Surgery-induced insulin resistance in human patients: relation to glucose transport and utilization


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Surgery-induced insulin resistance in human patients: relation to glucose transport and utilization. Am. J. Physiol. 276 (Endocrinol. Metab. 39): E754–E761, 1999.—To investigate the underlying molecular mechanisms for surgery-induced insulin resistance in skeletal muscle, six otherwise healthy patients undergoing total hip replacement were studied before, during, and after surgery. Patients were studied under basal conditions and during physiological hyperinsulinemia (60 µU/ml). Biopsies of vastus lateralis muscle were used to measure GLUT-4 translocation, glucose transport, and glycogen synthase activities. Surgery reduced insulin-stimulated glucose disposal (P < 0.05) without altering the insulin-stimulated increase in glucose oxidation or suppression of endogenous glucose production. Preoperatively, insulin infusion increased plasma membrane GLUT-4 in all six subjects (P < 0.05), whereas insulin-stimulated GLUT-4 translocation only occurred in three patients postoperatively (not significant). Moreover, nonoxidative glucose disposal rates and basal levels of glycogen synthase activities in muscle were reduced postoperatively (P < 0.05). These findings demonstrate that peripheral insulin resistance develops immediately postoperatively and that this condition might be associated with perturbations in insulin-stimulated GLUT-4 translocation as well as nonoxidative glucose disposal, presumably at the level of glycogen synthesis.

glucose transport; nonoxidative glucose disposal; glycogen synthesis

PHYSICAL TRAUMA AND STRESS typically induce a catabolic response in which the development of impaired glucose tolerance and peripheral insulin resistance constitute central features. A state of insulin resistance has been shown to be present after accidental trauma (3), burns (40), sepsis (28), and elective surgery (37). The degree of insulin resistance developing after surgical trauma is proportional to the surgical trauma (38) and persists for ~2–3 wk after uncomplicated abdominal surgery (37). Several years ago, it was suggested that stress-induced insulin resistance is associated with an increase in endogenous glucose production (32). However, recent studies using more accurate tracer technologies with labeled infusates during glucose clamp procedures suggest that the main site for postoperative insulin resistance is peripheral tissues (30), most likely skeletal muscle (8). The underlying molecular mechanisms through which surgical stress causes skeletal muscle insulin resistance are not known.

In patients who undergo surgery of moderate to severe degree, postoperative insulin resistance can be overcome if a sufficient amount of insulin is infused to maintain euglycemia (5). In fact, this study (5) demonstrated that both glucose uptake and whole body substrate utilization could be normalized in the presence of elevated insulin concentrations. These findings suggest that excessive insulin can compensate for the defects in insulin action, which is in contrast with earlier reports suggesting that stress-induced insulin resistance is due to a block in intracellular mechanisms that lead to the decrease in glucose uptake (3,12).

Recent interest in other insulin-resistant conditions, primarily diabetes, has focused on the glucose transport system as a potential site for defects in muscle glucose uptake. Under most conditions, glucose transport across the plasma membrane is the rate-limiting step for glucose utilization (23,41), and this process utilizes the GLUT-4 glucose transporter isoform (26). Studies in rat (18,27) and human (14,16) skeletal muscle have shown that the major mechanism for the increase in insulin-stimulated glucose uptake is through the translocation of GLUT-4 from an intracellular microsomal membrane location to the plasma membrane. Studies using animal models of insulin resistance have shown that the decrease in glucose uptake is associated with a defect in insulin-stimulated glucose transport (34) and GLUT-4 translocation (25). It is not known if insulin resistance due to surgery in human patients is also associated with defects in the muscle glucose transport system.

The aims of the present study were 1) to determine if postoperative insulin resistance is associated with alterations in the glucose transport system and/or intracellular metabolism of glucose and 2) to evaluate if reversal of postoperative insulin resistance by increased insulin infusion is associated with normalization of the glucose transport system and/or intracellular metabolism of glucose.

METHODS

Subjects

Six patients (5 male, 1 female) scheduled for total hip replacement were recruited for the study. Exclusion criteria were >65 yr of age, personal or family history of metabolic
insulin (Actrapid Human; Novo, Copenhagen, Denmark) was described below.

