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Laparoscopic Cholecystectomy Does Not Prevent the Postoperative Protein Catabolic Response in Muscle

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Objective

The authors determined the effect of laparoscopic cholecystectomy on protein synthesis in skeletal muscle. In addition to a decrease in muscle protein synthesis, after open cholecystectomy, the authors previously demonstrated a decrease in insulin sensitivity. This study on patients undergoing laparoscopic and open surgery, therefore, included simultaneous measurements of protein synthesis and insulin sensitivity.

Summary Background Data

Laparoscopy has become a routine technique for several operations because of postoperative benefits that allow rapid recovery. However, its effect on postoperative protein catabolism has not been characterized. Conventional laparotomy induces a drop in muscle protein synthesis, whereas degradation is unaffected.

Methods

Patients were randomized to laparoscopic or open cholecystectomy, and the rate of protein synthesis in skeletal muscle was determined 24 hours postoperatively by the flooding technique using L-($^2H_5$)phenylalanine, during a hyperinsulinemic normoglycemic clamp to assess insulin sensitivity.

Results

The protein synthesis rate decreased by 28% (1.77 ± 0.11%/day *vs.* 1.26 ± 0.08%/day, $p < 0.01$) in the laparoscopic group and by 20% (1.97 ± 0.15%/day *vs.* 1.57 ± 0.15%/day , $p < 0.01$) in the open cholecystectomy group. In contrast, the fall in insulin sensitivity after surgery was lower with laparoscopic (22 ± 2%) compared with open surgery (49 ± 5%).

Conclusions

Laparoscopic cholecystectomy did not avoid a substantial decline in muscle protein synthesis, despite improved insulin sensitivity. The change in the two parameters occurred independently, indicating different mechanisms controlling insulin sensitivity and muscle protein synthesis.

The laparoscopic technique is rapidly advancing in surgery, primarily because of its benefits in patient recovery. Compared with the open procedure, the patients have a shorter hospital stay and a quicker return to normal activities, including work.[1] Laparoscopic cholecystectomy has, therefore, become a routine procedure in many hospitals.[2] The reasons for the improved well-being after laparoscopic surgery are not fully understood, and because of the rapid change in routines with the introduction of the technique, it is becoming increasingly more difficult to perform randomized studies comparing this technique with conventional surgery.

One of the benefits from the laparoscopic technique may be related to a reduced metabolic change in response to surgical intervention, as compared with conventional surgery. Thus, the surgical trauma from conventional surgery induces muscle protein catabolism and negative nitrogen balance.[3] This is mainly because of the loss of amino acids from muscle proteins, which are transported from the periphery to the splanchnic area for oxidation, gluconeogenesis, ureagenesis, and protein synthesis.[4,5] This efflux of amino acids from muscle is enabled by an imbalance between the synthesis and degradation of muscle proteins. Surgery of moderate severity decreases the synthesis of muscle proteins, whereas degradation is less affected, as measured by the efflux of 3-methylhistidine, resulting in a net protein loss.[6–8]

Medium-size surgery, such as elective open cholecystectomy, induces a 30% decrease in muscle protein synthesis rate immediately after the operation, and a 50% decrease on the third postoperative day, regardless of whether total parenteral nutrition is given or not.[9,10] By contrast, minor surgery of the breast does not affect muscle protein synthesis.[11] However, the protein metabolic response to laparoscopic surgery has not been well characterized.

The aim of this study was to determine the effect of laparoscopic cholecystectomy on protein synthesis in skeletal muscle. However, we previously have demonstrated a decrease in insulin sensitivity after open cholecystectomy,[12] in addition to the decrease in muscle protein synthesis. Therefore, the present study on patients undergoing laparoscopic and open surgery included simultaneous measurements of protein synthesis and insulin sensitivity.

Table 1. COMPARISON OF PATIENT GROUPS

	Open Cholecystectomy	Laparoscopic Cholecystectomy
Female/male	4/2	4/2
Age (yrs)	38 ± 6	38 ± 3
Weight (kg)	86 ± 7	78 ± 6
Height (cm)	168 ± 5	171 ± 4
Intraoperative blood loss (mL)	105 ± 12	0
Operating time (min)	79 ± 8	87 ± 11

Data are expressed as mean ± SEM.

