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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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 attenuation 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 ß-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 oxygen, and isoflurane. During surgery, the patients were covered with a warming blanket to maintain normothermia, and 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 incremental 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 (0 indicates no pain and 10 indicates the worst pain imaginable). The delivery of morphine was adjusted to obtain a 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, pneumoperitoneum was 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 mesentery 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, 4 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 150 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 pentiaacetate compound, and the [6,6-2H2]glucose enrichment was measured using gas chromatography–mass spectrometry and electron-impact ionization. Plasma α-[1-13C]ketosiacaproate 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-
**Table 1. Kinetic Values of Leucine and Glucose Metabolism in the Fasted and Fed States**

| Table 1. Kinetic Values of Leucine and Glucose Metabolism in the Fasted and Fed States

<table>
<thead>
<tr>
<th></th>
<th>Open Group</th>
<th>Laparoscopic Group</th>
<th>P Value</th>
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<tbody>
<tr>
<td></td>
<td>Fasted</td>
<td>Fed</td>
<td>Fasted</td>
</tr>
<tr>
<td>Leucine Rₐ, µmol · kg⁻¹ · h⁻¹</td>
<td>123±24</td>
<td>118±29</td>
<td>123±19</td>
</tr>
<tr>
<td>Leucine oxidation, µmol · kg⁻¹ · h⁻¹</td>
<td>18±4</td>
<td>20±4</td>
<td>21±6</td>
</tr>
<tr>
<td>Protein synthesis, µmol · kg⁻¹ · h⁻¹</td>
<td>105±24</td>
<td>96±26</td>
<td>102±19</td>
</tr>
<tr>
<td>Glucose Rₐ, µmol · kg⁻¹ · min⁻¹</td>
<td>11.2±1.2</td>
<td>23.3±1.7</td>
<td>12.0±2.7</td>
</tr>
<tr>
<td>Endogenous glucose Rₘ, µmol · kg⁻¹ · min⁻¹</td>
<td>11.2±1.2</td>
<td>1.4±2.6</td>
<td>12.0±2.7</td>
</tr>
<tr>
<td>Glucose clearance, mL · kg⁻¹ · min⁻¹</td>
<td>2.2±0.2</td>
<td>2.5±0.6</td>
<td>2.3±0.3</td>
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**Abbreviation:** Rₐ, rate of appearance (endogenous glucose Rₐ was calculated by subtracting the rates of exogenous glucose infusion from the total glucose Rₐ).

*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.

Statistical analysis was performed using a 2-way multivariate analysis of variance, with 1 within-patient factor (effect of nutrition) and 1 between-patient factor (effect of the surgical technique). Assuming that the standard deviation of the within-patient factor is 3.0 and of the between-patient factor is 1.33, having 6 patients per group provides 84% power to detect an effect size of 0.66 for the within-patient factor (when the standard deviation of effects is approximately 3) using an F test with a type I error of .05. A comparable power is achieved for the interaction of effects of nutrition and type of surgery (82%) to detect an effect size of 0.66. However, the number of patients studied provided sufficient power (34%) to detect an effect of the surgery alone that was assumed to be low (effect size of 0.5 with a standard deviation of the effects of 1.33). Data are given as mean ± SD.

**RESULTS**

There were no differences in the open group vs the laparoscopic group regarding sex, age (59±17 years vs 69±10 years), body weight (67±12 kg vs 68±7 kg), height (171±10 cm vs 168±7 cm), American Society of Anesthesiologists II score (6 vs 6), and type of surgery. Preoperative fasting time, duration of surgery, and blood loss were also similar in both groups, and no patients received a blood transfusion. The visual analog scale score at rest was similar in the open group vs the laparoscopic group on the first day (1.5±0.9 vs 1.7±1.6) and at the beginning of the study on the second postoperative day (1.6±0.6 vs 1.3±1.4). On the first postoperative day, patients in both groups could sit in a chair, but none could walk.

During the study, plateaus in the enrichments of plasma α-[1-13C]ketosarcoproate, [6,6-2H₂]glucose, and expired 13CO₂ were achieved in the fasted and fed phases (coefficient of variation <4%) in both groups, permitting use of the steady-state equation. There were no significant effects of either type of surgery or nutrition on any aspect of protein metabolism (Table 1). Exogenous dextrose infusion suppressed endogenous glucose Rₐ to a similar extent in both groups (P = .01), although there was significantly greater suppression in the laparoscopic group (P = .01). Neither dextrose infusion nor laparoscopy affected glucose clearance.

As expected, dextrose infusion increased plasma glucose and insulin concentrations and decreased plasma glucagon levels in both groups (Table 2). No changes were observed in plasma lactate and cortisol levels during the fed state in either group. Oxygen consumption, carbon dioxide production, and RQ values were similar in both groups during the fasted state. With dextrose infusion, the RQ values increased in both groups (P = .02), but to a greater extent in the laparoscopic group (P = .001). In contrast, there were no changes in oxygen consumption and carbon dioxide production as a result of either surgery or dextrose infusion.

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.3

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.12 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 R3, amino acid oxidation. This is in contrast with findings from a previous study13 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 study13 with epidural analgesia might be explained by the protracted anticonvulsant 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. Semi-starvation 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 R3 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.7 With such a long period of starvation accompanied by surgical stress, we assume that glycogen stores would be easily depleted, making gluconeogenesis the major component of endogenous glucose production during the postoperative period.

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 reported7 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.14

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.15 This finding could be mainly related to the establishment of pneumoperitoneum and the direct stimulation of intra-abdominal viscera 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-

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Table 2. Plasma Concentrations of Circulating Metabolites and Hormones in the Fasted and Fed States*

<table>
<thead>
<tr>
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<tbody>
<tr>
<td></td>
<td>Fasted</td>
<td>Fed</td>
<td>Fasted</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>92 ± 7</td>
<td>171 ± 32</td>
<td>94 ± 9</td>
</tr>
<tr>
<td>Lactate, mg/dL</td>
<td>8 ± 3</td>
<td>8 ± 2</td>
<td>9 ± 2</td>
</tr>
<tr>
<td>Cortisol, µg/dL</td>
<td>13 ± 3</td>
<td>11 ± 3</td>
<td>14 ± 4</td>
</tr>
<tr>
<td>Insulin, µIU/mL</td>
<td>12 ± 4</td>
<td>50 ± 24</td>
<td>9 ± 4</td>
</tr>
<tr>
<td>Glucagon, pg/mL</td>
<td>87 ± 31</td>
<td>66 ± 56</td>
<td>84 ± 38</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 0.111.

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†Probability that the values are affected by parenteral alimentation.
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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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Previous Presentation: This study was presented in part at the Annual Meeting of the Canadian Anesthesiologists’ Society; June 13, 2003; Ottawa, Ontario.

REFERENCES