Site of insulin resistance after surgery: the contribution of hypocaloric nutrition and bed rest

Jonas NYGREN, Anders THORELL, Suad EFENDIC*, K. Sree NAIK† and Olle LJUNGQVIST

Department of Surgery, Karolinska Hospital, s-171 76, Stockholm, Sweden. *Department of Endocrinology, Karolinska Hospital, s-17 16, Stockholm, Sweden, and †Endocrine Research Unit, Mayo Clinic and Foundation, 200 First Street S.W., Rochester, MN, U.S.A.

(Received 4 December 1996; March 1997; accepted 27 March 1997)

1. Insulin resistance after surgery has been shown to be related to several important derangements in protein and fat metabolism. However, mechanisms of impaired glucose tolerance after surgery remain ill-defined.

2. Insulin sensitivity and glucose kinetics (6,6-D2-glucose) were studied in seven patients before and after elective surgery (surgery group), by two step-hyperinsulinaemic (0.3 and 0.8 munits kg-1 min-1), normoglycaemic (4.5 mmol/l) clamps. Six healthy subjects were studied, using the same protocol, before and after a similar period of bed rest and hypocaloric nutrition (fast/bed rest group) to delineate the effects of surgery per se.

3. Basal endogenous glucose production and whole-body glucose disposal was higher after surgery (P<0.001), whereas no change was found after fast/bed rest. During glucose clamps, the glucose infusion rates required to maintain normoglycaemia and whole-body glucose disposal decreased (P<0.001) after surgery, while endogenous glucose production increased (P<0.001). In the control subjects, levels of endogenous glucose production remained unchanged after fast/bed rest. In contrast, glucose infusion rates and whole-body glucose disposal during glucose clamps also decreased after fast/bed rest (P<0.01). However, the relative decrease in both these parameters was higher after surgery compared with after fast/bed rest (P<0.01).

4. After surgery, energy expenditure and fat oxidation increased (P<0.001), whereas glucose oxidation decreased (P<0.05). No significant change was found in glucose utilization postoperatively. After fast/bed rest, no change was found in energy expenditure. However, fat oxidation increased (P<0.01), whereas glucose oxidation and glucose utilization decreased (P<0.05).

5. In conclusion, impaired glucose tolerance develops after surgery as a result of decreased insulin-stimulated whole-body glucose disposal as well as increased endogenous glucose release. Despite the increase in endogenous glucose production, the reduction in endogenous glucose production with each elevation of insulin was unaffected by surgery. Perioperative bed rest and/or hypocaloric nutrition contribute to the decrease in insulin-stimulated whole-body glucose disposal in the postoperative state, whereas these factors have no effects on endogenous glucose production.

INTRODUCTION

A catabolic state occurs after accidental trauma [1], burns [2] and sepsis [1] as well as after surgery [3, 4] in humans. A major feature of the catabolic response during these conditions is the impairment of glucose tolerance and decrease in insulin sensitivity [4–7]. Recently, it was shown that the magnitude of the postoperative decrease in insulin sensitivity is related to the degree of surgical trauma [6, 7] and that the decrease in insulin sensitivity persists for 2–3 weeks after uncomplicated elective abdominal surgery [4]. Notably, despite variations in preoperative insulin sensitivity due to differences in age, body mass index (BMI) and gender, the relative changes in insulin sensitivity are reported to be quite consistent after any given surgical procedure [8].

The mechanisms of the postoperative decrease in insulin sensitivity remain to be clearly defined. It is unclear whether it is impaired insulin action in reducing endogenous glucose production (EGP) and/or decreased glucose uptake in insulin-sensitive tissues (i.e. skeletal muscle) that cause the impairment of glucose tolerance after surgery. In addition, it is not clear whether it is the surgical trauma alone that causes the postoperative decrease in insulin sensitivity, or if other factors may also contribute. The day of surgery also involves a period of bed-rest and hypocaloric nutrition. Prolonged periods of bed rest (i.e. 7 days or more) and 48 h fasting have been...
shown to decrease insulin sensitivity in healthy volunteers [9, 10]. To what extent hypocaloric nutrition and bed rest for only 24 h contribute to the decrease in glucose tolerance and insulin sensitivity seen postoperatively is not known.

Therefore, the aim of this study was to determine the relative roles of insulin action on endogenous glucose production and whole-body glucose disposal (WGD) in the impairment of glucose tolerance after surgery, and also the possible contribution of 24 h bed rest and hypocaloric nutrition to the decrease in insulin sensitivity that occurs in the first postoperative day.

