Time of peritoneal cavity exposure influences postoperative glucose production

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Purpose: To examine the effect of the duration of peritoneal cavity exposure on glucose metabolism after abdominal surgery.

Methods: In eight otherwise healthy patients (ASA I) with uterine myoma, endogenous glucose production (R_a glucose) was measured immediately before and two hours after abdominal hysterectomy by a stable isotope dilution technique using primed continuous infusions of $[6,6-^2H_2]$ -glucose. Plasma concentrations of glucose, lactate, insulin, glucagon, cortisol, epinephrine and norepinephrine were determined before, during (5 and 60 min after peritoneal incision, skin closure) and two hours after surgery. Pre- and postoperative glucose clearance was calculated as R_a glucose divided by plasma glucose concentration.

Results: R_a glucose increased from 11.8 ± 1.2 to $16.8 \pm 3.2 \mu\text{mol}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ two hours after hysterectomy ($P < 0.05$) with a correlation between the degree of increase and the time of peritoneal cavity exposure ($r = 0.859$, $P = 0.006$). Plasma glucose concentration increased after surgery from 4.7 ± 0.8 to $8.3 \pm 1.9 \text{ mmol}\cdot\text{l}^{-1}$ ($P < 0.05$), while glucose clearance decreased from 2.6 ± 0.4 to $2.1 \pm 0.4 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ($P < 0.05$). Plasma concentrations of cortisol and catecholamines increased after hysterectomy (cortisol from 6 ± 2 to $31 \pm 7 \mu\text{g}\cdot\text{dl}^{-1}$, epinephrine from 25 ± 14 to $205 \pm 132 \text{ pg}\cdot\text{ml}^{-1}$, norepinephrine from 182 ± 82 to $377 \pm 132 \text{ pg}\cdot\text{ml}^{-1}$, $P < 0.05$), whereas plasma lactate, insulin and glucagon concentrations remained unchanged.

Conclusion: The magnitude of increase of glucose production after abdominal hysterectomy is associated with the duration of peritoneal cavity exposure.

Objectif : Examiner l'effet du temps d'exposition de la cavité péritonéale sur le métabolisme du glucose après une chirurgie abdominale.

Méthode : Chez huit patientes en bonne santé (ASA I) présentant un myome utérin, la production endogène de glucose (glucose R_a) a été mesurée immédiatement avant et deux heures après l'hystérectomie abdominale par une technique de dilution isotopique stable en utilisant des perfusions continues amorcées avec du $[6,6-^2H_2]$ -glucose. Les concentrations plasmatiques de glucose, lactate, insuline, glucagon, cortisol, épinéphrine et norépinéphrine ont été déterminées avant, pendant (5 et 60 min après l'incision péritonéale, la fermeture cutanée) et deux heures après l'opération. La clairance du glucose préopératoire et postopératoire a été calculée ainsi : glucose R_a divisé par la concentration de glucose plasmatique.

Résultats : Le glucose R_a a augmenté de $11,8 \pm 1,2$ à $16,8 \pm 3,2 \mu\text{mol}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, deux heures après l'hystérectomie avec une corrélation entre le degré d'élévation et le temps d'exposition de la cavité péritonéale ($r = 0,859$, $P = 0,006$). La concentration de glucose s'est accrue après l'intervention, passant de $4,7 \pm 0,8$ à $8,3 \pm 1,9 \text{ mmol}\cdot\text{l}^{-1}$ ($P < 0,05$), pendant que la clairance a diminué de $2,6 \pm 0,4$ à $2,1 \pm 0,4 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ($P < 0,05$). Les concentrations de cortisol et de catécholamines ont augmenté après l'hystérectomie (cortisol : de 6 ± 2 à $31 \pm 7 \mu\text{g}\cdot\text{dl}^{-1}$, épinéphrine : de 25 ± 14 à $205 \pm 132 \text{ pg}\cdot\text{ml}^{-1}$, norépinéphrine : de 182 ± 82 à $377 \pm 132 \text{ pg}\cdot\text{ml}^{-1}$, $P < 0,05$), mais les concentrations de lactate, d'insuline et de glucagon sont restées les mêmes.

