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Type 2 Diabetes Mellitus and the Catabolic Response to Surgery

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Background: **The authors tested the hypothesis that the catabolic responses to colorectal surgery are amplified in the presence of type 2 diabetes mellitus.**

Methods: **Seven nondiabetic and seven diabetic patients underwent a 6-h stable isotope infusion study (3 h fasted, 3-h glucose infusion at 4 mg · kg^{-1} · min^{-1}) on the second postoperative day. Leucine rate of appearance (R_a), leucine oxidation, nonoxidative leucine disposal, and glucose R_a were assessed by L-[1-^{13}C]leucine and [6,6-$^{2}H_2$]glucose. Circulating concentrations of glucose, lactate, insulin, glucagon, and cortisol also were determined.**

Results: **Diabetic patients had a higher leucine oxidation than nondiabetic patients (P = 0.0003), whereas leucine R_a and nonoxidative leucine disposal were not different. Administration of glucose did not affect leucine kinetics regardless of whether patients were diabetic. In diabetic patients, glucose R_a was greater than in the nondiabetic group (P = 0.0032). Glucose infusion suppressed the endogenous glucose R_a to a lesser extent in diabetic than in nondiabetic patients (P = 0.0048). Plasma glucose concentrations were higher in diabetic than in nondiabetic patients (P = 0.0203), both in the postabsorptive and the fed state. Circulating concentrations of glucagon were higher (P = 0.0065) and concentrations of insulin were lower (P = 0.0146) in the presence of diabetes, resulting in a lower insulin/glucagon ratio (P = 0.0002). In diabetic patients, the insulin/glucagon ratio increased during glucose infusion to a lesser extent than in the nondiabetic group (P = 0.0014).**

Conclusion: **Protein catabolism after colorectal surgery is increased in patients with type 2 diabetes mellitus as reflected by an increased oxidative protein loss.**

THE endocrine response to surgical tissue trauma is characterized by the activation of the hypothalamopituitary and sympathoadrenergic system, resulting in increased circulating concentrations of cortisol, glucagon, epinephrine, and norepinephrine.[1] All these hormones inhibit insulin secretion and/or counteract the peripheral action of insulin, leading to a state of impaired tissue insulin sensitivity.[2,3] Insulin resistance is thought to be one of the principal mechanisms responsible for the catabolic responses to surgery, including stimulated amino acid oxidation, muscle proteolysis, and gluconeogenesis along with decreased glucose utilization and hyperglycemia.[4,5] The similarity between the metabolic changes associated with surgery and those typically observed in patients with type 2 diabetes mellitus gave rise to the term *diabetes of injury*.[1] It also has been suggested that the catabolic responses to surgery are augmented in type 2 diabetic patients.[6] However, there is little evidence to substantiate this assumption. Whereas hyperglycemia after cataract surgery was more pronounced, the metabolic and endocrine alterations after major abdominal surgical procedures have never been evaluated in patients with type 2 diabetes mellitus.[7]

The goal of the current study was to examine postoperative protein and glucose catabolism during fasting conditions and during a 3-h infusion of 4 mg · kg^{-1} · min^{-1} glucose in diabetic and nondiabetic patients undergoing colorectal surgery, the hypothesis being that the catabolic responses are amplified in the presence of type 2 diabetes mellitus.

Materials and Methods

Patients

With the approval of the Ethics Committee of the Royal Victoria Hospital (Montreal, Quebec, Canada), informed consent was obtained from seven patients with type 2 diabetes mellitus and seven nondiabetic patients. All patients had localized nonmetastatic adenocarcinoma of the rectosigmoid colon and were scheduled to undergo elective colorectal surgery. None of the patients had cardiac, hepatic, or renal disease. No subject had developed recent weight loss or had an albumin concentration below 35 g/l. Diabetes treatment included diet alone (n = 2), glyburide (n = 3; 2 patients, 10 mg/day; 1 patient, 5 mg/day), and glyburide (10 mg/day) combined with metformin (1,000 mg/day; n = 2). Diabetic subjects had been diagnosed with diabetes mellitus for an average of 6 ± 2 yr (mean ± SD). All patients, except two whose glucose values were 8.2 and 7.4 mM on hospital admission, had normal postabsorptive plasma glucose concentrations as determined on two occasions after overnight fasting before the operation.