Preliminary data from this study were presented at the XVII ESPEN Congress, Rome, Italy, 10–13 September, 1995 [11].

METHODS

Subjects

Seven patients (age 47±3 years, BMI 25±1 kg/m²; mean ±SEM) scheduled for medium to major size elective surgery were included in the study. The surgical diseases of the patients and the types of operations are summarized in Table 1. The patients were not on any medication, except for one patient who was under treatment with Hyoscyamin (Egazil Durett®, Hassle, Sweden) for irritable bowel disease. None of the patients had any history or signs of any metabolic diseases, including diabetes mellitus or kidney or liver disease. Fasting blood glucose levels, C-reactive protein and liver tests (bilirubin, alkaline phosphatase, aspartate aminotransferase and alanine aminotransferase) were normal in all subjects. Furthermore, six male healthy volunteers (age 24±1 years, BMI 22±1 kg/m²) were investigated in a separate study in order to determine the effect of the 24 h of hypocaloric nutrition and bed rest that routinely accompany the day of surgery. The study protocol was approved by the

Institutional Ethical Committee and, after full explanation of the purpose, nature and risk of all procedures, informed written consent was given by the subjects before entering the study.

Anaesthetics and peri/postoperative care

The anaesthetic and perioperative care of all patients were standardized. After an overnight fast, 5–7.5 mg of Ketobemidon sc. (Ketogan Novum®, Lundbeck, Denmark) was administered approximately 1 h before surgery as premedication to all patients. Induction of general anaesthesia was provided with thiopental-sodium (Pentothal® Natrium, Abbot, IL, U.S.A.), pancuronium (Pavulon®, Organon Teknika, The Netherlands) and suxamethon-chloride (Celocurin®-chloride, Pharmacia, Sweden) and maintained after oral intubation with inhalation of isofofarane (Forene®, Abbot) and a 30/70% mixture of oxygen and nitrous oxide. Glucopyrron (Robinul®, Robins, U.K.) or intravenous (i.v.) glucopyrnon-neostigmin (Robinul-Neostigmine®, Robins) 0.2 mg was used in six patients. Four patients received an epidural catheter for peri- and postoperative anaesthesia using 8–10 ml of 0.25–0.5% bupivacaine and adrenaline (Marcan®-adrenaline, Astra, Sweden) every 2–4 h. Four patients also received perioperative treatment with 2 g of cefotaxim (Claforn®, Hoechst, Germany) and 1.5 g of i.v. metronidazolom (Flagyl®, Rhöne-Poulenc Rorer, Sweden). During the first 24 h after surgery, patients were given 2000–3000 ml of i.v. glucose infusions (25 mg/ml, Rehydrex®, Pharmacia, Sweden). The operating time, perioperative blood loss and treatment with dextrane (Plasmodex®, Pharmacia), albumin (Albumin®, Pharmacia), ephedrin (Efedrin®, Pharmacia) and blood transfusions are shown in Table 1. Postoperative analgesia was provided with intramuscular/i.v. injections of ketobemidon (Ketog Novum®) or 8–10 ml of 0.25% Marcan®-adrenaline in the epidural catheters. No other