Conclusion : L'importance de l'accroissement de la production de glucose à la suite d'une hystérectomie abdominale est associée au temps d'exposition de la cavité péritonéale.

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HYPERGLYCEMIA is a prominent feature of the metabolic response to surgery.¹ The hyperglycemic response to surgery has been widely studied and been shown to depend on patient age,² anesthetic technique,³ severity of tissue trauma⁴ and type of surgery.⁵ In contrast, the effect of the duration of surgical trauma on glucose metabolism has received little attention.

Measurement of plasma glucose concentration alone does not allow insight into dynamic biochemical processes. For instance, an increased blood glucose concentration might be the consequence of either increased glucose production or diminished glucose clearance or both. The kinetics of glucose metabolism in humans can be followed by stable isotope tracers. By using primed continuous infusion of [6,6-²H₂]-glucose endogenous glucose production and whole body glucose clearance, an index of the ability of tissues to take up glucose, can be determined. Assessment of perioperative glucose kinetics helps to clarify the underlying dynamic mechanisms of the pathophysiology of glucose metabolism after surgery and, thus, provides a rationale for therapeutical interventions.

The objective of this study was to investigate the influence of the time of peritoneal cavity exposure during abdominal hysterectomy on postoperative glucose metabolism using a stable isotope dilution technique.

Patients and methods

The protocol of this cohort study was approved by the Hospital Ethical Committee and informed consent was obtained from all patients. Eight otherwise healthy women (44 ± 5 yr, ASA 1) with a mean body weight of 69 ± 10 kg and a mean height of 162 ± 10 cm undergoing elective abdominal hysterectomy for uterine myoma were consecutively investigated. None of the patients was suffering from cardiac, hepatic, renal or metabolic disorders or receiving medication.

Anesthesia

Patients received premedication (20 mg chlorazepate) three hours before surgery, which was performed between 1000 and 1100 by the same surgical team. Anesthesia was induced with 5 mg·kg⁻¹ thiopental and 1.5 µg·kg⁻¹ fentanyl, and orotracheal intubation was facilitated with 1.5 mg·kg⁻¹ succinylcholine. Anesthesia was maintained with desflurane at end-tidal concentrations between 4.0-6.0% to keep heart rate and arterial pressure within 20% of pre-induction values. The patients' lungs were ventilated with oxygen 30% in nitrous oxide to normocapnia. The degree of muscle relaxation was monitored using the train-of-four-ratio,

and supplemental doses of vecuronium bromide were administered to achieve complete muscle relaxation. Hemodynamic monitoring was performed using automatic blood pressure measurement and a three lead ECG monitor. Cardiac output was measured by thoracic bioimpedance (Non Invasive Continuous Cardiac Output Monitor NCCOM 3-R7, Bomed Medical Manufacturing Ltd., Irvine, CA). All patients were covered with a warming blanket to maintain normothermia. Ringer's solution was infused at a rate of 6 ml·kg⁻¹·hr⁻¹ during hysterectomy and 2 ml·kg⁻¹·hr⁻¹ after surgery. Postoperative pain intensity was estimated using a 10 cm visual analogue scale (VAS), where 0 = no pain and 10 = unbearable pain. Pain was treated with piritramide *iv* to achieve a VAS score below 4.

Study protocol

The stable isotope [6,6-²H₂] glucose (99% ²H) was obtained from Mass Trace (Woburn, MA) and prepared under sterile conditions in the hospital pharmacy. An aliquot of tracer was dissolved in a known volume of sterile water. The solution was passed through a 0.22 µm filter into injection bottles. The bottles were sealed, heat sterilized at 121°C for 15 min, and kept at 4°C until administration. Each set of solutions was confirmed to be free of pyrogens (LAL Pyrogen test, Whittaker Bioproducts, Walkersville, MD).

