Effect of Laparoscopic Colon Resection on Postoperative Glucose Utilization and Protein Sparing

An Integrated Analysis of Glucose and Protein Metabolism During the Fasted and Fed States Using Stable Isotopes

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Hypothesis: Using a stable isotope method to quantify postoperative changes in glucose and protein metabolism, patients undergoing laparoscopic-assisted colon resection and receiving 4 mg · kg⁻¹ · min⁻¹ of dextrose intravenously will (1) have more pronounced suppression of endogenous glucose production, leading to (2) a greater reduction in whole-body protein breakdown.

Design: Randomized protocol study.

Setting: Tertiary health care center in Montreal, Quebec.

Patients: Twelve patients scheduled for colonic resection were randomly allocated to undergo either laparoscopic (n=6) or open (n=6) surgery.

Interventions: Patients underwent a 6-hour stable isotope infusion study (3 hours fasted and 3 hours fed with dextrose infusion) on postoperative day 2. Whole-body protein breakdown and synthesis, amino acid oxidation, and endogenous glucose production and clearance were measured during the postabsorptive state using L-[1-¹³C]leucine and [6,6-²H₂]glucose. Gas exchange and plasma concentrations of metabolites and hormones were also measured.

Main Outcome Measures: Endogenous glucose production and whole-body protein breakdown during the fasted and fed states.

Results: In the fasted state, laparoscopy did not affect protein and glucose metabolism. Dextrose infusion suppressed endogenous glucose production in both groups, with the greatest extent in the laparoscopic group (P = .01). Higher respiratory quotients (P = .001) in the latter group also indicated increased exogenous glucose oxidation. Neither surgical approach nor nutrition affected aspects of protein metabolism.

Conclusions: Laparoscopy for colon resection facilitates whole-body glucose uptake and utilization and oxidation of exogenous glucose with no protein-sparing effect. The laparoscopic approach modulates gluconeogenesis, although it is not sufficient in the presence of exogenous energy to promote nitrogen retention.

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THERE IS A LARGE AMOUNT OF data demonstrating that certain aspects of the surgical stress response are attenuated by laparoscopic surgery.¹ These aspects include fewer inflammatory responses, decreased pain and pulmonary dysfunction, decreased rate of wound infection, and attenuated postoperative hypoxemia.² The earlier recovery³ after laparoscopic surgery might be explained by the lesser intensity of tissue damage, as assessed by plasma levels of acute-phase response mediators.⁴-⁶

Major abdominal surgery is associated with significant hormonal, inflammatory, and related metabolic changes, resulting in increased concentrations of counter-regulatory hormones that, in turn, stimulate gluconeogenesis, with muscle proteins becoming a source of gluconeogenic precursors. The rationale for providing glucose to surgical patients is based on its nitrogen-sparing properties. Exogenous glucose suppresses gluconeogenesis, thereby decreasing the need to supply gluconeogenic amino acids and redirecting nitrogen for reincorporation into proteins and minimizing the oxidation of amino acids for energy production.⁷

Net balance of body protein can be calculated as the difference between total nitrogen intake and nitrogen loss. Studies that applied isotope tracer methods showed that the principal biochemical mechanisms responsible for enhanced pro-
tein wasting after surgery are increased protein breakdown and amino acid oxidation. In an attempt to control for alterations in patients' nutritional status and to adequately assess the dynamic aspects of glucose metabolism, such as endogenous glucose production, the rate of glucose production can be measured during the postabsorptive and fed states, therefore mimicking a more naturalistic condition.

The present study was designed to test the hypothesis that the suppression of endogenous glucose production and the attainment of protein breakdown by intravenous dextrose infused at a rate of 4 mg·kg⁻¹·min⁻¹ would be more pronounced in patients undergoing laparoscopy than in those undergoing laparotomy colon resection. To characterize glucose and protein metabolism during the early postoperative period, a stable isotope method was applied, and the changes in glucose production, glucose clearance, whole-body protein breakdown, protein synthesis, and amino acid oxidation were assessed during the fasted and fed states.