PATIENTS AND METHODS

Materials

Deuterium-labelled phenylalanine (L-[ring-$^2H_5$]phenylalanine), 99 atom percent (Tracer Technologies, Somerville, MA), was dissolved in sterile water together with unlabelled phenylalanine (Ajinomoto Company, Tokyo, Japan) to a concentration of 20 g/L and an enrichment of 7.5 or 15 atoms percent excess (APE). The solutions were prepared, heat-sterilized, and stored in sterile containers. Isomeric purity of the labelled amino acid was confirmed by gas chromatography on a 50-m WCOT-fused silica column, initial dose 0.22 mm, coated with an optically-active liquid phase XE-60S-Val-x-Pea (Chromapak UK Ltd, London, United Kingdom).

Subjects and Experimental Protocol

Twelve metabolically healthy patients who were randomized to undergo either laparoscopic (n = 6) or open (n = 6) cholecystectomy participated in the study, and their characteristics are given in Table 1. Within 5 days before the operation, the rate of muscle protein synthesis was determined in the postabsorptive state. Simultaneously, hyperinsulinemic normoglycemic glucose clamps were performed to assess insulin sensitivity. On the day of the operation, the patients received a subcutaneous injection of cetobemidon hydrochloride (Ketogan, Lundbeck, Copenhagen, Denmark), and all the operations were started before 10.30 A.M. Patients in both groups were given an induction with thiopental sodium (Penthotal Natrium, Abbot Laboratories, Sweden) and suxamethonium (Celocurin-klorid, Kabi Pharmacia, Stockholm, Sweden), followed by anesthesia with isoflurane (1–3.5%, Forene, Abbot Laboratories, North

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Chicago, IL) and a 30/70% mixture of oxygen/nitrous oxide.

The open cholecystectomy was performed through a right subcostal incision, and perioperative cholangiography was normal in all patients. The laparoscopic cholecystectomy was performed by using 4 trocars—two 5-mm trocars in the right side of the abdomen and two 10-mm trocars in the midline position. The intraperitoneal pressure was 10 to 13 mm Hg.

The patients undergoing an open cholecystectomy received an intercostal blockade of 10 mL of prilocaine (Citanest, Astra, Sweden, 10 mg/mL) postoperatively. On request, all the patients received 1 mL cetobemidon hydrochloride (Ketogan, Lundbeck, Copenhagen, Denmark) subcutaneously for postoperative pain relief. Perioperatively, the patients received 2.000 to 3.000 mL glucose 25 mg/mL (Rehydrex, Kabi Pharmacia, Stockholm, Sweden), and the intravenous infusion was withdrawn at midnight before the postoperative measurement. On the first postoperative morning, the determination of muscle protein synthesis was repeated during a hyperinsulinemic normoglycemic clamp, as before.

The hyperinsulinemic normoglycemic clamp was performed using a Biostator (Life Science Instruments, Miles Laboratories, Elkhart, IN), as described previously.[12,13] At this insulin infusion rate, the glucose infusion rate (M-value) reflects the sensitivity to insulin in extrahepatic tissues, even in the postoperative situation (Nygren et al., unpublished observations, 1993, employing isotope techniques). After approximately 60 minutes, a steady state was attained and the clamp was maintained for another 60 minutes. During this steady state condition, the rate of glucose infusion was taken as a measure of the sensitivity for insulin; M-value (mg glucose/kg body weight/minute). Thereafter, the measurement of muscle protein synthesis rate was made during a 90-minute period. The flooding dose technique involved an intravenous injection of phenylalanine (45 mg/kg, 2%, 7.5 APE—first determination and 15 APE–second determination) given in an antecubital vein over 10 minutes. Venous blood samples were taken from the opposite arm before (time 0), and at 5, 10, 15, 30, 60, and 90 minutes after the phenylalanine injection for determination of the isotope enrichment of phenylalanine in plasma and at time 0 for analysis of the glucose and hormone concentrations in serum. Ninety minutes after the start of the isotope injection, biopsies were done on the muscle to measure of the enrichment of L-($^2H_5$)phenylalanine in muscle proteins. Before the second measurement of the rate of muscle protein synthesis, a muscle biopsy was taken for the determination of the basal isotope enrichment.

The nature, purposes, and potential risks of the experiments procedures were explained to the subjects, who all gave their consent. The research protocol was approved by the Ethics Committee of the Karolinska Hospital, Stockholm, Sweden.

Muscle Biopsy Technique

Percutaneous muscle biopsies of approximately 100 mg wet weight were taken from the lateral portion of the quadriceps femoris muscle using the Bergström needle.[14] They were obtained under local anesthesia of the skin 15 to 20 cm above the knee. The biopsy material was dissected carefully to remove visible fat and connective tissues, frozen in liquid nitrogen within 60 seconds, and stored at −80 C.