Surgical and Anesthesia Care

The patients were prepared for surgery in a standardized fashion. Solid food intake stopped after breakfast the day before surgery, and only clear liquids were allowed until 22:00. All operations were performed by the same surgeon and at the same time of the day (between

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08:00 and 12:00). Anesthesia was standardized and performed by the same anesthesiologist (T. S.). All patients received intraoperative epidural anesthesia combined with general anesthesia. General anesthesia was induced with intravenous thiopentone and maintained with 35% nitrous oxide in oxygen and isoflurane. Epidural catheters were inserted before induction of general anesthesia between T9 and T11. Bupivacaine, 0.5% (15–20 ml), was injected to produce a confirmed bilateral segmental sensory block from T4 to L2. Additional 0.25% bupivacaine (5–10 ml) was injected 1–2 h later. At the end of surgery, 0.1% epidural bupivacaine supplemented with 2 μg/ml fentanyl was administered continuously at a rate of 10–15 ml/h and maintained for at least 48 h. The segmental sensory level of analgesia was assessed twice a day using a blunted needle and ice, and the infusion was adjusted to maintain a bilateral sensory block between T7 and L2. Pain treatment in both groups was adjusted to obtain a visual analog scale score of less than 4 at rest (visual analogue scale from 0 = no pain to 10 = worst pain imaginable).

All patients received hypocaloric nutritional supplementation with glucose from 08:00 to 20:00 on the first postoperative day (100 ml/h glucose, 5%) followed by infusion of 0.9% sodium chloride (100 ml/h) until the study period. No patient received insulin treatment postoperatively unless the blood glucose concentration as determined every 8 h exceeded 10 mM.

Experimental Protocol

All tests were performed in the fasted state beginning at 08:00 in the morning of the second day after surgery. After a 3-h period of fasting, a solution of crystallized beet sugar (10% dextrose anhydrous; Avebe, Foxhol, Holland) was infused at 4 $mg \cdot kg^{-1} \cdot min^{-1}$ for 3 h. The solution was prepared by the hospital pharmacy during sterile conditions and tested for sterility, stability, and absence of pyrogens before infusion. The beet dextrose solution was chosen because of its low ^{13}C content and therefore the lack of significant perturbation of $^{13}CO_2$ enrichment in expired air.[8]

Plasma kinetics of leucine and glucose were determined by using tracer quantities of L-[1-^{13}C]leucine (99% ^{13}C) and [6,6-$^2H_2$]glucose (99% ^2H) obtained from Cambridge Isotope Laboratories (Cambridge, MA). Before each infusion study, sterile solutions of isotopes were prepared in the hospital pharmacy and kept at 4°C until administration.

A superficial vein in the dorsum of the hand was cannulated, and the cannula was kept patent with saline. A second superficial vein in the contralateral arm was cannulated to provide access for the infusion of the stable isotopes. Blood and expired air samples were collected before the infusion to determine baseline enrichments. Priming doses of 1 μmol/kg $NaH^{13}CO_3$, 4 μmol/kg L-[1-^{13}C]leucine, and 22 μmol/kg [6,6-$^2H_2$]glucose were administered and followed immediately by infusions of 0.06 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ L-[1-^{13}C]leucine lasting 6 h. [6,6-$^2H_2$]glucose was infused at a rate of 0.22 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ during the first 3 h (fasted period) and then changed to 0.44 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ during the 3 h of glucose administration. Toward the end of each 3-h study period, four blood and expired breath samples were collected at 10-min intervals. Each blood sample was transferred immediately to a heparinized tube, centrifuged at 4°C (3,000*g*, 15 min) and stored at −70°C. Breath samples were collected in a 2-l latex bag and transferred immediately to 20-ml vacutainers.

Gaseous Exchange

Indirect calorimetry (Datex Deltatrac, Helsinki, Finland) was performed in the last hour of the fasted state and toward the end of the glucose infusion period. The subjects were lying in a semirecumbent position (20°), breathing room air in the ventilated hood. Oxygen consumption and carbon dioxide production were measured. The values of oxygen consumption, carbon dioxide production, and respiratory quotient represent an average of the data obtained during a 20-min period on each occasion, with a coefficient of variation less than 10%. Energy expenditure and respiratory quotient were calculated. Carbohydrate and lipid oxidation rates were calculated using standard formulas.[9] Protein oxidation was calculated using the measured rate of leucine oxidation and assuming that leucine represents 8% of total body protein.[10]

