Insulin resistance after surgery: normalization by insulin treatment

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(Received 30 October 1989/14 May 1990; accepted 23 May 1990)

SUMMARY

1. Injury is known to be associated with variable degrees of tissue insensitivity to insulin. We measured insulin resistance in a group of non-obese, glucose-tolerant patients undergoing major elective surgery with an uncomplicated post-operative course.

2. Shortly after surgery, hyperglycaemia (7.3 ± 0.6 versus 4.2 ± 0.3 mmol/l glucose pre-surgery, mean ± SEM, P < 0.01) with normal insulin concentrations (73 ± 15 versus 64 ± 18 pmol/l) suggested the presence of insulin resistance. Counter-regulatory hormones were raised, whole-body protein oxidation was doubled (P < 0.01) and energy expenditure was up by 18% (P < 0.01).

3. Insulin sensitivity was quantified by clamping plasma glucose concentrations at 5.6 mmol/l during 24 h of total parenteral nutrition (15% protein, 55% glucose and 30% fat, supplying 1.25 times the measured resting energy expenditure) with a variable infusion of exogenous insulin. After surgery, eight times more insulin was needed than before surgery (14.14 ± 1.15 versus 1.78 ± 0.29 pmol min⁻¹ kg⁻¹, P < 0.001) to maintain euglycaemia.

4. After surgery, stimulation of net carbohydrate oxidation (18.8 ± 1.4 versus 17.2 ± 1.8 μmol min⁻¹ kg⁻¹ pre-operatively, not significant), suppression of lipolysis and lipid oxidation and inhibition of ketogenesis occurred to the same extent as before surgery. Of the infused nutrients, the glucose was all oxidized, amino acids replaced endogenous protein losses (= neutral nitrogen balance) and lipids were stored. Insulin administration caused no further increment in oxygen consumption or energy expenditure.

5. We conclude that: (a) uncomplicated surgery causes severe insulin resistance, the effects of which insulin can reverse; and (b) with an energy supply only slightly in excess of demand, insulin supplementation preserves body protein and energy stores effectively.

Key words: energy expenditure, glucose clamp, insulin resistance, surgical stress.

Abbreviations: FFA, free fatty acids; GH, growth hormone; HDL, high-density lipoprotein; T₃, tri-iodothyronine; T₄, thyroxine; TPN, total parenteral nutrition; TSH, thyroid-stimulating hormone.

INTRODUCTION

In man as well as in experimental animal models, injury of any kind, trauma, surgery, sepsis or burn, causes distinct metabolic changes [1–4]. Among them, increased protein and energy turnover are adaptive responses to rapid tissue destruction that are invariably present. Quite characteristic of injury is also a rise in plasma glucose concentrations that has been termed 'stress diabetes' or 'diabetes of injury'. In stress diabetes, glucose disposal is thought to be impeded by the presence of variable degrees of tissue insensitivity to insulin [5, 6]. The entity, sites and mechanisms of such insulin resistance have been widely investigated [7, 8] but still are the subject of controversy. For example, by using the euglycaemic and hyperglycaemic clamp techniques, Black et al. [6] concluded that in injured patients insulin-mediated glucose disposal is impaired only at maximally stimulating insulin concentrations, suggesting that responsiveness (i.e. maximal response) rather than sensitivity to the hormone is reduced [9]. It has been, however, the clinical experience of several investigators that glucose disposal and oxidation can be normalized in injured patients provided that a large enough glucose load is administered [10–13]. Furthermore, critically ill patients typically show a greater reliance on lipid oxidation for energy production [12–15], yet carbohydrate oxidation can be normal or elevated [10,
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Fig. 1. Flow-chart of the study design. Sampling refers to blood drawing. IC stands for indirect calorimetry. The two short arrows indicate the IC measurements of energy expenditure that were used to estimate caloric need before and after surgery (see the Methods section).