**METHODS**

**PATIENTS**

The study was approved by the ethics committee of the McGill University Health Centre. Twelve patients scheduled for elective colorectal surgery were admitted to the study, and written informed consent was obtained from all participants. Patients were randomly allocated to either the laparoscopic group or the open group, and randomization was performed using sealed envelopes and computer-generated random allocation. None of the patients had any major cardiac, hepatic, or metabolic disorders or received any medications known to affect metabolism, such as corticosteroids or β-blockers. None of the studied patients had experienced recent weight loss or had a plasma albumin concentration of less than 3.5 g/dL.

All patients received general anesthesia using thiopental sodium, fentanyl citrate, rocuronium bromide, nitrous oxide in 0.9% isotonic sodium chloride solution was infused at a rate of 6 mL·kg⁻¹·h⁻¹, followed by Ringer lactate at a rate of 100 mL/h during the first 48 hours. Patient-controlled analgesia with intravenous morphine sulfate was regulated so that the increment dose of drug was 1 to 2 mg, with a lockout of 7 minutes and a dose duration of 30 seconds. Postoperative pain intensity was measured at rest and on walking using a 10-cm visual analog scale score at rest of less than 4.

All patients were operated on by a surgical team trained in laparoscopic and open colorectal surgery. Regarding the laparoscopic technique, pneumoperitoneoscopically obtained after placing a 12-mm blunt-tipped Hasson cannula under direct vision into the peritoneal cavity through a small, vertical, infraumbilical incision, and it was maintained with carbon dioxide to a pressure of 12 mm Hg. This incision was later extended to 4 to 5 cm to deliver the colon for resection and reanastomosis. Three additional 5-mm trocars were placed under laparoscopic vision. For right colectomy, the colon was completely mobilized laparoscopically. The mesentry was divided after delivering the colon into the wound. The resection and anastomosis were performed extracorporeally. For left colon resection, the colon was mobilized laparoscopically. Vessels were divided intracorporeally. The colon was divided intracorporeally and delivered through the small incision. The anastomosis was completed intracorporeally using the double-stapled, end-to-end anastomotic, circular stapling technique. In the open technique, a lower midline incision was used to perform the resections. Routine drainage was not used.

All patients were studied on the second postoperative day beginning at 8 AM. This protocol study included 2 periods: a fasted state of 3 hours followed by a 3-hour fed state during which patients received a solution of crystallized beet sugar (10% Dextrose Anhydrous; Avebe, Foxhol, Holland) infused at 4 mg/kg per minute. The beet dextrose solution was chosen because of its low carbon 13 content and therefore its lack of perturbation of carbon dioxide 13 (13CO₂) enrichment in expired air.

**INTERVENTIONS**

The kinetics of whole-body leucine and glucose metabolism, that is, the rates of appearance (Ra) of leucine and glucose, and leucine oxidation were measured using an isotope dilution technique and the stable isotope tracers NaH13CO₃, L-[1-13C]leucine, and [6,6-2H₂]glucose (Cambridge Isotope Laboratories, Cambridge, Mass).

On the morning of the study, a superficial vein in the dorsum of the hand was cannulated, and the catheter was kept patent with heparinized saline and was used to withdraw the blood samples. A second catheter was placed in a vein of the contralateral arm to provide access for the infusion of [6,6-2H₂]glucose and L-[1-13C]leucine. After collecting blood and expired-air samples to determine baseline enrichments, priming doses of NaH13CO₃ (1 µmol/kg), L-[1-13C]leucine (4 µmol/kg), and [6,6-2H₂]glucose (22 µmol/kg) were administered, followed immediately by continuous infusion of L-[1-13C]leucine, 0.06 µmol·kg⁻¹·min⁻¹, and [6,6-2H₂]glucose, 0.22 µmol·kg⁻¹·min⁻¹. This continuous infusion was constant throughout the study. Toward the end of each 3-hour study period, blood and expired-air samples were collected at 10-minute intervals to determine isotopic enrichments. Blood samples for the analysis of plasma concentrations of metabolic substrates (glucose and lactate) and hormones (insulin, glucagon, and cortisol) were collected only once during each study, at 130 and 330 minutes. Each blood sample was immediately transferred to a heparinized tube and centrifuged at 4°C (at 3000 rpm for 15 minutes). The obtained supernatant was stored at −70°C until analysis. Expired air samples were collected in a 2-L latex bag and then transferred immediately to 10-mL tubes (BD Vacutainer; Becton Dickinson, Franklin Lakes, NJ) for 13CO₂ isotope enrichment analysis.