Isotopic Enrichments

Plasma [1-^{13}C]ketoisocaproate enrichment was determined by electron impact selected-ion monitoring gas chromatography–mass spectrometry using the method described by Mamer and Montgomery,[11] except that the t-butyldimethylsylyl rather than trimethylsylyl derivative was prepared. Expired ^{13}C-carbon dioxide enrichment was determined by isotope ratio mass spectrometry (Analytical Precision AP2003, Manchester, United Kingdom).[12] Plasma glucose was derivatized to its pentaacetate compound, and the [6,6-$^2H_2$]glucose enrichment was determined by gas chromatography–mass spectrometry using electron impact ionization.[12] In each analysis run, duplicate injections were always performed, and their means were taken to represent enrichment.

Plasma Metabolites and Hormones

Plasma glucose was measured by a glucose-oxidase method using the Analox GM7 glucose analyzer (Analox Instruments Limited, London, United Kingdom). Plasma lactate assay was based on lactate oxidase and was performed using the Synchron LX20Pro Clinical System (Beckman Coulter Inc., Palo Alto, CA). Plasma concentrations of cortisol were determined by an automated chemiluminescence system (ADVIA Centaur; Bayer Di-

agnostics, Dublin, Ireland). Circulating concentrations of insulin and glucagon were measured by sensitive and specific double antibody radioimmunoassays (Linco Research Inc., Palo Alto, CA).[13]

Calculations

When a physiologic and isotopic steady state exists, the rate of appearance (R_a) of unlabeled substrate in plasma can be derived from the plasma isotope enrichment (atom percentage excess [APE]) calculated by

$$R_a = (APE_{inf}/APE_{pl} - 1) \cdot F,$$

where F is the infusion rate of the labeled tracer, APE_{inf} is the tracer enrichment in the infusate, and APE_{pl} is the tracer enrichment in plasma, respectively. The APE values used in this calculation were the mean of the four APE values determined during steady state conditions obtained at each phase of the studies. The accuracy of the isotopic enrichments at isotopic plateau was tested by evaluating the scatter of values above their mean, expressed as coefficient of variation. A coefficient of variation of less than 5% was used as a confirmation of a valid plateau.

During steady state conditions, leucine flux (Q) is defined by the formula

$$Q = S + O = B + I,$$

where S is the rate at which leucine is incorporated into body protein, O is the rate of oxidation of leucine, B is the rate at which unlabeled leucine enters the free amino acid pool from endogenous protein breakdown, and I is the rate of leucine intake including tracer and diet. In the postabsorptive state, the sole source of the essential amino acid leucine for protein synthesis and oxidation is that derived from the breakdown of endogenous proteins. Plasma enrichment of [1-^{13}C]ketoisocaproate was used as the basis for calculating both flux and oxidation of leucine.[14] In the calculation of oxidation, factors of 0.76 for the fasting state and 0.81 during glucose infusion were applied to account for the fraction of ^{13}C-carbon dioxide released from leucine but retained within slow turnover rate pools of the body.[10,12,15]

In the fasted state, R_a glucose was equal to the endogenous production of glucose. During glucose infusion, endogenous glucose production was calculated by subtracting the glucose infusion rate from the total R_a glucose. The plasma glucose clearance rate was calculated as R_a glucose divided by the corresponding plasma glucose concentration.

Control Group

A small control group with three type 2 diabetic patients (two male, one female) who had adenocarcinoma of the colon was also studied. Diabetes treatment included diet alone (n = 1) or glyburide (n = 2; 10 mg/day) and none of the patients had cardiac, hepatic, or renal disease. Postabsorptive circulating albumin and glucose concentrations before the study were normal in all three subjects. Patients were prepared for surgery in the same standardized fashion as patients in the two study groups. Using the methods described above, leucine and glucose kinetics, circulating concentrations of metabolic substrate, and hormones as well as gaseous exchange were measured during postabsorptive conditions only, *i.e.*, no glucose was administered. Isotope infusions were performed over 3 h starting 4 h before the operation. Values were compared to results obtained in nondiabetic patients studied during the same conditions.[16]

Statistics

The primary endpoint of the study was leucine oxidation. On the basis of our previous studies, a difference of mean leucine oxidation of at least 4 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ between the two patient groups (between group effect) and between the two feeding states (within-group effect) was defined as metabolically relevant.[12] Assuming an SD as obtained previously, a repeated-measure design with two times seven patients achieves a power of 70% to detect a between-group effect size of 0.72 and a power of 99% to detect the within-group effect size of 0.88 with a type I error of 5%. This prospective power analysis was performed with PASS 2002 (Number Cruncher Statistical Systems, Kaysville, UT).