Methods

Subjects

Seven patients (two women and five men), undergoing left colon resection for non-metastatic neoplasia of the sigmoid colon, were studied. Their mean age was 51 ± 5 (mean ± SEM) years, their body weight was 65 ± 6 kg, their body surface area was 1.71 ± 0.1 m², and their body mass index was 23 ± 1 kg/m². All patients had normal tolerance to oral glucose [18], and a negative family history of diabetes mellitus. Before admission to the study, each patient received a complete medical work-up to rule out the presence of cardiovascular, respiratory, renal or endocrine disorders, and to document the absence of distant metastases. None of the patients had had a loss of > 10% of their habitual body weight over the preceding 3 months; nutritional status was further assessed by measuring skinfold (tricipital and subscapular) thickness and arm circumference, and by comparing them with age- and sex-adjusted expected values [19]. Serum proteins were 66 ± 2 g/l, of which albumin was 41 ± 2 g/l; the packed cell volume averaged 41 ± 2%; serum levels of creatinine, urea nitrogen, and electrolytes were all within the normal limits. No patient received any medication for at least 3 weeks before the study.

The nature, purpose and potential risks of the study were explained to all the patients before obtaining their consent to participate.

Procedures

For the pre-operative study, an antecubital vein was used for blood sampling, while TPN was administered through a catheter advanced from another antecubital vein into the vena cava. Surgery was performed (an average of 65 ± 8 h after the pre-operative study) at 08.00 hours. Anaesthesia was induced with pentobarbital and succinylcholine, and maintained with isofluorane and pancuronium. During surgery, serum electrolytes were monitored, and the fluid electrolyte balance was maintained; no D-glucose or blood was infused. Soon after surgery, patients were transferred to the Intensive Care Unit, where a central venous line was started, urine was collected via a bladder catheter and vital functions were monitored. During at least 48 h after surgery, the patients remained free of haemorrhagic, septic or other major complications, with a body temperature of < 37.5°C. Post-operative analgesia was the same for all patients (morphine, 0.1 mg/kg). Gastric drainage (via a naso-
gastric tube) averaged 0.830 ± 0.22 litre/day. Fluid losses via the peritoneal drainage were negligible.

Each patient was studied both before and after surgery (Fig. 1). Before surgery, blood measurements (see below) were obtained at 08.00 hours after an overnight (12 h) fast, again at 16.00 hours (20 h of fasting), and then at the end of 24 h of TPN until 16.00 hours on the next day. On the day of surgery, blood was drawn at 08.00 hours after a 12 h fast just before surgery, then at 16.00 hours (5–6 h after the completion of surgery), and thereafter at the end of 24 h of TPN; the study was then extended to 48 h of TPN. Therefore, each patient had seven time-point observations: (a) a baseline evaluation (after an overnight fast) before and after surgery; (b) an evaluation after exactly the same period of total fast (20 h) before and after surgery; (c) at the end of 24 h of TPN before and after surgery; and (d) after 48 h of TPN after surgery only.

Indirect calorimetry was performed at each blood sampling time (except on the day of surgery before the operation) and also after 8 h of TPN, before as well as after surgery (Fig. 1). Each indirect calorimetry measurement consisted of 60 min of continuous recording with a canopy system [20]. Five urine collections were taken, as shown in Fig. 1; the 8 h urine collections were used to correct the gas-exchange measurements made in the fasting state, and the 24 h collections were used to correct the corresponding calorimetric readings obtained at the end of the three 24 h periods of TPN administration. TPN consisted of a mixture of 33% (w/v) d-glucose (Sifra, Verona, Italy), 10% (w/v) Intralipid (Kabi Vitrum, Stockholm, Sweden) and 8.5% (w/v) Freamine III (Don Baxter, Trieste, Italy). Total caloric input was made to equal to 1.25 times the resting energy expenditure of each individual patient as measured (by indirect calorimetry) both before and after surgery after a 20 h fast (Fig. 1). The composition of TPN (15% of total calories as protein, 30% as lipid and 55% as glucose, with electrolytes, trace elements and vitamins added according to standard requirements) was the same in all patients.