Whole-body oxygen consumption and carbon dioxide production were measured using indirect calorimetry (Vmax 29N; SensorMedics, Yorba Linda, Calif) in the last hour of the fasted and fed periods. Measurements were performed for 20 minutes on each occasion, and mean values of oxygen consumption, carbon dioxide production, and respiratory quotient (RQ) were calculated, with a coefficient of variation of less than 10%.

Plasma glucose was derivatized to its penta-acetate compound, and the [6,6-2H₂]glucose enrichment was measured using gas chromatography–mass spectrometry and electron-impact ionization. Plasma α-[1-13C]ketosaccharate enrichment was determined using electron-impact selected-ion monitoring gas chromatography–mass spectrometry and the method previously described elsewhere. Expired 13CO₂ enrichment for the measurement of leucine oxidation was determined using isotope ratio mass spectrometry (AP2, 003; Analytical Precision, Manchester, England).

Plasma glucose levels were measured using a glucose analyzer (model GM7; Analox Instruments Ltd UK, London, En-
The results of the present study indicate that the administration of dextrose suppressed endogenous glucose production in both groups, with a significantly increased effect in the laparoscopic group, implying greater whole-body
glucose uptake compared with the open group. No significant effects of laparoscopy and dextrose administration on protein breakdown, amino acid oxidation, and protein synthesis were observed. Furthermore, postoperative protein breakdown and leucine oxidation in the fasted state were similar in both groups, which confirms that catabolism was not attenuated by using the endoscopic approach.

Laparoscopic-assisted colon resection could have the potential to improve postoperative recovery because it has been shown in several studies to cause less postoperative pain as a result of using a smaller incision, to accelerate bowel motility, and to allow rapid mobilization and shorter hospitalization, with earlier return to work.

The nitrogen-sparing effect of glucose has been demonstrated during the postoperative period, and it has been primarily ascribed to a decrease in urea production, an indirect variable of protein metabolism. A 3-hour infusion of dextrose at 4 mg/kg per minute, as used in the present study, suppressed glucose production in both groups but did not affect whole-body protein breakdown, as reflected by the unchanged leucine R and amino acid oxidation. This is in contrast with findings from a previous study on open colon resection under epidural anesthesia and analgesia in which the postoperative infusion of dextrose was associated with a significant decrease in amino acid oxidation. The difference in the findings between the present laparoscopic study and the previous study might be explained by the delayed catabolic effect of the epidural throughout the postoperative period, whereas the laparoscopic intervention was limited only at the intraoperative time.

Patients in the present study fasted for approximately 36 hours before surgery and received a minimal amount of glucose on the first postoperative day. Semistarvation is responsible for the progressive decrease in nitrogen excretion, followed by a decrease in the release of amino acids from the muscle and a decrease in whole-body glucose production. A correlation between leucine R and glucose production was observed in the fasted state, implying the availability of gluconeogenic amino acids liberated from the muscle for de novo gluconeogenesis in the liver. With such a long period of starvation accompanied by surgical stress, we assume that gly-