Measurement of Protein Synthesis

The measurement of the rate of muscle protein synthesis in man with the flooding technique has been described previously.[15,16] The determination of L-($^2H_5$)phenylalanine enrichment in both plasma samples and in samples of hydrolyzed protein was made by gas chromatography-mass spectrometry under electron impact-selective ion monitoring on a VG 12-253 quadruple mass spectrometer (VG Biotech, Altrincham, United Kingdom), as described previously.[16,17]

Calculations of Protein Synthesis Rate

The rate of muscle protein synthesis was calculated from the formula described previously: $k_s = (P_{(t)} - P_{(o)}) \times 100/A$.[15] k_s is the fractional synthesis rate of protein (% per day). $P_{(o)}$ and $P_{(t)}$ are the enrichments of phenylalanine in the tissue protein at the beginning and end of the incorporation period (APE) and A is the area under the curve for plasma free phenylalanine enrichment (APE × time in days). The calculation of area was made by assuming a linear change between successive time points.[15]

Blood Analyses

Serum glucose was analyzed by a glucose dehydrogenase method.[18] Radioimmunoassays were used for determination of serum insulin[19] and glucagon.[20]

Statistical Analysis

Data are presented as means and SEM. Comparison of mean values was performed by paired or unpaired Student's t test.[21]

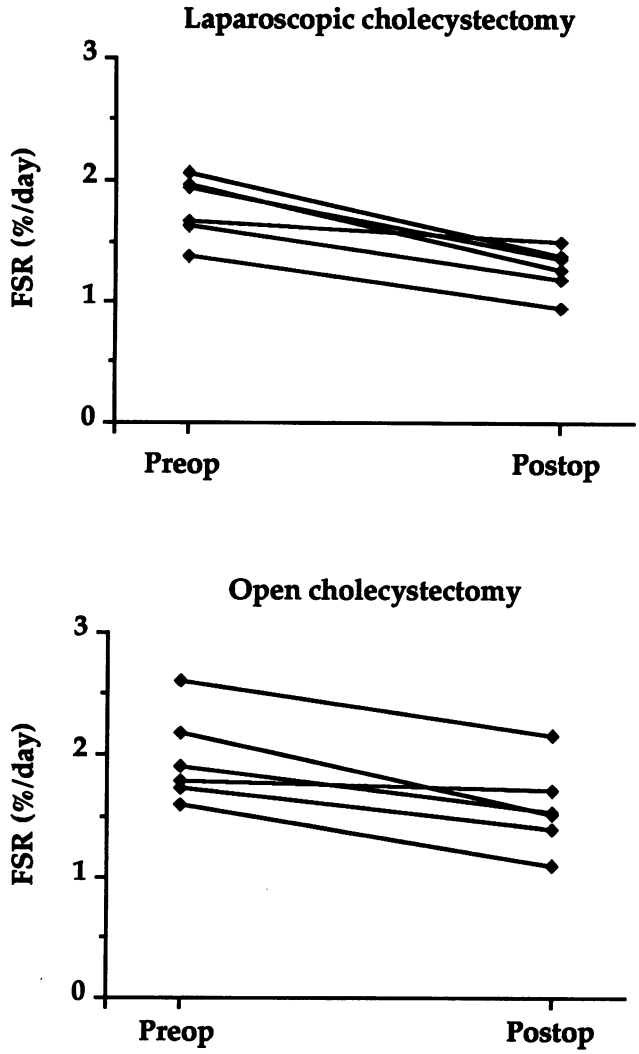

Figure 1. Muscle protein synthesis rate in metabolically healthy patients undergoing laparoscopic (n = 6) or open (n = 6) cholecystectomy. The data are given as fractional rates of synthesis (FSR as %/day).

RESULTS

Rate of Muscle Protein Synthesis

On the day after surgery, muscle protein synthesis decreased by 20 ± 4% (1.97 ± 0.15%/day to 1.57 ± 0.15%/day, $p < 0.01$) in the open cholecystectomy group and by 28 ± 4% in the laparoscopic cholecystectomy group (1.77 ± 0.11%/day to 1.26 ± 0.08%/day, $p < 0.01$) compared with preoperative values (Fig. 1). There was no statistically significant difference between the changes seen in the two groups, concerning the pre- and postoperative values or the change seen in synthesis rate. The rate of protein synthesis varied between individuals, with a range preoperatively of 100%, from 1.36%/day to 2.61%/day. However, pre- and postoperative measurements correlated well and the response to surgical trauma showed a less pronounced scatter, suggesting that the twofold variability reflects the interindividual variation.

