels are inversely regulated by insulin (8). Even though IGF-I activity was not measured directly, changes in levels of IGFBP-1 indicate that the insulin and glucose infusion resulted in maintaining or even improving the bioavailability of IGF-I. In contrast, the increased levels of IGFBP-1 found in the group undergoing surgery after the traditional fasting indicate a reduced bioavailability and action of IGF-I after surgery. Again, this difference could contribute to the overall metabolic situation after surgery.

Increased availability of lipids after trauma have been suggested to induce insulin resistance through the glucose-fatty acid cycle (44). In the present study, FFA levels and fat oxidation rates were higher after surgery in the control group than in the insulin group. Previous studies on healthy subjects, as well as on non-insulin-dependent diabetes mellitus patients, demonstrated that increased availability of lipids decreases insulin sensitivity and glucose oxidation even in the presence of simultaneous infusions of insulin (5, 18). However, if insulin was infused for 2 h before the start of the infusion of lipids, no changes in GIR or substrate oxidation rates were seen during clamps (5), suggesting that the adjustment of metabolism (i.e., with or without insulin) before the initiation of lipid infusion may be critical for FFA to exert this effect. It is possible that a parallel mechanism could contribute to the presently found differences between the groups.

Another difference between the two treatment groups was the finding of lower lactate levels in the control group during surgery. This was associated with a higher EGP in the controls. These findings may be due to a higher consumption of lactate for gluconeogenesis. Also, the higher lactate levels in the insulin group may be a result of the...
greater disposal of glucose resulting in a higher production of lactate. This, coupled with a suppressed EGP, may account for the difference between the groups. Previous studies indicate that the peripheral insulin resistance that develops after trauma may be due to a postreceptor defect (4). Thus changes in the glucose transport system have been suggested to be involved in the development of peripheral insulin resistance (24, 33). The current reduction of glucose disposal in the control group is consistent with a transport defect, since the relative part of glucose disposal being oxidized was unchanged after surgery. If anything, the trend of the data suggests that the decreased insulin sensitivity in the control group after surgery was accompanied primarily by a reduction in glucose storage while glucose oxidation was better preserved.

From the present investigation, we conclude that it is possible to keep important aspects of metabolism completely normal after surgery by changing the metabolic profile with insulin and glucose infusions started before surgery and maintained during surgery. Performing surgery with the patient in the fed state, in this case by providing insulin and glucose, instead of the traditional fasting state, makes possible a completely different starting point for postop nutrition and recovery.

We thank nurses Lotta Hylén and Caisa Alström for excellent technical assistance with the clamps, Peter Berg and Berit Rydlander for skillful assistance with the sample analyses, and the staff at the Department of Orthopedic Surgery for good cooperation.

This work was supported by grants from the Karolinska Institute, the Swedish Medical Research Council (09101, 18406, and 4224), the Swedish Diabetes Association, Fredrik and Ingrid Thüring’s Foundation, the Swedish Society of Medicine, Torsten and Ragnar Söderberg’s Foundation, National Institute of Health grants (RO1-DK-41973 and RR-00585), and Nutricia Corporate Research, Zoetermeer, The Netherlands.

Preliminary data from this study were reported at the 18th Congress of the European Society of Enteral and Parenteral Nutrition in Geneva, Sept. 8–11, 1996. Present address of O. Ljungqvist and A. Thorell: Huddinge Univ. Hospital, S-141 86 Huddinge, Sweden. Address reprint requests to O. Ljungqvist.

Received 4 June 1997; accepted in final form 10 March 1998.

REFERENCES


Ho, R. J.  


Ho, R. J.  