Free of connective tissue and fat, weighed, and processed as described previously (14). A small piece of muscle (0.1 g) was immediately frozen in liquid nitrogen and was used to measure glycogen synthase activity (see Glycogen Synthase Activity Measurements). The remaining muscle was rinsed in saline, dissected free of connective tissue and fat, weighed, and processed as described below.

After closure of fascia and skin, a constant infusion of insulin (Actrapid Human; Novo, Copenhagen, Denmark) started at a rate of 0.8 mU·kg⁻¹·min⁻¹, and a hyperinsulenic, normoglycemic clamp study was performed as described previously (37). After 1 h of insulin and glucose infusion, steady-state blood glucose concentration was achieved, and the clamp was continued for 1 h. Blood samples were taken at 30-min intervals during this period (0, 30, and 60 min) for determination of hormones and substrates. During the last 30 min of this period, indirect calorimetry was performed. At time 60 min, a second muscle biopsy (clamp) was taken through the previous incision. For this biopsy, the sample was taken from an area of the muscle that was adjacent but separate from fibers handled in the first biopsy.

During surgery, no glucose was infused during surgery. Blood sampling was performed after 80 min of surgery. An open muscle biopsy was taken from the lateral vastus muscle through the surgical wound immediately before closure of the muscle fascia (surgery). The biopsy was obtained after 92 ± 7 min of surgery. Indirect calorimetry was also performed during this period of surgery.

Postoperatively, insulin infusion (0.8 mU·kg⁻¹·min⁻¹) was started immediately postoperatively, and, when steady-state blood glucose concentration was achieved (74 ± 6 min postoperatively), another determination of insulin sensitivity, substrate oxidation rates, and glucose turnover was performed during the final 30 min of the 2-h clamp (postoperative clamp). At this time, a biopsy was taken through a separate incision in the healthy leg, in the same area as in the preoperative situation, following the same procedures as the basal and clamp samples. The distance between the two incisions was ~5 cm.

Feedback clamp. Glucose infusion rates during insulin infusion were expected to be lower postoperatively. To explore the possible reversal of concomitant defects postoperatively in other cellular parameters, restoration of preoperative rates of glucose disposal (Rd) by increased insulin infusion was performed using a feedback clamp. At 136 ± 12 min postoperatively, the patients were thus given a continuous glucose infusion at the same rate as during the preoperative clamp, while maintaining normoglycemia by variable infusions of insulin (feedback clamp).

Study Protocol

The study protocol is illustrated in Fig. 1.

Preoperatively. The preoperative measurements were performed 7 ± 1 days before surgery. All measurements were performed after an overnight fast. After blood sampling for basal isotopic enrichment, a primed-constant infusion of [6,6-²H₂]glucose was started (see Glucose Turnover Measurements and Indirect Calorimetry). After 2 h of infusion, indirect calorimetry (Deltatrac; Dansjöö; see Ref. 13) was performed for 30 min (see Glucose Turnover Measurements and Indirect Calorimetry) and during this period blood samples were taken every 10 min for determination of basal glucose turnover. At the end of this period (basal), blood samples were taken for the determination of basal glucose, urea, and hormone concentrations. After instillation of 5–15 ml of Citanest for local anesthesia of the skin and subcutaneous tissue, an open muscle biopsy (basal) of ~1 g was obtained from the vastus lateralis muscle through an incision of 4 cm ~12 cm above the knee joint of the healthy leg as described earlier (14). A small piece of muscle (~0.1 g) was immediately frozen in liquid nitrogen and was used to measure glycogen synthase activity (see Glycogen Synthase Activity Measurements). The remaining muscle was rinsed in saline, dissected free of connective tissue and fat, weighed, and processed as described below.

After closure of fascia and skin, a constant infusion of insulin (Actrapid Human; Novo, Copenhagen, Denmark) was provided with the occasional use of 2.5–7.5 mg morphine (Esucos; UCB, Brussels, Belgium) and/or 5 mg iv piperazinylphentiazine (Esucos; UCB, Brussels, Belgium). Postoperatively, analgesia was provided with the open muscle biopsy procedure of lateral vastus muscle during basal conditions (basal and surgery) and during hyperinsulenic (~60 µU/ml) normoglycemic (4.5 mmol/l) clamp. The postoperative clamp was immediately followed by a stable infusion of glucose given at the same rate as during the preoperative clamp, while maintaining normoglycemia by variable infusions of insulin (feedback clamp).