Analyses of variables were performed using two-factorial analysis of variance for repeated measures. If no significant change was detected between the two measurements (glucose, lactate, cortisol, insulin, glucagon) after 150 and 180 min of glucose infusion, the average values were compared with the one value determined before glucose administration. Significant effects induced by glucose administration were assumed when *P* values for time dependency were less than 0.05. Influences by diabetes were accepted as significant when the interaction term of the analysis of variance was below 0.05. All analyses were performed using the General Linear Model in SPSS 11.0 for Windows (SPSS Inc., Chicago, IL).

Results

Patients

There were no differences between the two groups regarding sex, age, or body mass index of patients (table 1). Estimated blood loss never exceeded 400 ml, and no patient received a blood transfusion. No patient required insulin treatment in the postoperative course.

Leucine and Glucose Kinetics

In all experiments, a plateau in the enrichments of plasma [1-^{13}C]ketoisocaproate, [6,6-$^{2}H_2$]glucose, and ^{13}C-carbon dioxide was achieved (coefficient of varia-

Table 1. Characteristics of the Patients

	Nondiabetic Patients	Diabetic Patients
Sex, n, female:male	4:3	3:4
Age, yr	60 ± 13	56 ± 22
BMI, kg/m^2	23 ± 3	23 ± 4
Surgery, n		
Colectomy	2	1
Left hemicolectomy	2	2
Low anterior resection	3	4
Duration of surgery, min	205 ± 84	214 ± 57

Values are presented as mean ± SD.

BMI = body mass index.

tion < 5%), permitting the use of the steady state equation. Diabetic patients had a higher leucine rate of oxidation than nondiabetic patients ($P = 0.0003$), whereas leucine R_a and nonoxidative leucine disposal were not different (table 2). Administration of glucose had no significant effect on leucine kinetics regardless of whether patients were diabetic (table 2). In diabetic patients, the postabsorptive endogenous and total glucose R_a were greater than in the nondiabetic group ($P = 0.0032$; table 2). Glucose infusion suppressed the endogenous R_a to a lesser extent in diabetic than in nondiabetic patients ($P = 0.0048$; table 2). In the nondiabetic group, glucose clearance during glucose feeding was higher than in diabetic patients ($P = 0.0007$; table 2).

Metabolic Substrates and Hormones

Plasma glucose concentrations were significantly higher in diabetic than in nondiabetic patients ($P = 0.0203$), both in the postabsorptive state and during the administration of glucose (table 3). Circulating concentrations of glucagon were higher ($P = 0.0065$) and circulating concentrations of insulin were lower ($P = 0.0146$) in patients with diabetes, resulting in a lower insulin/glucagon ratio ($P = 0.0002$; table 3). In diabetic patients, the insulin/glucagon ratio increased during glucose infusion to a lesser extent than in the nondiabetic group ($P = 0.0014$; table 3). Significant negative correlations between the R_a glucose and the insulin/glucagon ratio ($r^2 = 0.173$, $P = 0.028$) and between protein oxidation and insulin/glucagon ratio were observed ($r^2 = 0.186$, $P = 0.022$).

Gaseous Exchange

In the fasted state, oxygen consumption ($P = 0.0417$), protein oxidation ($P = 0.0006$), and lipid oxidation ($P = 0.0349$) were higher, whereas carbohydrate oxidation was lower in diabetic ($P = 0.0170$) compared with nondiabetic patients (table 4). During the administration of glucose, the respiratory quotient ($P = 0.0288$) increased and lipid oxidation ($P = 0.0172$) decreased in the two groups (table 4).

Control Group

Values obtained in the small control group of diabetic patients studied before surgery for colorectal cancer indicate that leucine oxidation, protein oxidation, and leucine rate of appearance are not increased when compared with nondiabetic patients with colorectal cancer who were preoperatively studied during identical conditions (table 5).[16] Circulating concentrations of glucose and lipid oxidation rates seem to be increased, whereas circulating insulin concentrations and carbohydrate oxidation rates seem to be lower in diabetic patients (table 5).