Table 1. Characteristics of seven patients undergoing elective uncomplicated surgery. Patients operated on for malignancy all had localized disease as indicated by histological examination. Patients with Crohn’s disease or diverticulosis were operated on at a state of non-active disease without clinical or laboratory signs of ongoing inflammation. M, male; F, female; EDA, epidural anaesthesia. Mean values (±SEM) are given at the end of columns.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Gender</th>
<th>BMI (kg/m²)</th>
<th>Surgical disease</th>
<th>Type of operation</th>
<th>Time of surgery (min)</th>
<th>Blood loss (ml)</th>
<th>EDA (+/-)</th>
<th>Blood transfusion (ml)</th>
<th>Ephedrin (mg)</th>
<th>Dextran/albumin (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>55</td>
<td>M</td>
<td>26</td>
<td>Adenocarcinoma of the prostate</td>
<td>Radical prostatectomy</td>
<td>188</td>
<td>1500</td>
<td>+</td>
<td>262</td>
<td>17.5</td>
<td>2000/500</td>
</tr>
<tr>
<td>38</td>
<td>M</td>
<td>29</td>
<td>Crohn’s disease</td>
<td>Perineal extirpation of the rectum</td>
<td>103</td>
<td>600</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0/300</td>
</tr>
<tr>
<td>56</td>
<td>F</td>
<td>25</td>
<td>Diverticulitis chronic coli</td>
<td>Resection of the sigmoid</td>
<td>100</td>
<td>200</td>
<td>-</td>
<td>0</td>
<td>5</td>
<td>0/0</td>
</tr>
<tr>
<td>40</td>
<td>M</td>
<td>24</td>
<td>Adenocarcinoma of the kidney</td>
<td>Nefrectomy</td>
<td>92</td>
<td>300</td>
<td>-</td>
<td>0</td>
<td>0</td>
<td>0/0</td>
</tr>
<tr>
<td>55</td>
<td>M</td>
<td>27</td>
<td>Adenocarcinoma of the prostate</td>
<td>Radical prostatectomy</td>
<td>100</td>
<td>2600</td>
<td>-</td>
<td>1411</td>
<td>5</td>
<td>3000/1000</td>
</tr>
<tr>
<td>41</td>
<td>M</td>
<td>24</td>
<td>Diverticulitis chronic coli</td>
<td>Resection of the sigmoid</td>
<td>130</td>
<td>200</td>
<td>+</td>
<td>0</td>
<td>15</td>
<td>0/0</td>
</tr>
<tr>
<td>47</td>
<td>M</td>
<td>22</td>
<td>Crohn’s disease</td>
<td>Perineal extirpation of the rectum</td>
<td>107</td>
<td>1000</td>
<td>+</td>
<td>532</td>
<td>10</td>
<td>1000/00</td>
</tr>
<tr>
<td>47±3</td>
<td>6/1</td>
<td>25±0.8</td>
<td></td>
<td></td>
<td>132±17</td>
<td>914±334</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
pharmacological treatment was given during the course of this study.

**Study design**

All patients underwent the same study protocol twice. At 08.00 hours the day before surgery (preop) as well as at the same time on the first postoperative day (postop) a normoglycaemic, hyperinsulinaemic, two-step clamp [Actrapid®, Novo, Copenhagen, Denmark] insulin infusion rates 0.3 and 0.8 munits kg⁻¹ min⁻¹ for 120 min at each level using the artificial pancreas (Biostator®, Life Science Instruments, Elkhart, IN, U.S.A.) [12] was performed after an overnight fast, as previously described [4]. The same experimental design was used in healthy volunteers both the day before ('preop') as well as after 24 h of strict bed-rest ('postop'). During this 24 h period, the subjects were not allowed to eat or drink, but similarly to the patients, they received 2000 ml, 25 mg/ml, i.v. glucose infusions (Rehydrex®, Pharmacia). For simplicity, this group will be called the fast-bed rest group. Two subsequent hyperinsulinaemic, normoglycaemic clamps separated by 48 h has, in our hands, not been shown to influence insulin sensitivity measurements [the relative change in glucose infussion rates between the two clamps was 8±9% (n = 5, P = 0.7) for subjects aged 40±8 years, BMI 23±1 kg/m²; J. Nygren, M. Soop, A. Thorell and O. Ljungqvist, unpublished work].

Primed (5 mg/kg), continuous (2.4 mg kg⁻¹ h⁻¹) infusions of [6,6²H₂]glucose (Isotec Inc., Miamisburg, OH, U.S.A.) were given for 150 min before (-150 to 0 min) as well as throughout (0 to +240 min) the clamp. The [6,6²H₂]glucose was sterile, non-progenic and proven to be >96% pure by HPLC. The infusion was performed with a syringe pump (Perfusor®-secura, B-Braun, Melsungen, Germany).

To minimize changes in plasma [²H]glucose enrichment during the clamp, [6,6²H₂]glucose was added to the glucose infusate [13, 14]. The amount of this tracer added to the cold glucose infusion was estimated to be 1.25 g/100 g of glucose preoperatively and 0.85 g/100 g of glucose postoperatively. These estimations were based on previous data [8, 15].

Glucose appearance and disappearance were calculated using a modified Steeles equation, taking into account the varying tracer infusion rates [13, 14, 16]. The glucose volume of distribution was estimated to be 250 ml/kg and the pool correction factor 0.65. EGP was calculated by subtracting the glucose infusion rate from the tracer-determined rate of appearance [13, 14].