Anesthetic and Operative Procedures

In all patients, surgery was commenced between 1040 and 1340. The same anesthetic procedures were employed in all patients. Premedication was provided immediately before departure from the ward to the surgical department with injection of 5–15 mg im morphine (Morfin Pharmacia) according to body weight. Spinal anesthesia was provided with 15–18 mg bupivacain (Marcain Spinal; Astra, Södertälje, Sweden) immediately before the operation. No need for additional analgesia was recorded in any of the patients during surgery. Sedation was provided on demand with the occasional use of 1.25–2.5 mg midazolam (Dormicum; Roche, Basel, Switzerland) and/or 5 mg iv piperazinylphentiazine (Esucos; UCB, Brussels, Belgium). Postoperatively, analgesia was provided with the occasional use of 2.5–7.5 mg morphine, either intravenously or intramuscularly.

Total hip replacement was performed using the posterior approach with the patients in the side position. The mean ± SE duration of surgery and peroperative blood loss was 124 ± 4 min and 1,316 ± 177 ml, respectively. The postoperative course was uneventful in all patients, and no complications were noted. Postoperative X-ray examination was performed on the first or second postoperative day and found to be satisfactory in all patients. The mean ± SE hospital stay was 6 ± 1 days.

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infusion was discontinued. The glucose infusion was continued at the same rate to prevent hypoglycemia for another hour.

**Blood Sample Analyses**

Blood glucose and plasma lactate were analyzed using the glucose (22) and lactate (6) oxidase method, respectively (Yellow Springs Instruments, Yellow Springs, OH). Free fatty acids were determined after lipid extraction of plasma according to Ho (19). Serum insulin was analyzed by RIA using an antibody developed in our laboratory (15). Plasma glucagon (9) and serum cortisol (17) were analyzed using RIA methods.

**Glucose Turnover Measurements and Indirect Calorimetry**

Glucose turnover measurements were performed using a sterile, nonpyrogenic, and HPLC-purified (>96% purity) stable isotope of glucose (α-[6,6-3H]glucose; ISOTEC) as described earlier (29). To minimize changes in plasma glucose tracer enrichments during the clamp, tracer was added to the glucose infusate according to Finegood et al. (10, 11). Indirect calorimetry was performed during 30 min-periods. Timed sampling of urine for analysis of urinary urea excretion was performed. After correction for changes in urea pool size (35), energy expenditure, respiratory quotients, substrate oxidation rates, and nonoxidative Rd were calculated.

**Skeletal Muscle Plasma Membrane Fractionation and Marker Enzyme Analyses**

Muscle samples were immediately washed in saline, blotted dry, and weighed. The muscle was minced and then homogenized in a buffer containing 250 mM sucrose and 20 mM HEPES, pH 7.4, and was frozen in liquid nitrogen. Plasma membranes were isolated using our procedure that has been described for use with human skeletal muscle (14). Protein concentrations in the homogenate and plasma membrane fractions were determined by the Bradford (4) method. The plasma membrane marker enzyme, 5'-nucleotidase, was measured in the homogenate and the plasma membrane fraction to determine purity and recovery of plasma membranes (2).

**Glucose Transport Activity in Plasma Membrane Vesicles**

Glucose transport activity was assessed by D-[14C]glucose and L-[3H]glucose uptake in plasma membrane vesicles under equilibrium exchange conditions at 25°C using a rapid filtration technique as described previously (25). Briefly, membranes were preequilibrated with a HEPES-buffered Krebs-Ringer solution containing 5 mM of D- and L-glucose. Initial rates of L- and D-glucose were determined from the linear portion of a graph of influx versus time, and facilitated transport was calculated by subtracting the initial rate of L-glucose influx from that of D-glucose.

**Glycogen Synthase Activity Measurements**

Glycogen synthase activity was measured by the filter paper method of Thomas et al. (36). Total glycogen synthase activity was determined in the presence of 6.7 mM glucose 6-phosphate and 6.7 mM UDP-[14C]glucose, whereas the "independent form" (I form) of the enzyme was measured in the absence of glucose 6-phosphate. Glycogen synthase activity is expressed as nanomoles per milligram protein per minute.