All patients were studied on the day of surgery after fasting for ten hours overnight. A superficial vein in the dorsum of the hand was cannulated and the cannula kept patent with saline. A second cannula was inserted into a superficial vein of the contralateral arm to provide access for the infusion of [6,6-²H₂]-glucose. A priming dose of [6,6-²H₂]-glucose 4 mg·kg⁻¹ was administered at 0800 and followed by continuous infusion of [6,6-²H₂]-glucose 0.05 mg·kg⁻¹·min⁻¹ for 120 min. Postoperative [6,6-²H₂]-glucose infusion commenced immediately after extubation and also was continued for 120 min. The amount of tracer infused was determined directly by weighing the tracer initially and at the end of the infusion. Blood samples were collected before isotope infusions to determine baseline ²H enrichment and after 100, 110 and 120 min of pre- and postoperative isotope infusions, when the tracer was assumed to have reached an isotopic steady state. Prior to obtaining any blood the hand was warmed in a heated air box to achieve arterialized blood (SaO₂ > 95%). Plasma concentrations of circulating metabolites and hormones were determined after 110 min of pre- and postoperative isotope infusion and during the operation (5 and 60 min after incision of the peritoneum and at the end of surgery when the skin was closed). Each blood sample collected was transferred to a heparinized tube and cen-

trifuged at 4°C. The plasma obtained was stored at -20°C until analysis. A schematic representation of the procedure is shown in Figure 1.

Analytical methods

The isotopic enrichment of [6,6-²H₂]-glucose was determined by gas chromatography-mass spectrometry as previously described.⁶ Endogenous glucose production (R_a glucose: rate of appearance of glucose) was derived from the relationship:

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

where APE_{inf} and APE_{pl} (APE : atom percent excess) are the tracer enrichments in the infusate (inf) and plasma (pl) at steady state, and I is the tracer infusion rate. The APE values used in this calculation were the mean of the three APE s determined after 100, 110 and 120 min of pre- and postoperative isotope infusion, respectively. The accuracy of the isotopic enrichments at isotopic plateau was tested by evaluating the scatter of the three APE values above their mean, expressed as coefficient of variation. A coefficient of variation < 5% was used as a confirmation of a valid plateau. The clearance rate of glucose was calculated as R_a glucose divided by the plasma glucose concentration obtained at isotopic plateau after 110 min of isotope infusion.

Plasma concentrations of glucose and lactate were measured by using enzymatic kits (Boehringer Mannheim GmbH, Mannheim, Germany). The mean intra-assay and inter-assay coefficients of variance were 3.0% and 4.5% for glucose and 2.5% and 4.0% for lactate, respectively.

Insulin, glucagon and cortisol were analyzed with radioimmunoassays (INS-RIA-100, Medgenix Diagnostics, Brussels, Belgium for insulin, Double

Antibody Glucagon RIA, Diagnostic Products Corporation, Los Angeles, CA, for glucagon, DSL-2000 SP Aktive® Cortisol, Diagnostic System Laboratories, Sinsheim, Germany for cortisol). The mean intra-assay and inter-assay coefficient of variance was 5.6% and 8.3% for insulin, 4.8% and 8.0% for glucagon and 3.0% and 7.0% for cortisol. For the analysis of epinephrine and norepinephrine blood was drawn in lithium-heparinate monovettes containing 10 μ l·ml⁻¹ of a solution of 61 g·l⁻¹ glutathione and 76 g·l⁻¹ ethyleneglycol-bis(β -aminoethylether)-N,N-tetraacetate (EGTA) for stabilization. Catecholamine concentrations were quantified by means of reversed phase high performance liquid chromatography (HPLC, Chromakon 500, Kontron, Eiching, Germany) with electrochemical detection as described earlier.⁷ The mean intraassay and interassay coefficients of variance were 5.0% and 4.5% for epinephrine and 3.2% and 2.5% for norepinephrine, respectively.