Insulin Sensitivity

Table 2 shows the basal concentration of glucose and insulin in plasma. Basal values did not differ between the groups preoperatively, whereas the glucose concentration was increased postoperatively in the open cholecystectomy group. The preoperative glucagon concentration was 70 ± 17 pg/mL in the open cholecystectomy group and 52 ± 8 pg/mL in group undergoing laparoscopy. However, postoperatively, an increase in the glucagon concentration was observed in the open cholecystectomy group but not in the laparoscopic group (101 ± 16 pg/mL and 54 ± 7 pg/mL [$p < 0.05$], respectively). Table 2 also shows the concentrations of glucose and insulin during the clamp and the calculated values for insulin sensitivity (M), expressed as mg glucose/kg/minute, necessary to maintain euglycemia. Although there was no demonstrable change in insulin concentration between the pre- and postoperative values for either patient group, the concentrations of insulin were different between the groups. However, this difference would have minimal effect on the comparison of insulin sensitivity between laparoscopic and open surgery because data for each group have been expressed as changes in M-values, on a paired basis, rather than as absolute values. The laparoscopic method resulted in a significantly smaller decline in insulin sensitivity than open surgery (22 ± 2% *vs.* 49 ± 5%; $p < 0.05$). The change observed in insulin sensitivity was unrelated to the simultaneously recorded alterations in fractional protein synthesis rate.

DISCUSSION

In this study, the protein synthesis rate in skeletal muscle was measured before and 24 hours after open and laparoscopic cholecystectomy. The results revealed that laparoscopic cholecystectomy, in the early postoperative period, induced a decrease in muscle protein synthesis of a similar magnitude to that seen after conventional open cholecystectomy. Thus, the observation of a faster clinical recovery after laparoscopic surgery occurs despite a 28% decrease in muscle protein synthesis. This indicates that a significant reduction in muscle protein synthesis rate does not necessarily have a marked impact on the overall well-being after surgery because the patients undergoing laparoscopic surgery all were back to work within a week after the operation.

It has long been a clinical observation that more traumatic surgery generally leads to a longer period of recovery. Moreover, an increasingly greater response with increasing severity of surgery has been established for pa-

Table 2. SERUM CONCENTRATIONS OF INSULIN, GLUCOSE, AND THE M-VALUES IN PATIENTS UNDERGOING OPEN OR LAPAROSCOPIC CHOLECYSTECTOMY BEFORE AND DURING THE HYPERINSULINEMIC EUGLYCEMIC CLAMP

	Glucose (mmol/L)		Insulin (μ U/mL)		Insulin Sensitivity	
	Basal	Clamp	Basal	Clamp	M-value (mg/kg/min)	M %
Open cholecystectomy (n = 6)						
Preoperative	5.2 ± 0.2	4.8 ± 0.1	23 ± 2	70 ± 4	3.3 ± 0.2	100
Postoperative	6.1 ± 0.2*	4.9 ± 0.1	26 ± 3	77 ± 6	1.6 ± 0.1*	51 ± 5*
Laparoscopic cholecystectomy (n = 6)						
Preoperative	5.0 ± 0.2	4.8 ± 0.1	14 ± 2	60 ± 3†	4.0 ± 0.7	100
Postoperative	5.2 ± 0.2	4.9 ± 0.1	14 ± 1	56 ± 2†‡	2.9 ± 0.5*‡	77 ± 8*†

Data are expressed as mean and SEM.
* $p < 0.05$, significantly different from the preoperative value.
† $p < 0.05$.
‡ $p < 0.01$, significantly different from the same time point in the open cholecystectomy group.

rameters such as impaired glucose tolerance and insulin resistance, as well as nitrogen losses.[22–24] This suggests that the alteration in body metabolism to a state of catabolism is one of the key factors influencing recovery after surgical trauma. However, this relationship does not appear to hold time with laparoscopic surgery. Other studies of laparoscopic cholecystectomy have shown that the nitrogen balance is as negative as after open cholecystectomy.[25] Furthermore, no differences have been seen in the effect of surgery on the concentrations of glutamine, total ribosomes, and polyribosomes between laparoscopic cholecystectomy and open cholecystectomy on the second postoperative day.[25]