**Materials**

The GLUT-4 antibody was provided by Dr. R. J. Smith (Joslin Diabetes Center). Reagents for SDS-PAGE and protein assays were from Bio-Rad Laboratories (Richmond, CA). DNase was purchased from Worthington Biochemicals (Freehold, NJ). 125I-protein A was obtained from ICN Biomedicals (Costa Mesa, CA). Other standard chemicals and reagents were from Fisher Scientific (Lexington, MA) or Sigma Chemical (St. Louis, MO).

**Statistics**

Values are given as means ± SE. Blood samples taken repeatedly during the steady-state clamp periods are given as mean values during this period. Statistical significance was accepted at P < 0.05 using Wilcoxon's signed rank test.

**RESULTS**

**Plasma Concentrations of Substrates and Hormones**

Fasting blood glucose concentrations were normal in all patients (preoperative basal; sample 1). Glucose concentrations were successfully maintained at ∼4.5 mmol/l during the preoperative, postoperative, and feedback clamps. The mean coefficient of variation during the pre- and postoperative clamps was 4.6%. Lactate concentrations remained low during the study. Insulin infusion resulted in reduced plasma free fatty acid concentrations during both the preoperative and postoperative clamps (P < 0.05).

**Circulating concentrations of hormones in the preoperative basal state were all in the normal range (Table 1). Insulin infusion increased insulin concentrations and reduced glucagon concentrations during both the pre- and postoperative clamps (P < 0.05). During surgery, plasma concentrations of glucagon and cortisol were reduced compared with basal (P < 0.05). During the feedback clamp (sample 5), insulin infusion was increased, resulting in plasma insulin concentrations increasing by 1.5-fold compared with the postoperative clamp (P < 0.05). Concomitantly, cortisol concentrations were higher compared with the preoperative clamp (P < 0.05).

**Glucose Kinetics**

During the preoperative clamp, insulin increased the Rd by 28% (Table 2). The basal Rd was lower during surgery compared with the preoperative condition. The insulin-stimulated Rd during the postoperative clamp
Table 1. Plasma levels of substrates and hormones in patients undergoing surgery for total hip replacement

<table>
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<tr>
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<th>Preoperatively</th>
<th>Postoperatively</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Basal</td>
<td>Preoperative clamp</td>
</tr>
<tr>
<td>Blood glucose, mmol/l</td>
<td>5.0 ± 0.1</td>
<td>4.5 ± 0.1*</td>
</tr>
<tr>
<td>Blood lactate, mmol/l</td>
<td>0.7 ± 0.1</td>
<td>0.8 ± 0.1</td>
</tr>
<tr>
<td>FFA, µmol/l</td>
<td>886 ± 112</td>
<td>251 ± 72*</td>
</tr>
<tr>
<td>Insulin, µU/ml</td>
<td>16 ± 2</td>
<td>62 ± 6*</td>
</tr>
<tr>
<td>Glucagon, pg/ml</td>
<td>48 ± 2</td>
<td>42 ± 1*</td>
</tr>
<tr>
<td>Cortisol, nmol/l</td>
<td>229 ± 38</td>
<td>238 ± 21</td>
</tr>
</tbody>
</table>

All values are given as means ± SE; n = 6 patients. Plasma levels of substrates and hormones in patients during steady-state basal conditions and hyperinsulinemic clamp (plasma insulin = 65 µU/ml) 1 wk before surgery for hip replacement (basal and preoperative clamp) and during the day of surgery, during the last 30 min of surgery (surgery), during hyperinsulinemic clamp begun immediately after completion of surgery (postoperative clamp), and during glucose infusion matching the infusion recorded during the preoperative clamp, maintaining normoglycemia with the use of additional and variable insulin infusions as necessary (feedback clamp). Differences assessed using nonparametric statistical evaluations. FFA, free fatty acids. *P < 0.05 vs. basal; †P < 0.05 vs. preoperative clamp; ‡P < 0.05 vs. postoperative clamp.

was 30% lower than during the preoperative clamp. During the feedback clamp, the R_{ox} increased to levels seen during the preoperative clamp. In the preoperative situation, insulin infusion resulted in a 79% reduction in endogenous glucose production (Table 2). Postoperatively, insulin was as effective (−85%), and the further increment in insulin concentrations during the feedback clamp resulted in an almost complete suppression of endogenous glucose production.