Statistics

Analysis of variance for repeated measures with *post hoc* analysis by Student-Newman-Keuls test was used to examine within-group changes in hemodynamics and plasma concentrations of metabolites and hormones. Differences between pre- and postoperative endogenous glucose production and plasma glucose clearance were analyzed by Student's *t* test. The relationships between

FIGURE 1 Time course of the infusion of [6,6-²H₂]-glucose and collection of blood for the pre- and postoperative measurement of plasma [6,6-²H₂]-glucose enrichment (O) before and during 100, 110 and 120 min of isotope infusion. Sampling times for the determination of plasma concentrations of intermediary substrates and hormones (■) before, during (I: 5 min, II: 60 min after peritoneal incision; III: skin closure) and after hysterectomy.

FIGURE 2 Correlation between the duration of the exposure of the peritoneal cavity and the postoperative increase of endogenous glucose production (increase of endogenous glucose production = $0.39 + (0.05 \cdot \text{peritoneal cavity exposure})$, $P = 0.006$, $r = 0.859$).

time of peritoneal cavity exposure (independent variable) and metabolic changes (endogenous glucose production, plasma glucose clearance, concentrations of metabolites and hormones) were calculated by linear regression analysis. Results are given as means $\pm$ SD. A probability of < 0.05 was accepted as significant.

Results

Estimated blood loss did not exceed 300 ml (230 ± 53 ml) and did not necessitate blood transfusion. The mean amount of piritramide required for postoperative pain treatment was 15 ± 3 mg. Hemodynamics data are presented in Table I. No alterations of mean arterial pressure, heart rate and cardiac output occurred during the study period.

Plateau enrichment of $[6,6-^2\text{H}_2]$ -glucose was achieved in all infusions, and the coefficient of variation was $0.36 \pm 0.47\%$ before and $1.02 \pm 2.05\%$ after hysterectomy. Individual values of pre- and postoperative R_a glucose, glucose plasma concentration and glucose clearance are presented in Table II. The R_a glucose increased after surgery in all patients and the degree of the postoperative increment positively correlated with the duration of the exposure of the peritoneal cavity ($r = 0.859$, $P = 0.006$, Figure

2). Glucose clearance decreased from 2.6 ± 0.4 to 2.1 ± 0.4 $\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ after hysterectomy ($P < 0.05$) without any correlation between the magnitude of postoperative decrease and the time of peritoneal cavity exposure ($r = 0.441$).

Plasma concentrations of circulating metabolites and hormones are presented in Table III. Plasma glucose concentration increased 60 min after the incision of the peritoneum and remained elevated after surgery ($P < 0.05$). The postoperative increase of plasma glucose concentration did not correlate with the duration of the exposure of the peritoneal cavity ($r = 0.069$). Plasma catecholamine and cortisol concentrations increased during and after the operation ($P < 0.05$) without showing any correlation with the duration of peritoneal cavity exposure (epinephrine: $r = 0.0502$, norepinephrine: $r = 0.203$, cortisol: $r = 0.410$). Lactate, glucagon and insulin concentrations showed no significant perioperative changes.

Discussion

The results of the present study demonstrate that the postoperative increase in endogenous glucose production correlates with the duration of exposure of the peritoneal cavity. In contrast the postoperative rise in plasma glucose concentration did not show any correlation.

TABLE I Measurements of cardiovascular status before, during and two hours after surgery.

	Before Surgery	During Surgery†			Two hours After Surgery
		I	II	III	
MAP (mm Hg)	94 ± 12	94 ± 15	89 ± 8	95 ± 13	93 ± 8
Heart Rate (beat·min ⁻¹)	76 ± 10	76 ± 14	76 ± 12	80 ± 17	80 ± 16
Cardiac Output (l·min ⁻¹)	5.3 ± 1.2	4.5 ± 0.9	4.6 ± 0.8	5.4 ± 1.1	5.7 ± 1.2

† I: 5min, II: 60min after peritoneal incision, III: skin closure. MAP: mean arterial pressure.