Table 2. Leucine and Glucose Kinetics

	Nondiabetic Patients		Diabetic Patients		*P* Values		
	Fasted	Glucose	Fasted	Glucose	Glucose*	Diabetes†	Interaction‡
Leucine rate of appearance, $\mu mol \cdot kg^{-1} \cdot h^{-1}$	116 ± 29	113 ± 30	133 ± 26	120 ± 15	0.2164	0.3374	0.4660
Leucine oxidation, $\mu mol \cdot kg^{-1} \cdot h^{-1}$	20 ± 4	17 ± 5	29 ± 9	29 ± 5	0.4483	0.0003	0.5916
Nonoxidative leucine disposal, $\mu mol \cdot kg^{-1} \cdot h^{-1}$	96 ± 26	96 ± 37	104 ± 21	92 ± 16	0.2885	0.8586	0.3146
Glucose rate of appearance, $\mu mol \cdot kg^{-1} \cdot min^{-1}$	9.8 ± 1.6	23.2 ± 2.6	15.3 ± 2.1	24.6 ± 1.8	< 0.0001	0.0032	0.0044
Endogenous glucose rate of appearance, $\mu mol \cdot kg^{-1} \cdot min^{-1}$	9.8 ± 1.6	1.6 ± 1.6	15.3 ± 2.1	3.9 ± 1.2	< 0.0001	0.0002	0.0048
Glucose clearance, $ml \cdot kg^{-1} \cdot min^{-1}$	2.0 ± 0.3	2.4 ± 0.4	2.1 ± 0.5	1.8 ± 0.4	0.4480	0.3325	0.0007

Values are presented as mean ± SD.

* Probability that values are influenced by intravenous glucose. † Probability that values are influenced by diabetes regardless of whether glucose was administered. ‡ Probability that the effect of glucose is greater in one distinct group.

Table 3. Circulating Concentrations of Metabolites and Hormones

	Nondiabetic Patients		Diabetic Patients		*P* Values		
	Fasted	Glucose	Fasted	Glucose	Glucose*	Diabetes†	Interaction‡
Glucose, mM	5.0 ± 0.5	10.0 ± 0.8	7.6 ± 2.4	14.3 ± 4.5	< 0.0001	0.0203	0.0877
Lactate, mM	1.0 ± 0.2	1.0 ± 0.2	1.2 ± 0.3	1.2 ± 0.3	0.3284	0.1653	0.8419
Cortisol, nM	446 ± 201	323 ± 139	380 ± 83	289 ± 109	0.3870	0.4891	0.6038
Insulin, pM	102 ± 18	328 ± 148	80 ± 46	160 ± 96	0.0011	0.0146	0.0631
Glucagon, pM	27 ± 5	17 ± 5	41 ± 16	28 ± 13	0.0190	0.0065	0.7712
Insulin/glucagon	4 ± 1	21 ± 6	2 ± 1	6 ± 3	< 0.0001	0.0002	0.0014

Values are presented as mean ± SD.

* Probability that values are influenced by intravenous glucose. † Probability that values are influenced by diabetes regardless of whether glucose was administered. ‡ Probability that the effect of glucose is greater in one distinct group.

Discussion

The results of this study indicate that the catabolic responses to colorectal surgery are increased in patients with type 2 diabetes mellitus as reflected by a 50% greater amino acid oxidation, glucose production, and glucose plasma concentration compared with nondiabetic patients during fasting conditions. Administration of glucose inhibited endogenous glucose production to a lesser extent in diabetic than in nondiabetic patients. These findings lend further support to the previous assumption that type 2 diabetes mellitus accentuates the metabolic abnormalities produced by surgical tissue trauma; combined infusions of epinephrine, cortisol, and glucagon have been shown to cause a greater hyperglycemic response in diabetic subjects than in healthy volunteers.[17] Others have also shown that after minor surgery, glucose plasma concentrations were increased to a greater extent in type 2 diabetic patients,[7] who demonstrate signs of an acute-phase response even in the absence of injury.[5] Patients in the present protocol were observed postoperatively only. Hence, our study design does not allow us to dissect the metabolic effects of surgery from those induced by diabetes mellitus *per se*.