Energy Expenditure and Substrate Utilization

Insulin infusion during both the preoperative and postoperative clamp increased the rate of glucose oxidation by twofold (Fig. 2). The increase in R_{ox} during the feedback clamp was not associated with a further increase in glucose oxidation. Surgery had no effect on the basal rate of glucose oxidation. The rates of fat oxidation were reduced by insulin stimulation pre- as well as postoperatively and were not affected by surgery (Table 2). During the feedback clamp, there was no further reduction in the rate of fat oxidation. Basal rates of nonoxidative R_{n} during surgery were significantly lower than basal rates measured preoperatively (Fig. 2). Insulin stimulation did not significantly alter nonoxidative R_{n} preoperatively, and postoperative rates were not different compared with the preoperative clamp. However, the rates of nonoxidative R_{n} were still significantly lower than basal. When glucose uptake was restored to preoperative rates by increased insulin infusion during the feedback clamp, a significant increase in nonoxidative R_{n} was observed.

Glycogen Synthase Activity

Basal rates of skeletal muscle glycogen synthase activity (I form) were significantly lower after surgery compared with the preoperative period (Fig. 3). In both the pre- and postoperative clamps, insulin infusion raised plasma insulin concentrations to ~60 µU/mL, which did not result in an increase in the I form of glycogen synthase activity. However, when the insulin infusion was increased during the feedback clamp, resulting in a mean plasma insulin concentration of 92 µU/mL, there was a significant increase in the I form of glycogen synthase activity. Total glycogen synthase activity was not statistically different among the various sampling periods (Table 2); however, there was a tendency for total glycogen synthase activity to parallel the I form of glycogen synthase. When expressed as percent I form, these same trends were also observed but did not reach statistical significance (data not shown).

Skeletal Muscle GLUT-4

Plasma membrane recovery and enrichment. Total protein in the starting homogenate was not signifi-

Table 2. Endogenous glucose production, energy expenditure, substrate oxidation, homogenate GLUT-4, and total glycogen synthase activity in patients undergoing surgery for total hip replacement

<table>
<thead>
<tr>
<th></th>
<th>Preoperatively</th>
<th>Postoperatively</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Basal</td>
<td>Preoperative clamp</td>
</tr>
<tr>
<td>Glucose disposal, mg·kg(^{-1})·min(^{-1})</td>
<td>2.30 ± 0.10</td>
<td>2.95 ± 0.31*</td>
</tr>
<tr>
<td>Endogenous glucose production, mg·kg(^{-1})·min(^{-1})</td>
<td>2.29 ± 0.12</td>
<td>0.49 ± 0.13*</td>
</tr>
<tr>
<td>Nonprotein energy expenditure, kcal·kg(^{-1})·day(^{-1})</td>
<td>21.8 ± 0.6</td>
<td>20.7 ± 0.8*</td>
</tr>
<tr>
<td>Fat oxidation, mg·kg(^{-1})·min(^{-1})</td>
<td>1.00 ± 0.08</td>
<td>0.51 ± 0.13*</td>
</tr>
<tr>
<td>Homogenate GLUT-4, arbitrary units</td>
<td>12.3 ± 0.4</td>
<td>7.6 ± 0.3*</td>
</tr>
<tr>
<td>Total glycogen synthase activity, nmol·mg(^{-1})·min(^{-1})</td>
<td>307 ± 67</td>
<td>248 ± 36</td>
</tr>
</tbody>
</table>

For details, see Table 1. All values are given as means ± SE; n = 6 patients. Differences assessed using nonparametric statistical evaluations. *P < 0.05 vs. basal; †P < 0.05 vs. preoperative clamp; ‡P < 0.05 vs. postoperative clamp.
Significantly different among the conditions studied (124 ± 5 mg; mean ± SE of all samples) and represents 10.3 ± 0.3% of the total muscle weight. The total protein recovered in the plasma membrane fraction (0.61 ± 0.5 mg) was also not different among the conditions. There were no differences in homogenate 5'-nucleotidase activities (97 ± 14 nmol·mg⁻¹·h⁻¹) in any of the conditions studied. Plasma membrane 5'-nucleotidase activity was not significantly different in the preoperative conditions compared with the surgery and postoperative conditions (2,123 ± 132 nmol·mg⁻¹·h⁻¹). The enrichment of this plasma membrane marker enzyme was 26.1 ± 1.7-fold over the starting homogenate. The recovery of 5'-nucleotidase activity was 12.0 ± 0.7% for all of the conditions studied.