Whereas protein synthesis was inhibited similarly by open and laparoscopic surgery, the reduction in the sensitivity of glucose uptake to insulin was much attenuated by the laparoscopic procedure. In fact, the alterations in these two parameters occurred without any relation. This suggests that whatever mediators and mechanisms are responsible for the changes observed, the pattern of alterations in insulin sensitivity and muscle protein synthesis differ. The development in insulin resistance after surgery may be related to the degree of tissue damage induced. Such a notion is supported by the finding of greater insulin resistance with greater magnitude of surgery.[24] In contrast, the change in protein synthesis rate may be mediated by factors associated with the intra-abdominal procedure per se. Thus, it may be speculated that the change in protein synthesis rate in muscle after surgery may be more of an "on-off" phenomenon, perhaps triggered by the abdominal manipulation in itself. This suggestion is supported by the fact that extra-abdominal (breast) surgery does not cause any change in muscle protein synthesis rate.[11] It also may be that the insufflation of carbon dioxide and the tension produced in the peritoneum and abdominal wall may trigger the protein synthesis responses found presently. The validity of this hypothesis may become apparent in the near future because new devices are being investigated in which insufflation of gases is avoided and the abdominal wall is lifted by retractors.

Although the clinical advantages of laparoscopic surgery have quickly become evident, the underlying mechanisms for these benefits still remain unclear. The release of stress hormones is considered to be partially responsible for the protein catabolism observed after surgery.[26] Accordingly, a stress hormone infusion (adrenaline, glucagon, cortisol) given for 6 hours to mimic the surgical trauma causes changes in glutamine, ribosomes, and protein synthesis in skeletal muscle after 24 hours that are comparable to those seen after cholecystectomy performed via laparotomy or laparoscopy.[25,27–29] Several investigators have studied if the laparoscopic technique is associated with less release of stress hormones perioperatively, as compared with the traditional open procedure. This however, seems not to be the case because all studies have reported similar endocrine responses, regardless of surgical technique for cholecystectomy.[30–32]

Other investigators have suggested that the lower cytokine release (i.e. interleukin-6), caused by reduced tissue damage, could be the explanation for the differences seen clinically, as lower levels of interleukin-6 were observed shortly after laparoscopic compared with open cholecystectomy.[30] In a preliminary study, we have been unable to confirm these findings 24 hours postoperatively.[33] Nevertheless, greater interleukin-6 release is reported

with increasingly greater surgery in patients undergoing elective surgery of varying severity, suggesting a connection between the degree of surgery and the release of this cytokine.[34] Although interleukin-6 release may reflect the degree of tissue damage and possibly even explain the difference in clinical appearance related to method of surgery, it still is not clear to what extent or at what level of release this specific cytokine will affect human body metabolism. We have made a preliminary report of a relationship between postoperative interleukin-6 levels and insulin resistance, whereas other have shown a stimulatory effect on acute-phase proteins, but the role of this cytokine in regulating protein metabolism and, more specifically, muscle protein synthesis remains to be determined.[35–37]

The metabolic response observed peri- and postoperatively is not only influenced by the severity of the trauma but also by the type of anesthesia. The sympatho-adrenal response is more effectively blocked by general anesthesia combined with epidural analgesia, or by volatile anesthesia with enflurane, than by general modified neuroleptic anesthesia.[38–40] Therefore, it could be argued that the choice of anesthetic influences the postoperative reduction of muscle protein synthesis through a modification of the sympatho-adrenal response. However, in this study, all the patients received volatile anesthesia using isoflurane and the decrease in muscle protein synthesis was of similar magnitude to earlier determinations 24 hours after open cholecystectomy employing a general modified neuroleptic anesthesia.[41] This suggests that neither isoflurane nor general modified neuroleptic anesthesia blocked the stress response sufficiently to alter the changes in protein metabolism. Also, neither general modified neuroleptic anesthesia nor volatile anesthesia using isoflurane has any separate effect on muscle protein synthesis.[9,11] Thus, the observed depression in muscle protein synthesis seems to be related to the surgical procedures, whereas modern anesthetic agents have little—if any—effect on this parameter.

In this study, the muscle protein synthesis rate was determined during a hyperinsulinemic normoglycemic clamp. The clamp procedure did not influence the measurement of protein synthesis, however, because an identical hyperinsulinemic normoglycemic glucose clamp has not been shown to alter muscle protein synthesis rate in healthy volunteers.[16] Furthermore, the muscle synthesis rate preoperatively and the relative decrease postoperatively in the open cholecystectomy group were similar to the values for a different group of open cholecystectomy patients who were studied under similar conditions, but without the glucose clamp.[41]

This study demonstrates that although laparoscopic surgery results in less discomfort to the patient and more rapid recovery, compared with conventional open surgery, not all of the metabolic disturbances are attenuated. Despite the improved insulin sensitivity, laparoscopy does not avoid a substantial decline in muscle protein synthesis.

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