TABLE II Endogenous glucose production (R_a glucose), glucose plasma concentration and glucose clearance before and two hours after surgery in patients ranked for the time of peritoneal cavity exposure. Significant differences: * $P < 0.05$ compared with before surgery.

Patient	Exposure (min)	R_a glucose ($\mu\text{mol}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$)		Glucose Concentration (mmol·l ⁻¹)		Glucose Clearance ($\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$)	
		Before Surgery	2 hrs After Surgery	Before Surgery	2 hrs After Surgery	Before Surgery	2 hrs After Surgery
1	45	9.5	10.5	4.8	5.6	2.0	1.9
2	65	11.3	16.3	3.7	8.8	3.1	1.9
3	75	12.2	16.6	4.4	8.1	2.8	2.0
4	78	11.4	14.9	4.0	6.7	2.9	2.2
5	80	11.1	17.0	5.2	12.2	2.1	1.4
6	110	12.9	19.0	6.1	9.1	2.1	2.1
7	141	12.6	19.1	4.3	8.3	2.9	2.3
8	148	13.1	21.2	5.2	7.8	2.5	2.7
Mean $\pm$ SD	93 ± 37	11.8 ± 1.2	$16.8 \pm 3.2^*$	4.7 ± 0.8	$8.3 \pm 1.9^*$	2.6 ± 0.4	$2.1 \pm 0.4^*$

TABLE III Plasma concentrations of circulating concentrations of substrates and hormones before, during and two hours after surgery. Significant differences: * $P < 0.05$ compared with before surgery.

	<i>Before Surgery</i>	<i>During Surgery†</i>	<i>II</i>	<i>III</i>	<i>Two hours After Surgery</i>
Glucose (Mmol·l ⁻¹)	4.7 ± 0.8	5.7 ± 0.6	7.2 ± 1.5*	7.2 ± 1.4*	8.3 ± 1.9*
Lactate (Mmol·l ⁻¹)	1.0 ± 0.3	1.2 ± 0.4	1.1 ± 0.3	1.1 ± 0.3	1.5 ± 0.4
Insulin (μu·ml ⁻¹)	7 ± 3	4 ± 2	5 ± 2	8 ± 4	8 ± 3
Glucagon (pg·ml ⁻¹)	53 ± 14	52 ± 8	59 ± 14	62 ± 14	61 ± 14
Cortisol (μg·dl ⁻¹)	6 ± 2	9 ± 5	22 ± 4*	21 ± 4*	31 ± 7*
Epinephrine (pg·ml ⁻¹)	25 ± 14	163 ± 139*	223 ± 118*	236 ± 234*	205 ± 132*
Norepinephrine (pg·ml ⁻¹)	182 ± 82	413 ± 140*	547 ± 237*	442 ± 172*	377 ± 132*

† I 5 min, II: 60 min after peritoneal incision, III: skin closure.

Post-absorptive glycogenolysis constitutes approximately 75% of total glucose output, the remaining 25% being derived from gluconeogenesis.⁸ As a result of increased concentrations of counter-regulatory hormones, a direct consequence of surgery, hepatic gluconeogenesis under perioperative conditions is stimulated to a greater degree.⁹ Gluconeogenesis in the liver is an energy consuming process and in the post-absorptive state accounts for 50% of hepatic oxygen consumption.¹⁰ Thus, any modification of hepatic gluconeogenesis by anesthetic or surgical interventions may presumably have an effect on the energy balance of the liver. In the present study we could not quantify the gluconeogenic contribution to total glucose production because tracer kinetics do not allow the identification of the specific biochemical pathway. Glucose production rate after hysterectomy (16.8 ± 3.2 mol·kg⁻¹·min⁻¹) was lower than corresponding values observed in patients after severe injury¹¹ and during sepsis¹² lending further support to previous findings that the magnitude of glucose production depends on the intensity of stress.⁹