Indirect calorimetry (Deltatrac®, Dansjöö, Sweden) [17, 18] was performed during the last 30 min of the basal period (-30 to 0 min) as well as during each steady-state period during the two-step clamp (+90 to +120 min and +210 to +240 min respectively). Urinary urea nitrogen excretion in patients was estimated to be 4.9 mg/min and 6.0 mg/min in the pre- and post-operative measurements respectively. This estimation was based on calculations from another group of patients studied at our laboratory performing the same protocol as in this study under similar clinical conditions. In volunteers, timed sampling of urine for analysis of urinary urea excretion was performed during clamps. After correction for changes in urea pool size [19], non-protein energy expenditure (EE), respiratory quotients, substrate oxidation rates, non-oxidative glucose disposal and glucose utilization (percentage of oxidized glucose disposal) were calculated.

**Sampling and analysis**

Arterial blood from a heated hand vein was taken as described previously [4]. Plasma samples for the determination of isotope enrichment levels were collected every 10 min during the last 30 min of the basal period and during the last 60 min of each level of insulin infusion during the clamp. The trimethylsilyl-0-methylxime derivative of plasma glucose was analysed in a gas chromatography mass spectrometer to measure [6,6²H₂]glucose isotopic enrichment in tracers, glucose infusates and plasma samples [20]. Glucose was measured immediately upon collection using the glucose oxidase method (Yellow Springs Instruments Co., Yellow Springs, OH, U.S.A.) [21]. Serum insulin was analysed by RIA using an antibody developed in our laboratory [22] and c-peptide was analysed by RIA using a commercially available kit (Novo Research, Bagsværd, Denmark). Serum cortisol [23] and plasma glucagon (Euro-Diagnostica AB, Malmö, Sweden) [24] were analysed using RIA. Plasma glycerol was measured using a peroxidase-coupled colorimetric assay [25]. Plasma amino acids were measured using reverse-phase HPLC (Hewlett Packard 1090 Series 2 HPLC, 1046 fluorescence and cooling system) [26]. Hormones and substrates were sampled at basal level and every 30 min, except at 30 and 150 min, during the clamps (+0, 60, 90, 120, 180, 210 and 240 min.).

**Statistics**

All data are given as means±SEM for sampling performed during the last 30 min at basal and during steady-state at low and high clamp levels (i.e. 90–120 min and 210–240 min respectively). Statistical significance was accepted at P<0.05 using analysis of variance for repeated measurements over time. As serum insulin levels were similar in all groups during both basal conditions and during clamps, comparisons were made between whole measurements as well as between different levels.
during the studies (basal, low and high). Statistical significance for single measurements (basal blood sampling, indirect calorimetry) within and between groups was accepted at $P < 0.05$ using Student's $t$-test, paired and unpaired respectively.

**RESULTS**

**Postoperative course**

All patients recovered without any postoperative complications. Patients were discharged from the

---

*Fig. 1. Blood glucose, serum insulin, GIR and plasma $[^{6,6}D_{2}H_{2}]$-glucose enrichment levels during two-step hyperinsulinaemic, normoglycaemic clamps in seven patients (left panels) both the day before (preop, open circles) as well as the day after surgery (postop, filled circles). The same protocol was also performed in six healthy subjects (right panels) both before ('preop', open squares) and after 24 h of bed-rest and hypocaloric nutrition ('postop', filled squares). All values are means ± SEM.*
hospital after 10±1 days. Patients operated on for malignancy (adenocarcinoma) (Table 1) were radically operated with no signs of residual tumour macroscopically or microscopically.

Substrates

Fasting blood glucose levels did not change significantly after surgery or in the controls after fast/bed rest (Figure 1). During clamps, normoglycaemia was maintained in both groups (4.5 mmol/l, Figure 1). The mean intra-individual coefficient of variation of blood glucose during clamps was 4.3%.

Plasma glycerol concentrations increased similarly after surgery (P<0.001) and fast/bed rest (P<0.001) (Figure 2). Plasma glycerol levels decreased during both the preop and postop clamps in both groups (P<0.05 compared with basal).

Plasma amino acid levels during the preop situation (Table 2) were similar between patients and controls, apart from glutamine which was lower (P<0.05) in the patient group. The total circulating amino acids decreased by 23% in patients after surgery (P<0.001). Almost half (46%) of this fall was due to the decline in glutamine (P<0.001) and alanine (Figure 2, P<0.001) and 23% was due to reductions in basic amino acids (P<0.001). There was no net change after fast/bed rest.