<p>| Table 2. Plasma Concentrations of Circulating Metabolites and Hormones in the Fasted and Fed States* |
|---------------------------------------------------|-------------------|-------------------|-------------------|-------------------|</p>
<table>
<thead>
<tr>
<th></th>
<th>Open Group</th>
<th>Laparoscopic Group</th>
<th></th>
<th>P Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose, mg/dL</td>
<td>Fasted</td>
<td>Fed</td>
<td>Fasted</td>
<td>Fed</td>
</tr>
<tr>
<td></td>
<td>92 ± 7</td>
<td>171 ± 32</td>
<td>94 ± 9</td>
<td>171 ± 18</td>
</tr>
<tr>
<td>Lactate, mg/dL</td>
<td>8 ± 3</td>
<td>8 ± 2</td>
<td>9 ± 2</td>
<td>10 ± 3</td>
</tr>
<tr>
<td>Cortisol, µg/dL</td>
<td>13 ± 3</td>
<td>11 ± 3</td>
<td>14 ± 4</td>
<td>10 ± 1</td>
</tr>
<tr>
<td>Insulin, µIU/mL</td>
<td>12 ± 4</td>
<td>50 ± 24</td>
<td>9 ± 4</td>
<td>46 ± 30</td>
</tr>
<tr>
<td>Glucagon, pg/mL</td>
<td>87 ± 31</td>
<td>66 ± 56</td>
<td>84 ± 38</td>
<td>28 ± 7</td>
</tr>
</tbody>
</table>

SI conversion factors: To convert cortisol to nanomoles per liter, multiply by 27.59; glucose to millimoles per liter, multiply by 0.0555; insulin to picomoles per liter, multiply by 0.0111.

*Values are presented as mean ± SD.
†Probability that the values are affected by parenteral alimentation.
‡Probability that the values are affected by the type of surgery regardless of whether nutrition was administered.
§Probability that the effect of nutrition is greater in 1 distinct surgery group.

The administration of dextrose for 3 hours statistically significantly inhibited endogenous glucose production in both groups, with the greatest effect in the laparoscopic group. In addition, statistically significantly higher RQ values were reported, indicating increased glucose oxidation. Large doses of exogenous glucose administered to surgical patients beyond the amount necessary have been reported to inhibit gluconeogenesis, resulting in an increase in glucose oxidation, thereby minimizing the amount of amino acids oxidized for energy production. Although we did not measure glucose oxidation, the calorimetric data, showing high RQ values after dextrose infusion, provided indirect evidence that glucose oxidation was increased in the laparoscopic group. On the basis of the present results, it is therefore possible to propose that the intravenous infusion of sufficient exogenous glucose after laparoscopic surgery minimized the need for amino acid oxidation for energy supply but had no effect in sparing body protein. In view of the limited effectiveness of supplementing dextrose alone in patients undergoing laparoscopic colon resection to correct protein catabolism, future studies will need to assess the use of amino acids besides energy to suppress protein catabolism and facilitate protein synthesis.

The present study protocol was not designed to elucidate the factors responsible for greater suppression of endogenous glucose production in the laparoscopic group. Nevertheless, it is legitimate to speculate on the underlying metabolic mechanisms. Laparoscopic surgery has been shown to mount a perioperative endocrine and metabolic response (elevated levels of plasma cortisol, corticotropin, glucagon, and catecholamines and hyperglycemia) similar to the one initiated by open surgery. This finding could be mainly related to the establishment of pneumoperitoneum and the direct stimulation of intraabdominal visceral and diaphragmatic structures. The extent of this intense endocrine and metabolic stimulation decreases during the first 8 postoperative hours, whereas it continues for 24 hours after open colectomy. In contrast, the inflammatory response, as assessed by measuring circulating serum levels of interleukin 1 and inter-
leukin 6 is reported to be significantly less in the laparoscopic group. Serum levels of interleukin 6 have been shown to be proportional to the severity of surgical trauma and the extent of tissue damage, with peak effect 6 hours after surgery. Interleukin 6 is a primary stimulus for the hepatic synthesis of acute-phase proteins, protein catabolism, stimulation of gluconeogenesis, increase in lipolysis, and fluid retention. Therefore, it is possible that the considerable endocrine changes induced during laparoscopy initiated perioperative changes in glucose and protein metabolism, as seen in the present study. The attenuated inflammatory response and the production of cytokines resulting from less tissue damage would attenuate the overall imposed metabolic response, resulting in better oxidative utilization of glucose, although insufficient to induce protein-sparing capacity in the laparoscopic group.

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REFERENCES