During TPN, plasma glucose concentrations were measured at half-hourly intervals, and an exogenous infusion of regular insulin (Actrapid; Novo Industri, Copenhagen, Denmark) was started at initial rates of 1.5 pmol min⁻¹ kg⁻¹ pre-operatively (6.0 pmol min⁻¹ kg⁻¹ post-operatively), and then empirically adjusted every hour to maintain plasma glucose at ~5.6 mmol/l both before and after surgery. The insulin infusion was given via a separate pump (model A975, Harvard Apparatus) at precisely known flow rates.

Respiratory gas exchange was evaluated by a computerized, open-circuit canopy system as previously described [20]. Plasma glucose was measured by the glucose oxidase method (Beckman Glucose Analyzer; Beckman Instruments, Fullerton, CA, U.S.A.). Blood levels of lactate, pyruvate, 3-hydroxybutyrate, alanine and glycerol were assayed in perchloric acid extracts by fluorimetry, with between-assay coefficients of variation ranging from 3 to 9%. Plasma free fatty acids (FFA) were measured by an enzymatic method (Wako Chemical GmbH, Neuss 1, West Germany), with a coefficient of variation of 5%. Non-protein urine nitrogen was measured by the Kjeldhal method [21]. Serum insulin growth hormone (GH), cortisol, prolactin, glucagon, testosterone, thyroxine (T₄), tri-iodothyronine (T₃) and thyroid-stimulating hormone (TSH) concentrations were assayed by standard radioimmunological methods (kits purchased from Biodata, Milano, Italy and Sorin, Saluggia, Italy). Serum triacylglycerol, total cholesterol and high-density lipoprotein (HDL)-cholesterol were measured by specific enzymatic methods. Urine catecholamine (adrenaline, noradrenaline and dopamine) concentrations were measured by h.p.l.c.

Data analysis

Protein oxidation was estimated by multiplying non-protein urinary nitrogen excretion (= urine flow multiplied by non-protein urine nitrogen concentration) by 6.25 [22]. Changes in the urea nitrogen pool were estimated from changes in blood urea nitrogen concentrations, and taken into account in the calculation of urine nitrogen excretion [23]. Nitrogen loss into gastric drainage was calculated as the product of gastric aspirate volume multiplied by the non-protein nitrogen concentration in the gastric aspirate (25 mmol/l) [24]; this loss (averaging 16 ± 4 μmol/min) was added to urine nitrogen excretion in order to obtain a correct estimate of whole-body protein oxidation. Net whole-body rates of carbohydrate and lipid oxidation were calculated from gas-exchange measurements (indirect calorimetry) and non-protein nitrogen excretion by using equations explicitly derived elsewhere [25]. It should be recalled that, when gluconeogenesis from alanine is present, the calculated rates of carbohydrate oxidation are the net balance between true glucose oxidation and gluconeogenesis from alanine, i.e. calorimetry underestimates carbohydrate oxidation. Furthermore, deamination of alanine on its way to glucose leads to an overestimation of protein oxidation (as judged from urinary nitrogen excretion) to the extent that the nitrogen liberated in this pathway is not promptly replaced by transamination (with alanine) of other amino acids destined to complete oxidation. Finally, net lipid oxidation is underestimated by an amount equal to ~10% of the rate of gluconeogenesis from alanine [25]. The finding of non-protein respiratory quotient values greater than 1 indicates the occurrence of net lipid synthesis, i.e. lipogenesis de novo in excess of concomitant lipid oxidation. In this case, a modified equation to calculate net carbohydrate oxidation [25] was used. The terms 'glucose oxidation' and 'carbohydrate oxidation', and 'energy production' and 'energy expenditure', are used interchangeably.