Different methods have been applied to assess the effect of the duration of surgery on glucose metabolism. Using the euglycemic insulin clamp technique a decrease of glucose utilization after 13 hr of plastic surgery has been reported.¹³ More recently, impaired glucose tolerance and diminished insulin secretion in response to intravenous glucose have been observed during prolonged radical neck surgery.¹⁴ Glucose clamp techniques and intravenous glucose tolerance tests require the administration of large amounts of

exogenous glucose and insulin with potential impact on glucose metabolism, especially when performed during surgical stress. In contrast, isotope dilution techniques infusing small doses of the stable isotope tracer [6,6-²H₂]-glucose measure endogenous glucose production and clearance at whole body level without any influence on the metabolic milieu. Since, in the physiologic steady state, whole body glucose uptake equals the rate of endogenous glucose production glucose uptake increased after abdominal hysterectomy in this study.¹⁵ However, an increased rate of whole body glucose uptake does not necessarily reflect an enhanced ability of the tissues to take up glucose, because glucose uptake increases proportionally as blood concentrations rise. This may be because most glucose uptake occurs in non-insulin-sensitive tissues, and the rate of uptake is to a large extent determined by the diffusion gradient for glucose. Thus, the rate of glucose uptake has to be corrected for the prevailing plasma glucose concentration. The resulting value, i. e. the glucose clearance rate, represents an index of the ability of tissues to take up glucose. Postoperative glucose clearance in our patients decreased after surgery, which was accompanied by an increase of endogenous glucose production indicating that both metabolic processes contributed to the hyperglycemic response observed after surgery.

The biochemical factors initiating, regulating and sustaining the hyperglycemic response to surgical trauma have not all been identified. Triple hormone infusion of catecholamines, glucagon and cortisol, however, can induce the changes in carbohydrate

metabolism occurring in the period immediately following trauma.¹⁶ As expected, epinephrine, norepinephrine and cortisol concentrations increased during and after the operation, whereas insulin and glucagon concentrations remained unchanged. Several studies demonstrated that the magnitude of increases of plasma cortisol and catecholamine concentrations depends on the severity of trauma.^{17,18} The results of the current study revealed no correlation between the duration of surgical trauma and the amount of the postoperative increase of these hormones.

Attempts were made to standardize anesthesia care and postoperative pain treatment and therefore causing minimal influence on glucose metabolism in our patients. The independent effect of desflurane on glucose metabolism has not been investigated, but inhaled anesthetic agents *per se* exhibit only minor, non significant metabolic effects under clinical conditions.¹⁹ A recent study on the metabolic impact of halothane, however, demonstrated that halothane caused a brief increase of blood glucose concentration five minutes after induction of anesthesia in adolescents.²⁰ This rise in plasma glucose concentration could be ascribed to stimulation of endogenous glucose production, which was not paralleled by a concomitant increase in peripheral glucose uptake. This finding is reminiscent of the results obtained with other anesthetics showing that isoflurane²¹ and sevoflurane^{14,22} also are capable of suppressing insulin secretion and altering glucose utilization. Thus, it cannot be ruled out that desflurane anesthesia contributed to hyperglycemia and decreased glucose clearance observed in this study. Because plasma insulin concentration did not change during and after surgery and the duration of action of desflurane is short, the effect of desflurane on glucose metabolism two hours after surgery must have been minimal. Therefore, the alterations in postoperative glucose metabolism presumably were the consequence of surgical trauma and not of the anesthetic agent.

In conclusion, hyperglycemia in the immediate period following abdominal hysterectomy is the result of decreased glucose clearance and increased endogenous glucose production, and the magnitude of this increment is associated with the duration of the exposure of the peritoneal cavity.

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