Insulin deficiency can be associated with increased protein breakdown and oxidation as seen during type 1 diabetes mellitus.[18,19] The rate of leucine appearance[20–22] as well as the inhibition of protein breakdown by insulin[23] in type 2 diabetic patients under good or moderate glucose control, however, seems to be normal. In poorly controlled and obese type 2 diabetic subjects, protein breakdown as assessed by the [^{15}N]glycine method was increased as compared with a nondiabetic, weight-matched control group.[24,25] Except for two studies involving poorly controlled type 2 diabetic populations,[5,21] no studies have demonstrated increased leucine oxidation in diabetic patients. Although the majority of studies suggest that type 2 diabetes mellitus does not alter amino acid kinetics,[20,22,26] no information is available in patients with diabetes *and* colorectal cancer. Leucine appearance and oxidation in subjects with poorly controlled type 2 diabetes studied after a 10-h overnight fast were not significantly different from values observed in nondiabetic patients with lung cancer.[5] The results obtained in our small control group of patients before surgery also indicate that protein oxidation and breakdown are not increased in diabetic patients with colorectal cancer when compared with nondiabetic subjects.

It has long been recognized that type 2 diabetes mellitus leads to a moderate increase in glucose production and gluconeogenesis during postabsorptive conditions.[5,21,27,28] Increased glucose production rates have also been reported in well-nourished patients with malignant disease.[29,30] Glucose production rates in type 2 diabetic patients and nondiabetic subjects with cancer were increased to a similar extent as compared to

Table 4. Gaseous Exchange

	Nondiabetic Patients		Diabetic Patients		*P* Values		
	Fasted	Glucose	Fasted	Glucose	Glucose*	Diabetes†	Interaction‡
Oxygen consumption, ml/min	200 ± 32	196 ± 38	252 ± 54	242 ± 46	0.3886	0.0417	0.7242
Carbon dioxide production, ml/min	151 ± 19	158 ± 32	189 ± 41	183 ± 35	0.9637	0.0697	0.4344
Respiratory quotient	0.76 ± 0.03	0.81 ± 0.04	0.75 ± 0.02	0.76 ± 0.02	0.0288	0.0091	0.1087
Protein oxidation, g/d	52 ± 16	43 ± 17	80 ± 21	80 ± 15	0.4801	0.0006	0.5074
Carbohydrate oxidation, g/d	40 ± 32	109 ± 61	35 ± 28	45 ± 39	0.0576	0.0170	0.1394
Lipid oxidation, g/d	102 ± 32	78 ± 23	128 ± 29	117 ± 28	0.0172	0.0349	0.3324

Values are presented as mean ± SD.

* Probability that values are influenced by intravenous glucose. † Probability that values are influenced by diabetes regardless of whether glucose was administered. ‡ Probability that the effect of glucose is greater in one distinct group.

Table 5. Control Group

	Diabetic Patients			
	A	B	C	Nondiabetic Patients*
Age, yr	67	71	66	52 ± 20
BMI, kg/m^2	26.9	26.6	29.1	25.0 ± 3.0
Leucine rate of appearance, μmol · kg^{-1} · h^{-1}	108	120	103	100 ± 17
Leucine oxidation, μmol · kg^{-1} · h^{-1}	22	19	14	18 ± 5
Nonoxidative leucine disposal, μmol · kg^{-1} · h^{-1}	86	101	89	83 ± 14
Glucose rate of appearance, μmol · kg^{-1} · min^{-1}	12.7	13.3	15.3	9.9 ± 1.0
Glucose, mM	6.8	5.4	8.7	4.8 ± 1.1
Lactate, mM	1.2	0.8	1.0	1.1 ± 0.3
Cortisol, nM	153	350	200	400 ± 153
Insulin, pM	22	45	30	99 ± 21
Glucagon, pM	22	22	13	19 ± 5
Insulin/glucagon	1	2	3	5 ± 2
Oxygen consumption, ml/min	265	208	225	203 ± 23
Carbon dioxide production, ml/min	195	157	173	160 ± 15
Respiratory quotient	0.74	0.75	0.77	0.79 ± 0.02
Protein oxidation, g/d	80	55	45	53 ± 23
Carbohydrate oxidation, g/d	16	42	73	86 ± 20
Lipid oxidation, g/d	144	106	111	87 ± 21

* Reference values are the mean of 12 nondiabetic patients (5 male, 7 female) studied under the same conditions and published previously.[16]
BMI = body mass index.

healthy volunteers.[5] The effect of diabetes mellitus on glucose kinetics in patients with intestinal cancer is unknown. The findings in our control patients, however, seem to demonstrate that postabsorptive glucose production rates and circulating glucose concentrations are increased, whereas carbohydrate oxidation is decreased in the presence of diabetes and colorectal carcinoma.