All data are expressed as means ± SEM. Rates are given as μmol min⁻¹ kg⁻¹ body weight. For each parameter, pairs of mean group values were compared by the use of Student’s paired t-test. When more than two mean group values were compared, one-way analysis of variance for repeated measures was used. To simultaneously test the effect of surgery and TPN, two-way analysis of variance for doubly repeated measures was employed on four sets
RESULTS

In the 12 h- and 20 h-fasted states before surgery, plasma glucose concentrations averaged 4.3 ± 0.3 and 4.2 ± 0.3 mmol/l, respectively. Four hours after starting TPN, plasma glucose had risen to a peak of 6.3 ± 0.3 mmol/l (P<0.01); by adjusting the exogenous insulin infusion, plasma glucose was reduced to 5.6 mmol/l within the next 4 h and was clamped at this level until the end of day 1 of TPN (Fig. 2). On the day of surgery, plasma glucose was 4.5 ± 0.3 mmol/l before operation. After surgery (20 h fast), plasma glucose was significantly higher (7.3 ± 0.6 mmol/l, P<0.01) than at the corresponding time before surgery. Starting TPN was followed by a further increase in glycaemia (to a peak of 9.8 ± 0.4 mmol/l), and it was not until 12 h later that the exogenous insulin infusion was able to bring plasma glucose levels down to 5.6 mmol/l, where they were clamped until the end of day 2 of TPN (Fig. 2).

After a 2 h fast, plasma insulin concentrations averaged 72 ± 11 and 63 ± 13 pmol/l on the day of the pre-operative study and day of surgery, respectively. After a 20 h fast, plasma insulin was 64 ± 18 pre-operatively and 73 ± 15 pmol/l post-operatively (not significant). The amount of insulin required to maintain euglycaemia during 24 h of TPN before surgery averaged 1.78 ± 0.29 pmol min⁻¹ kg⁻¹, yielding mean plasma insulin concentrations of 332 ± 108 pmol/l at the end of 24 h of TPN. With TPN after surgery, the exogenous insulin demand averaged 14.14 ± 1.15 pmol min⁻¹ kg⁻¹ during the first 24 h (yielding plasma concentrations of 1187 ± 300 pmol/l at the end of day 1 of TPN) and 8.40 ± 1.65 pmol min⁻¹ kg⁻¹ during the next day (plasma levels of 905 ± 119 pmol/l) (Fig. 2). Thus, insulin requirements during TPN were eight-fold greater after surgery (P<0.001) for the first 24 h, and fell by ~50% (P<0.05) during the next day. With TPN, exogenous glucose was infused at a constant rate of 16.1 ± 0.5 pmol min⁻¹ kg⁻¹ before surgery and 18.1 ± 0.9 pmol min⁻¹ kg⁻¹ after surgery.

The blood levels of several intermediary metabolites are reported in Table 1. It can be appreciated that pre-operatively the progression of the fast (from 12 to 20 h) was marked by an increase in FFA, glycerol and

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Before surgery</th>
<th>After surgery</th>
<th>P (TPN)</th>
<th>P (surgery)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactate (mmol/l)</td>
<td>0.93 ± 0.17</td>
<td>1.27 ± 0.13</td>
<td>&lt;0.05</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Pyruvate (μmol/l)</td>
<td>75 ± 8</td>
<td>91 ± 9</td>
<td>&lt;0.05</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>FFA (μmol/l)</td>
<td>463 ± 78</td>
<td>818 ± 120</td>
<td>&lt;0.01</td>
<td>NS</td>
</tr>
<tr>
<td>Glycerol (μmol/l)</td>
<td>87 ± 11</td>
<td>154 ± 22</td>
<td>NS</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>3-Hydroxybutyrate (μmol/l)</td>
<td>409 ± 146</td>
<td>1356 ± 423</td>
<td>&lt;0.01</td>
<td>NS</td>
</tr>
<tr>
<td>Alanine (μmol/l)</td>
<td>424 ± 34</td>
<td>353 ± 36</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>
Table 2. Plasma lipid concentrations in seven patients in the fasting state and after TPN before and after elective surgery

<table>
<thead>
<tr>
<th></th>
<th>Before surgery</th>
<th>After surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(12 h fast)</td>
<td>(20 h fast)</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>4.5 ± 0.2</td>
<td>3.8 ± 0.1</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>0.75 ± 0.08</td>
<td>0.65 ± 0.05</td>
</tr>
<tr>
<td>Triacylglycerols</td>
<td>1.21 ± 0.1</td>
<td>1.18 ± 0.1</td>
</tr>
</tbody>
</table>

Values are means ± SEM. P values refer to statistical significance for the effect of TPN and surgery, determined by two-way analysis of variance. Abbreviation: NS, not significant.