Aromatic amino acids increased after surgery (P<0.001), whereas decreased levels were found after fast/bed rest (P<0.001) as compared with the preop situation. Branched-chain amino acids were not significantly changed after surgery, whereas increased levels (P<0.001) were found after fast/bed rest.

Hormones

Postabsorptive serum insulin (Figure 1) and c-peptide levels (results not shown) did not change after surgery or after fast/bed rest. Serum insulin levels increased during clamps to mean concentrations of approximately 215 and 430 pmol/l at low and high levels of insulin infusion respectively. No significant differences were found in insulin levels between any of the clamps.

Basal serum cortisol levels did not change significantly after surgery (456±37 compared with 551±85, P>0.05, preop and postop measurements respectively) or after fast/bed rest (447±22 compared with 472±4385, P>0.05, 'preop' and 'postop' respectively).

Plasma glucagon levels (Figure 2) increased after surgery (P<0.001), whereas no change was found after fast/bed rest compared with the pretreatment situation. After surgery, glucagon levels were higher as compared with glucagon levels after fast/bed rest (P<0.05).

Glucose kinetics

Plasma isotope-enrichment levels (Figure 1) were stable during all measurements, with mean intra-individual coefficients of variation of 5.9% at the different steady-state levels (basal, low and high insulin).

At basal level, WGD (Figure 3) was lower in patients as compared with controls before treatment (P<0.01), whereas no change was found in EGP between the groups. After surgery, basal EGP and WGD increased (P<0.001). After fast/bed rest, no change was found in basal EGP or WGD.

During glucose clamps, lower levels of glucose infusion rates (GIR) (P<0.05, Figure 1) and WGD (P<0.01, Figure 3) were found in patients as compared with controls before treatment. No significant difference was found between the groups in endogenous glucose production either at the low or at the high level of insulin infusion before treatment. Both groups displayed totally suppressed EGP.
Table 2. Plasma amino acids (μmol/l) at basal state as well as during normoglycaemic, hyperinsulinaemic two-step clamps (0.3 and 0.8 munits kg⁻¹ min⁻¹) in seven surgical patients both before (preop) elective surgery and on the first postoperative day (postop). The same protocol was also performed in six healthy controls both before (preop) and after 24 h of bed rest and hypocaloric i.v. nutrition (postop). All values are means±SEM. *+P<0.01, **+P<0.001 compared with preop. +P<0.05, ++P<0.01, +++P<0.001 compared with patients; analysis of variance.

<table>
<thead>
<tr>
<th>Amino acid</th>
<th>Preop</th>
<th>Postop</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Basal</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>490±27</td>
<td>438±14</td>
</tr>
<tr>
<td>Controls</td>
<td>579±23</td>
<td>520±17</td>
</tr>
<tr>
<td>Ala</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>313±21</td>
<td>300±14</td>
</tr>
<tr>
<td>Controls</td>
<td>261±29</td>
<td>262±13</td>
</tr>
<tr>
<td>Branched-chain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>438±23</td>
<td>373±10</td>
</tr>
<tr>
<td>Controls</td>
<td>451±14</td>
<td>363±9</td>
</tr>
<tr>
<td>Aromatic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>117±9</td>
<td>105±4</td>
</tr>
<tr>
<td>Controls</td>
<td>111±3</td>
<td>95±4</td>
</tr>
<tr>
<td>Basic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>389±22</td>
<td>357±15</td>
</tr>
<tr>
<td>Controls</td>
<td>362±21</td>
<td>347±11</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>2316±58</td>
<td>2114±42</td>
</tr>
<tr>
<td>Controls</td>
<td>2395±87</td>
<td>2115±52</td>
</tr>
</tbody>
</table>

Fig. 3. EGP, and glucose disposal (WGD) both at the basal state and during two-step hyperinsulinaemic, normoglycaemic clamps in seven patients (left panels) both the day before (preop, open circles) and the day after surgery (postop, filled circles). The same protocol was also performed in six healthy subjects (right panels) both before (preop, open squares) and after 24 h of bed rest and hypocaloric nutrition (postop, filled squares). All values are means±SEM.
under the high-insulin clamp conditions. After surgery, levels of EGP increased ($P<0.001$), whereas levels of GIR and WGD decreased at both insulin infusion rates ($P<0.001$). Despite the 22% increase in EGP after surgery, the degree of suppression of EGP during each level of insulin infusion was comparable with that observed during the preop situation. Thus, the change ($\delta$) in the individual slopes of the correlation between EGP and insulin were unchanged after surgery ($-0.006 \pm 0.007$, $P$ = not significant, one sample t-test, Figure 4). Postabsorptive levels of EGP and plasma glucagon ($r = 0.82$, $P = 0.04$) correlated after surgery.