Muscle homogenate GLUT-4 protein. There was no difference in total muscle GLUT-4 content between the preoperative basal condition (sample 1) and surgery (sample 3), indicating that 80 min of surgery did not affect the total amount of GLUT-4 in the muscle (Table 2). As has previously been observed (1), 2 h of insulin infusion decreased total muscle GLUT-4 concentrations in the muscle homogenate by 37% during the preoperative clamp. In contrast, muscle homogenate GLUT-4 protein was not decreased in response to insulin infusion during the postoperative clamp.

Plasma membrane GLUT-4 protein. In the preoperative situation, insulin infusion resulted in a 1.8 ± 0.3-fold increase in plasma membrane GLUT-4 protein content (P < 0.05, Fig. 4), with each individual subject showing an increase. There was no effect of spinal anesthesia and surgery on the abundance of GLUT-4 in the plasma membranes. During the postoperative insulin infusion, the mean plasma membrane GLUT-4 protein content was not statistically increased from the basal or the surgery biopsies. Interestingly, the individual response to insulin infusion postoperatively was highly variable. In three patients, plasma membrane GLUT-4 increased by approximately twofold, in one patient there was no change, and in two patients plasma membrane GLUT-4 was lower than basal after insulin infusion. Thus, although the effect of insulin on plasma membrane GLUT-4 in the preoperative situation was consistent and significantly increased, this did not occur in the postoperative situation. Although glucose uptake was increased during the feedback clamp, the plasma membrane GLUT-4 content did not change (Fig. 4).

Glucose transport in plasma membrane vesicles. Preoperatively, insulin infusion increased vesicular glucose transport by 2.6-fold above basal (Fig. 5). After surgery, there was a 2.1-fold increase in glucose trans-
port in response to insulin infusion compared with basal. The postoperative increase in vesicular transport in response to insulin infusion was not different compared with the preoperative condition.

**DISCUSSION**

This study demonstrates that a state of insulin resistance develops in extrahepatic tissues immediately after elective surgery for total hip replacement. This insulin resistance is associated with altered insulin-stimulated GLUT-4 translocation and perturbations in insulin action. The possible effect of the anesthesia on insulin action is not possible to single out with the present protocol. However, in another study in patients undergoing total hip replacement using the same type of anesthesia as in the present study (30), the patients were infused with insulin during surgery. In that study, sampling occurred during "early" surgery (i.e., immediately after opening of the muscle fascia). During this period (after ~1 h of anesthesia), there were no alterations in insulin-stimulated R_d, endogenous glucose production, or glucose oxidation compared with basal values, suggesting that this type of anesthesia is of minor importance per se for insulin action on glucose metabolism. In the current study, the reduction in basal R_d, energy expenditure, and endogenous glucose production during surgery, however, is most likely an effect of the neural block induced by the spinal anesthesia and is similar to previous reports (24). There was no difference in insulin-induced suppression of endogenous glucose production between the preoperative and postoperative clamps (85 ± 7 vs. 83 ± 4%), consistent with our earlier study showing no effect of surgery on endogenous glucose production when the postoperative clamp was performed 24 h after surgery (29). These data provide additional evidence in support of the hypothesis that the surgery-induced disturbance in glucose metabolism is located mainly in skeletal muscle, at least after surgery of moderate to severe degree.

The preoperative R_d for our patients was <3 mg·kg⁻¹·min⁻¹, which is in the lower range of insulin sensitivity for nondiabetic surgical patients (37, 38). This, however, is in agreement with our previous experiences with healthy subjects in the same age range as those included in the present study (59 ± 3 y; see Ref. 30). During the preoperative clamp, the insulin-stimulated increase in whole body R_d was not accompanied by an increase in nonoxidative R_g or glycogen synthase activity. This is consistent with our recent work showing that the increase in R_d with 2 h of low-dose insulin infusion (0.8 mU·kg⁻¹·min⁻¹) in healthy subjects with low insulin sensitivity is solely
due to enhanced glucose oxidation (M. Soop, A. Thorell, and O. Ljungqvist, unpublished observations). Thus the lack of an increase in nonoxidative $R_d$ in the patients from the current study may be the “normal” response to low-dose insulin stimulation in patients with relatively low insulin sensitivity.