3-hydroxybutyrate, and a decrease in lactate, pyruvate and alanine. When the separate effects of TPN and surgery were analysed (by two-way analysis of variance), TPN plus insulin was associated with an increase in lactate and pyruvate concentrations and a large decrease in FFA, glycerol and 3-hydroxybutyrate levels. Surgery per se, on the other hand, increased lactate and pyruvate levels further, had no effect on lipid substrates and was associated with a significant decrement in blood alanine concentrations (Table 1).

Surgery per se was found to be associated with a marked rise in circulating cortisol (P<0.01), glucagon (P<0.01) and prolactin (P<0.05) concentrations and in total urinary catecholamine excretion (P<0.01), and with a significant fall in serum T₃ (P<0.01) and testosterone levels (P<0.05). T₄ and TSH concentrations were not altered by either surgery or TPN. On the other hand, TPN itself caused a significant (P<0.05) increase in GH levels and a small decline (P<0.05) in testosterone concentrations. When pre- and post-surgery data were analysed together, serum cortisol concentrations bore a strong direct relation to the exogenous insulin infusion rate (r=0.78, P<0.001) (Fig. 3).

After surgery, circulating triacylglycerol concentrations fell by 30% (from 1.18 ± 0.10 mmol/l after a 20 h fast to 0.91 ± 0.08 mmol/l, P<0.01), whereas TPN did not change them significantly (Table 2). Serum total cholesterol levels declined by 0.2–0.5 mmol/l after 24 h of TPN both before and after surgery. In addition, the surgical stress itself was associated with a 30–40% decrease in serum cholesterol. Because no significant change in HDL-cholesterol occurred, the ratio of HDL-cholesterol to total cholesterol was actually increased during the entire study period.

The pattern of substrate oxidation is shown in Fig. 4. Net carbohydrate oxidation fell by 20% with progressing fast before surgery (P<0.05) and increased by ~90% with TPN plus insulin (to rates of 17.2 ± 1.8 μmol min⁻¹ kg⁻¹, P<0.001). After surgery, net carbohydrate oxidation was 7.9 ± 0.8 μmol min⁻¹ kg⁻¹ (not significant versus the 20 h fast value pre-operatively) and rose to 18.8 ± 1.4 μmol min⁻¹ kg⁻¹ (P<0.001) at 24 h of TPN. Net lipid oxidation rose 35% (P<0.05) between 12 and 20 h of
fast before surgery, and was similarly suppressed by TPN pre- as well as post-operatively ($P<0.01$ for the effect of TPN). After surgery, a small net lipid synthesis was observed in some patients (Fig. 4). Analysis of the pooled pre- and post-surgery data showed glucose oxidation and plasma FFA concentrations to be negatively related to one another ($r=0.72$, $P<0.001$).

Pre-operatively, protein oxidation averaged $3.5\pm 0.6$ pmol min$^{-1}$ kg$^{-1}$ after an overnight fast, and $4.6\pm 0.7$ pmol min$^{-1}$ kg$^{-1}$ throughout 24 h of TPN (not significant). Post-operatively, protein oxidation doubled (to $8.8\pm 3.4$ pmol min$^{-1}$ kg$^{-1}$, $P<0.01$). Subsequently, TPN was without effect on protein oxidation ($7.9\pm 1.8$ and $8.2\pm 1.0$ pmol min$^{-1}$ kg$^{-1}$ at 24 and 48 h, respectively, not significant).

Energy expenditure averaged $4.2\pm 0.3$ kJ/min both at 12 and 20 h of fast pre-operatively, and was not significantly changed by TPN (Fig. 5). Surgery, on the other hand, was associated with a 18% increase in energy expenditure (to $4.7\pm 0.5$ kJ/min, $P<0.01$), which TPN maintained throughout the 2 days of observation.