After fast/bed rest, levels of GIR and WGD decreased ($P<0.001$) at both levels of insulin infusion, whereas no change was found in EGP. However, the relative reduction in GIR in surgery was about twice as great at the high clamp level ($P<0.05$) as compared with that found after fast/bed rest ($-47 \pm 9\%$ and $-22 \pm 6\%$ for patients and controls respectively). Furthermore, the reduced increment in WGD during clamps was significantly

Table 3. At basal state and during normoglycaemic, hyperinsulinaemic two-step clamps (0.3 and 0.8 units kg$^{-1}$ min$^{-1}$) in seven surgical patients both before (preop) elective surgery and on the first postoperative day (postop). The same protocol was also performed in six healthy controls both before ('preop') and after 24 h of bed rest and hypocaloric i.v. nutrition ('postop'). All values are means $\pm$ SEM. *$P<0.05$, **$P<0.01$, ***$P<0.001$ compared with preop, †$P<0.05$ compared with patients; analysis of variance.

<table>
<thead>
<tr>
<th></th>
<th>Basal</th>
<th>Low</th>
<th>High</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose oxidation (mg min$^{-1}$ kg$^{-1}$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>1.02 $\pm$ 0.31</td>
<td>1.38 $\pm$ 0.38</td>
<td>2.82 $\pm$ 0.40</td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>0.54 $\pm$ 0.32</td>
<td>1.41 $\pm$ 0.30</td>
<td>3.01 $\pm$ 0.48</td>
<td></td>
</tr>
<tr>
<td>Non-oxidative glucose disposal (mg min$^{-1}$ kg$^{-1}$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>1.36 $\pm$ 0.31</td>
<td>1.31 $\pm$ 0.42</td>
<td>2.92 $\pm$ 0.73</td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>1.98 $\pm$ 0.37</td>
<td>2.79 $\pm$ 0.54</td>
<td>5.93 $\pm$ 1.02</td>
<td></td>
</tr>
<tr>
<td>Glucose utilization (% uptake oxidized)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>42.5 $\pm$ 13.8</td>
<td>52.5 $\pm$ 15.0</td>
<td>52.3 $\pm$ 8.0</td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>22.8 $\pm$ 12.3</td>
<td>34.5 $\pm$ 6.5</td>
<td>35.9 $\pm$ 7.9</td>
<td></td>
</tr>
<tr>
<td>Fat oxidation (mg min$^{-1}$ kg$^{-1}$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>1.19 $\pm$ 0.12</td>
<td>1.06 $\pm$ 0.56</td>
<td>0.56 $\pm$ 0.20</td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>1.36 $\pm$ 0.12</td>
<td>1.13 $\pm$ 0.09</td>
<td>0.57 $\pm$ 0.14</td>
<td></td>
</tr>
<tr>
<td>Non-protein EE (kcal 24 h$^{-1}$ kg$^{-1}$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>24.4 $\pm$ 1.0</td>
<td>23.7 $\pm$ 1.4</td>
<td>24.6 $\pm$ 1.3</td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>27.6 $\pm$ 1.2</td>
<td>27.2 $\pm$ 1.3</td>
<td>28.9 $\pm$ 1.3</td>
<td></td>
</tr>
</tbody>
</table>

$\dagger$ kcal = 4.184 kJ.
greater following surgery than after fast/bed rest alone \((-88 \pm 6\% \text{ compared with } -40 \pm 7\%, P<0.01, \text{Mann–Whitney } U\)-test).

**Indirect calorimetry**

Before treatment, no change was found in resting EE, substrate oxidation rates, non-oxidative glucose disposal or glucose utilization (i.e. the relative part of glucose disposal being oxidized) between the groups (Table 3).

After surgery, EE and fat oxidation increased \((P<0.001)\), whereas glucose oxidation decreased \((P<0.05)\). No significant change was found in non-oxidative glucose disposal or glucose utilization after surgery.

After fast/bed rest, no change was found in EE or non-oxidative glucose disposal. However, fat oxidation increased \((P<0.01)\), whereas glucose oxidation and glucose utilization decreased \((P<0.05)\).