Administration of glucose in the current study did not affect the leucine rate of appearance and oxidation regardless of whether patients were diabetic. This finding is consistent with observations in healthy subjects[31] and surgical patients[32] showing that the infusion of glucose at rates increasing the circulating insulin concentration to a level similar to that in the current protocol does not influence protein breakdown and amino acid oxidation. In contrast, administration of insulin resulting in circulating insulin concentrations greater than 150 microunits/ml blocks the release of muscle amino-nitrogen,[33] whereas insulin clamped at a serum level of 80 microunits/ml induces a decrease in whole body leucine release.[34]

The inhibitory effect of exogenous glucose on endogenous glucose production has been shown to depend on the dose of glucose infused and the physiologic state of the subject. Glucose administered at 4 mg · kg^{-1} · min^{-1} almost completely suppresses endogenous glucose production in healthy volunteers, whereas glucose applied at the same rate in patients after trauma and during sepsis diminishes glucose production by 50% only.[35,36] In the current study, the inhibitory action of glucose on the endogenous rate of appearance was less pronounced in diabetic than in nondiabetic patients. In addition, during glucose administration, the glucose clearance and carbohydrate oxidation were less in the presence of diabetes. This is in accordance with the limited suppressibility of endogenous glucose production and abnormal peripheral glucose utilization typically observed in diabetes mellitus.[37–39] Thus, the ability of ambient glucose at moderately increased circulating insulin concentrations to regulate glucose metabolism was impaired in the current group of diabetic patients. This defect involved both blunted inhibition of endogenous glucose production and decreased stimulation of glucose uptake and oxidation.

Because the current study was not designed to identify the biochemical factors causing the discrepancy between the catabolic responses in diabetic and nondiabetic patients, we can only speculate about the underlying mechanisms. Lower circulating insulin concentrations accompanied by greater circulating glucagon concentrations in the diabetic group and negative correlations between the insulin/glucagon ratio and glucose production as well as protein oxidation suggest that changes in the insulin/glucagon system were responsible. The crucial roles of insulin and glucagon in initiating and modifying postoperative protein and glucose metabolism have been well established[40]; in fact, significant correlations between glucagon plasma concentrations and leucine oxidation rates were recently demonstrated in diabetic subjects.[18] However, the observation of similar changes in the insulin/glucagon system before surgery in the current control group, *i.e.*, lower plasma insulin concentrations accompanied by a lower insulin/glucagon ratio, indicates that other mechanisms, including alterations in the sympathoadrenergic or inflammatory system, may have contributed.

We acknowledge several limitations of this study. Before surgery, hemoglobin A_{1c} concentrations were not determined in the diabetic patient population. Although

preoperative plasma glucose concentrations indicated good or moderate control and none of the patients required insulin treatment, the quality of glucose control could not be quantified in our patients. It must be noted, however, that the quality of treatment seems to have only little effect on amino acid metabolism in type 2 diabetic patients,[26] most likely because of different sensitivities of glucose and amino acid metabolism to insulin.[20] Oral glucose tolerance tests were not performed, and hemoglobin A_{1c} concentrations were not measured in our nondiabetic patients before surgery. Therefore, the possibility that subjects with undiagnosed diabetes entered the study cannot be entirely excluded.

Plasma concentrations of free fatty acids were not measured after surgery, neither in the fasted nor in the fed state. Increased circulating concentrations of free fatty acids have been shown to contribute to the loss of glucose effectiveness in poorly controlled type 2 diabetes.[37] Hence, the determination of free fatty acids may have provided further explanation for the limited suppression of endogenous glucose production by glucose in the diabetic patients.

In summary, this study presents the first integrated analysis of postoperative changes in protein and glucose metabolism in type 2 diabetic patients undergoing elective resections of colorectal cancer. The enhancement of postoperative protein oxidation in diabetic patients most likely indicates an increased catabolic response to surgery, whereas the alterations in glucose metabolism can be at least in part attributed to changes induced by diabetes mellitus *per se*.

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