The substrate balances achieved at the end of 24 h of TPN under conditions of euglycaemic hyperinsulinaemia before and after surgery are compared in Fig. 6. As can be seen, net carbohydrate oxidation matched infused glucose both pre- and post-operatively. Before surgery, net lipid oxidation (i.e. lipid oxidation minus lipid synthesis de novo) was positive, and amounted to 34% of infused lipids; after surgery, net lipid oxidation was not significantly different from zero. Protein oxidation, on the other hand, made up for ~50% of infused amino acids pre-operatively but equalled this infusion post-operatively.

**DISCUSSION**

By selection, the patients in this study were non-obese, middle-aged individuals with normal glucose tolerance, who underwent major abdominal surgery but had no widespread malignancy or other systemic diseases, and who experienced an uneventful post-operative course. Thus, this group of patients constitute a model of uncomplicated surgical stress. In addition, each patient was studied before as well as after the operation, while TPN was fixed in nutrient composition and tailored to individual energy needs. Under these controlled conditions, the following observations were made.

First, a few hours after the end of surgery patients exhibited a modest increase in plasma glucose ($7.3$ versus $4.2$ mmol/l) but not in plasma insulin ($73$ versus $64$ pmol/l) concentrations compared with fasting for the same length of time before surgery. Thus, on the one hand 'normal' circulating insulin levels were unable to maintain euglycaemia, and on the other hand the resulting hyperglycaemia failed to stimulate endogenous insulin release. Descriptively, this is a picture of insulin resistance. Metabolic correlates of this insulin resistance were a modest increment in lactate and pyruvate concentrations (presumably a result of the hyperglycaemia) and an increase in glycerol levels (indicative of accelerated lipolysis). The marked increase in protein oxidation and energy expenditure were the expected hallmarks of surgery-induced hypercatabolism [3]. With regard to the hormonal background, circulating levels of the major counter-regulatory hormones (cortisol, glucagon, prolactin, GH) and urinary output of catecholamines were all increased after surgery [4, 27]. In addition, low serum $T_3$ levels with normal concentrations of $T_4$ and TSH indicated that surgical stress, like other non-thyroidal illnesses [28], may cause a 'euthyroid sick syndrome'. The associated decrease in serum testosterone concentrations was further evidence for a widespread interference of stress with the endocrine system [29]. The surge of counter-regulatory hormones must have acted synergistically to produce insulin resistance [30] and, in the case of catecholamines, also to inhibit glucose-induced insulin release [31].
The glucose clamp during TPN provided a quantification of the insulin resistance. Because the exogenous glucose flux was almost identical before and after operation, the amount of insulin needed to achieve and maintain euglycaemia is a measure of tissue response to the hormone. Thus, the second major, and somewhat surprising, finding was that, even in the absence of septic or other complications, surgery-induced insulin resistance is severe. For comparison with other known states of insulin resistance, one can calculate an M/I ratio (i.e. the ratio of glucose infusion rate to prevailing plasma insulin concentration [17]). Over the last 10 hours of TPN, when steady-state conditions of plasma glucose levels and insulin infusion rates prevailed (Fig. 2), M/I was 48 (nmol of glucose min⁻¹ kg⁻¹ per pmol/l insulin) pre-operatively and 15 such units post-operatively, a 70% reduction compared with the 40% decrease typically seen in diabetes mellitus or obesity [32]. It should be emphasized that the exogenous glucose infusion rate may have underestimated the actual total rate of glucose utilization to the extent that there was ongoing endogenous (hepatic) glucose production. Such a possibility is unlikely in the pre-operative state, in which an insulinemia of ~350 pmol/l (50 m-units/l) sustained for 24 h must suppress glucose production virtually completely [32]. Post-operatively, on the other hand, even much higher insulin levels (1000-1500 pmol/l) may not completely shut down hepatic glucose output if gluconeogenesis, which is less sensitive to insulin inhibition than glycogenolysis [33, 34], is active.