**DISCUSSION**

The novel findings of the present study are that the postoperative impairment of glucose tolerance is mainly due to a combination of an increase in EGP and a decrease in insulin sensitivity, with regard to insulin-stimulated WGD. As the suppressibility of EGP by insulin is unchanged after surgery, the decrease in insulin sensitivity is mainly due to a decrease in insulin-stimulated WGD, indicating a decreased sensitivity to insulin in peripheral tissues. Bed rest and/or hypocaloric nutrition during the day of surgery contributes to the postoperative decrease in whole-body insulin sensitivity, since this ‘perioperative treatment’ alone resulted in a significant reduction in insulin-stimulated WGD but no change in EGP.

Insulin sensitivity was assessed in the current study using physiological levels of insulin. The lower infusion rate was chosen to achieve insulin levels where changes in EGP could be detected [27]. The higher rate of infusion was used to elevate insulin to levels seen after a normal standard meal [28] and was primarily intended to assess changes in peripheral insulin sensitivity. At this level of hyperinsulinemia, EGP is expected to be totally depressed, at least in healthy individuals [29]. Since glucose uptake during insulin clamps has been shown to be small in splanchnic tissues [30], the decrease in insulin sensitivity demonstrated in the current study could mainly be accounted for by a decrease in glucose uptake in skeletal muscle. The kidney, in addition to the liver, also produces glucose [31]. Thus, all results regarding endogenous glucose production are the net result of glucose release from both of these organs.

Although the patients in the present study displayed a decrease in insulin sensitivity after surgery, basal glucose and insulin levels tended to increase. This is similar to other recent reports on basal glucose and insulin levels following surgery [4, 5]. This moderate change differs from some older studies [32, 33]. Despite the minor changes in basal glucose and insulin levels, a pronounced reduction in insulin sensitivity developed following surgery.

Several factors and mechanisms have been suggested to promote insulin resistance after trauma and surgery [1, 34–38]. Increased release of the counter-regulatory hormones has been reported to be an important mediator of post-traumatic catabolism [39]. However, in our previous studies on the development of postoperative insulin resistance, only small increments in cortisol, catecholamines and growth hormones have been found in the circulation during and after surgery [8]. The changes in the levels of these hormones could not be related to the decrease in insulin sensitivity after surgery. This was also the finding in the present study where cortisol was only marginally and insignificantly elevated. Glucagon levels were higher after surgery. The effect of glucagon on the regulation of EGP is well established [40]. It is likely that the postoperative increase in EGP relates to increased levels of glucagon. This is supported by the finding that postabsorptive EGP after surgery was significantly related to glucagon levels.

Although it was well established that cortisol, glucagon and catecholamines could cause a reduction in insulin sensitivity [39], the release of these hormones was not necessarily the main cause for the reduction in insulin sensitivity after surgery. This finding led to studies of other potential mediators, such as cytokines. However, apart from a weak correlation between postoperative changes in interleukin-6 levels and changes in postoperative insulin sensitivity \((r = 0.33, P = 0.01, n = 41)\), no relations between the levels of the cytokines and the postoperative decrease in insulin sensitivity were found [8].

Another factor potentially contributing to decreased insulin sensitivity is increased lipolysis, resulting in increased glucose–fatty acid cycle rate [41]. In the current study, glycerol levels and fat oxidation rates increased in a similar fashion both after surgery and after bed rest/hypocaloric nutrition alone. The relative amount of glucose disposal being oxidized did not change after surgery, suggesting that a substantial part of the decrease in glucose disposal after surgery is due to changes in glucose transport. However, after fast/bed rest a smaller proportion of glucose disposal was oxidized. This suggests that the glucose–fatty acid cycle contributes to the overall decrease in postoperative extrahepatic insulin sensitivity due to fast/bed rest.

Another important factor is probably the availability of gluconeogenic substrates. Surgery has been shown to be associated with increased levels of gluconeogenic substrates such as alanine, glycerol, pyruvate and lactate [5]. It was demonstrated in the present study that glycerol levels increased post-
operatively. However, the levels of alanine and glycogenic amino acids remained low. Since we did not measure the kinetics of these amino acids, it is unclear whether increased flux or turnover of these amino acids occurs or not.