Surgery resulted in a reduction in nonoxidative $R_d$, whereas the capacity to oxidize glucose was not affected. The ability of insulin to stimulate glucose oxidation was not altered by the surgical procedure. The reduction in nonoxidative $R_d$ observed during surgery was not normalized by insulin during the postoperative clamp, whereas, during the feedback clamp, when more insulin was infused, a complete restoration occurred. Thus, as shown in Fig. 2, the reduction in $R_d$ during surgery and the postoperative clamp could be fully attributed to a reduction in nonoxidative $R_d$. Furthermore, the increase in nonoxidative $R_d$ during the feedback clamp could completely account for the normalization in $R_d$.

Because glycogen synthase activities were reduced during surgery, it is possible that the decrease in nonoxidative $R_d$ results from a block at the level of glycogen synthesis. Although the reduction in nonoxidative $R_d$ could be attributed to reduced glycogen formation, increased glycogen breakdown, or a combination of both, the low plasma concentrations of lactate throughout the study suggest that increased glycogenolysis could not account for a decrease in skeletal muscle $R_d$. The fact that the glycogen synthase activities were reversed during the postoperative clamp while nonoxidative $R_d$ was not might be explained by the fact that the biopsy for the glycogen synthase activity measurement was taken at the end of the 30-min period used for the calorimetry sampling. It is therefore conceivable that the perturbation in intracellular glucose handling associated with elective surgery is at least in part, as in the case of non-insulin-dependent diabetes mellitus (7), due to disturbances in the glycogen synthetic pathway.

Because defects in glucose transport have been suggested to be involved in the development of non-insulin-dependent diabetes (43), as well as other insulin-resistant states (21, 25, 31, 34), we hypothesized that the development of postoperative insulin resistance would be associated with a concomitant alteration in insulin-stimulated glucose transport and GLUT-4 translocation. Preoperatively, insulin increased plasma membrane GLUT-4 in all patients. The mean increase was 1.8-fold, which is comparable to the effects of insulin infusion (16, 43) and oral glucose ingestion (14) in healthy volunteers. During the postoperative clamp, however, plasma membrane GLUT-4 was only increased in three out of six patients. Although mean insulin-stimulated plasma membrane GLUT-4 was not significantly reduced post- vs. preoperatively, there was no significant increase after surgery compared with basal values. There was, moreover, no increase in plasma membrane GLUT-4 when normalization of preoperative glucose uptake was accomplished by increased insulin infusion during the feedback clamp. Despite this dysregulation of GLUT-4 translocation, there was no effect of surgery on insulin-stimulated glucose transport in isolated plasma membrane vesicles. The data therefore suggest that, at least in some patients, the surgical procedure induces a rapid translocation defect, without affecting the actual flux of glucose in vesicular membrane preparations. Whether this defect is located in the insulin-signaling pathway or in GLUT-4 trafficking to the plasma membrane is not known and is currently under investigation. Interestingly, in a recent animal study (34), surgery-induced insulin resistance was shown to be associated with a reduction in insulin-stimulated glucose transport and an increase in insulin receptor phosphorylation and phosphatidylinositol 3-kinase activity.

The current finding that there is a significant reduction in muscle homogenate GLUT-4 with insulin infusion in the preoperative condition but not the postoperative condition also supports our hypothesis that the glucose transport system is altered after surgery. This is consistent with previous studies showing that, in normal subjects, a 4-h insulin clamp decreases total muscle GLUT-4 protein, whereas, in subjects with insulin-resistant conditions, there is no change in GLUT-4 protein during the same insulin clamp (1, 42). Increased GLUT-4 degradation may be a compensatory mechanism by the muscle to adapt to hyperinsulinemia, which might be impaired during insulin-resistant states.

In summary, elective surgical trauma induces marked alterations in glucose metabolism during the immediate postoperative period. This includes a reduction in peripheral glucose uptake and nonoxidative $R_d$. On the cellular level, the data suggest that these impairments include defects in both skeletal muscle GLUT-4 translocation and glycogen synthesis. In contrast, glucose and fat oxidation are not affected by the surgical stress. The perturbations in whole body $R_d$, nonoxidative $R_d$, and glycogen synthase activity could be fully restored by increased insulin infusion.

We thank all of the staff at the Department of Orthopedic Surgery for excellent collaboration, in particular Dr. Johan Isacsson for skillful assessing of the biopsies during surgery.

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