In the present study, gluconeogenesis was not measured directly, and can only be presumed to have been ongoing on the basis of the raised levels of counter-regulatory hormones and the surgery-associated decrease in blood alanine concentrations (Table 1). However, glucose synthesis de novo contributes only some 3.5 μmol min⁻¹ kg⁻¹ to the total glucose output (10-12 μmol min⁻¹ kg⁻¹) of normal fasting man [35], and the high insulin levels maintained in our patients for 24 h after surgery made it unlikely that gluconeogenesis could have added more than 5-6 μmol min⁻¹ kg⁻¹ to the total glucose flux. Even in the latter case, the M/I ratio after surgery would still be only 40% of its pre-surgery value.

Third, by clamping glucose flux we could show that insulin supplementation during TPN can overcome all aspects of the insulin resistance of surgical stress.

(1) Glucose oxidation at the end of 24 h of TPN was similar before and after surgery, and reached near-maximal values (in man glucose oxidation plateaus at 19-22 μmol min⁻¹ kg⁻¹ even with pharmacological doses of insulin [36]). Importantly, total glucose oxidation equaled the infused glucose load both pre- and post-operatively (Fig. 4), indicating that body glycogen deposits were maintained. Incidentally, if there was more gluconeogenesis after than before surgery, this surplus of glucose flux was not allowed to produce hyperglycaemia but was instead oxidized. In this regard, it should be borne in mind that indirect calorimetry measures the net sum of glucose oxidation and gluconeogenesis; when the latter is significant, true glucose oxidation is higher. Therefore, the overall flux of pyruvate oxidation might have been even larger after than before surgery.

(2) Insulin treatment during TPN restrained lipolysis, as judged from circulating FFA and glycerol levels, and blocked ketogenesis, as reflected in blood 3-hydroxybutyrate concentrations, as effectively after as before surgery. The balance between lipid oxidation and lipid synthesis de novo, as estimated by calorimetry, was about even under both circumstances (Fig. 4). Thus, insulin action on lipid metabolism also could be normalized by insulin treatment in our patients. It is of interest that insulin resistance improved considerably (50%) already during the second day of TPN plus insulin in parallel with a decline in plasma cortisol levels (Fig. 3), suggesting that the strong time dependence of stress-induced insulin resistance reflects the time-course of anti-insulin hormonal activity.

(3) Total protein oxidation, which was measured as precisely as possible by accurate urine and gastric juice collection, doubled after surgery, but was very closely replaced by the amino acids in TPN (Fig. 5). Thus, insulin treatment during TPN was able to prevent a negative nitrogen balance. It is likely that a sufficient substrate supply (amino acids) and the strong inhibition of protein degradation by hyperinsulinaemia [37] acted in concert to promote a protein synthetic rate that matched protein loss. In fact, to the extent that gluconeogenesis from alanine contributed to nitrogen excretion, true protein oxidation was even smaller than estimated, and nitrogen was in slight positive balance.

An important feature of the present study design is that caloric supply was adjusted to the individual, measured energy needs (i.e. the resting energy expenditure), but with a rather small (25%) allowance for voluntary muscle activity. Because this adjustment was made both before and after surgery, the stress-induced increase in energy requirement was precisely accounted for. By doing so, TPN did not cause any increase in oxygen consumption, which is undesirable in patients with diminished cardiopulmonary reserve [38]. Furthermore, caloric overfeeding, which may lead to fatty infiltration of the liver and dyslipidaemia [39], was avoided. In our patients, serum triacylglycerols and total cholesterol concentrations both fell after surgery, and net lipid synthesis was negligible (Fig. 4). More than two-thirds of the infused lipid load before surgery, and all of it after surgery, were not oxidized during 24 h of TPN, leading to a positive (post-operative) energy balance of 1.6 MJ (or 25% of actual energy expenditure). Thus, the 25% surplus of calories allowed by design was all channelled to fat deposition (some 50 g/day), presumably in adipose tissue [40].

In conclusion, even uncomplicated surgery causes severe insulin resistance, the effects of which insulin can reverse. With an energy supply only slightly in excess of demand, insulin supplementation preserves body protein and energy stores effectively.

ACKNOWLEDGMENTS

We thank the patients who participated in this study for their generous co-operation, and the personnel of the
Intensive Care Unit for their scrupulous performance. We are indebted to Demetrio Ciociaro and Giovanna Sanna for their excellent technical help.

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