Thus, with regard to the mediators of the postoperative decrease in insulin sensitivity, more recent literature suggests that the mediators may not solely be the counter-regulatory hormones. The surgical trauma in itself is of course important for the postoperative decrease in insulin sensitivity, and we have previously shown that the degree of postoperative insulin resistance is related to the magnitude of the surgical trauma [7] as well as to the surgical technique (i.e. open compared with laparoscopic cholecystectomy) [6]. It seems as if the release of stress hormones after surgery may not be as prominent today as it was 10 or 20 years ago. A lesser stress hormone response today may have several explanations, such as changes in anaesthetics and other pharmacological developments, the use of epidural anaesthesia [42] and continuous changes in surgical techniques.

The present data suggest that the perioperative feeding regime may be yet another routine to question.

The suppressibility of EGP by insulin was unchanged postoperatively. This finding is in contrast with a previous study by Brandi et al. [5] in which an impaired response of EGP to insulin was demonstrated. The reason for the differences between this and the present study is not clear. One explanation could be that the development of insulin resistance with regard to EGP may become more evident in more severely stressed patients than those currently studied. However, Shaw and Wolfe [43] suggested an 'all or none response' in EGP after trauma, since EGP was similarly increased in patients despite different injury severity scores. If those observations are accurate, the present findings of preserved suppressibility of endogenous glucose production by insulin may extend to even more severe cases of trauma than those currently studied. Thus, in severely burned patients, Wolfe et al. [35] demonstrated normal suppressibility of EGP by insulin in the presence of elevated EGP.

The difference between insulin action on glucose production and glucose uptake after surgery may be due to different rate-limiting steps in insulin action and therefore potential sites of insulin resistance in hepatic/renal and peripheral tissues [44]. Turk et al [45] recently reported that non-insulin dependent diabetes mellitus patients displayed peripheral insulin resistance and increased EGP during normoglycaemic, hyperinsulinaemic glucose clamps. In addition, similar to the present findings after surgical stress, a normal hepatic response to insulin was found.

The group of healthy subjects were younger than the patient group, but all participants in both of these groups served as their own controls. We have previously not been able to find any correlation between the relative change in insulin sensitivity after surgery and preoperative insulin sensitivity, age, sex or BMI during a standardized surgical procedure (n = 47, open cholecystectomy) [8]. Similarly, in the control group as well as in a currently ongoing follow-up study (J. Nygren, M. Soop, A. Thorell and O. Ljungqvist, unpublished work) we have not been able to find any relation between age or pretreatment insulin sensitivity and changes in insulin sensitivity after hypocaloric nutrition and/or bed rest. Thus, it seems unlikely that any differences in these parameters altered the trends of events presently under study. Newman and Brodows [10] showed in healthy subjects, using a hyperinsulinaemic glucose clamp, that whole-body glucose utilization decreased after a 48 h fast. Since no tracers were used, no distinction between EGP or glucose disposal could be made. In the present study in healthy controls, no change in EGP could be seen either at basal conditions or during clamps as a result of 24 h fast/bed rest. During insulin infusions, significant (20–30%) reductions in insulin-stimulated glucose uptake were found as a response to 24 h of bed-rest and hypocaloric nutrition. The purpose of the control study was to single out the effects of anaesthesia and surgery from other related variables possibly contributing to the alterations in insulin sensitivity following surgery. Thus, the relative importance of bed rest as compared with hypocaloric nutrition for the decrease in insulin sensitivity remains to be investigated. Nevertheless, the finding that even a short period (24 h) of bed rest and low-caloric intake causes a substantial reduction in peripheral insulin sensitivity has clinical implications. These findings suggest that patient mobilization and/or nutrition early after or even before surgery [46, 47] may help to minimize post-surgical derangements in metabolism.

From the present findings it can be concluded that patients on the day after surgery, develop impaired glucose tolerance as a result of decreased insulin-stimulated WGD as well as increased endogenous glucose release. Despite the increase in endogenous glucose production, the reduction in endogenous glucose production with each elevation of insulin was unaffected by surgery. Perioperative bed rest and hypocaloric nutrition contribute to the decrease in insulin-stimulated WGD in the postoperative state, while these factors have no effects on endogenous glucose production.

ACKNOWLEDGMENTS

We thank nurses Lotta Hylén and Cajsa Almström for excellent assistance with the clamps. This work was supported by grants from the Karolinska Institute, the Swedish Medical Research Council (No. 09101), the Swedish Diabetes Association, Fredrik and Ingrid Turings foundation, The Swedish Society of Medicine, National Institute of Health.
Grants (ROI, DK-41973) and Nutricia, AS, The Netherlands.

REFERENCES