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REVIEW ARTICLE/BRIEF REVIEW

Perioperative catabolism
Catabolisme périopératoire

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Abstract

Purpose *This article reviews the pathophysiology, clinical relevance, and therapy of the catabolic response to surgical stress.*

Principle findings *The key clinical features of perioperative catabolism are hyperglycemia and loss of body protein, both metabolic consequences of impaired insulin function. Muscle weakness and (even moderate) increases in perioperative blood glucose are associated with morbidity after major surgery. Although the optimal glucose concentration for improving clinical outcomes is unknown, most medical associations recommend treatment of random blood glucose* $> 10\ mmol{\cdot}L^{-1}$. *Neuraxial anesthesia blunts the neuroendocrine stress response and enhances the anabolic effects of nutrition. There is evidence to suggest that the avoidance of preoperative fasting prevents insulin resistance and accelerates recovery after major abdominal surgery.*

Conclusions *Current anticatabolic therapeutic strategies include glycemic control and perioperative nutrition in combination with optimal pain control and the avoidance of preoperative starvation. All these elements are part of Enhanced Recovery After Surgery (ERAS) programs.*

Résumé

Objectif *Cet article examine la physiopathologie, la pertinence clinique et le traitement de la réponse catabolique au stress chirurgical.*

Constatations principales *Les principales caractéristiques cliniques du catabolisme périopératoire sont l''hyperglycémie et la perte de protéines corporelles, deux conséquences métaboliques de la perturbation de la fonction insulinique. Une faiblesse musculaire et des augmentations (même modérées) du glucose sanguin en périopératoire sont associées à une morbidité après des interventions chirurgicales majeures. Bien que la concentration optimale du glucose pour l''amélioration des aboutissements cliniques soit inconnue, la plupart des sociétés médicales recommandent le traitement aléatoire de la glycémie* $> 10\ mmol{\cdot}L^{-1}$. *L''anesthésie neuraxiale émousse la réponse au stress neuroendocrinien et favorise les effets anaboliques de la nutrition. Des données probantes suggèrent que l''évitement du jeûne préopératoire prévient la résistance à l''insuline et accélère la récupération après chirurgie abdominale majeure.*

Conclusions *Les stratégies thérapeutiques actuelles anticataboliques incluent le contrôle glycémique et la nutrition périopératoire en association avec un contrôle optimal de la douleur et l''évitement du jeûne préopératoire. Tous ces éléments font partie des programmes de Récupération rapide après la chirurgie (RRAC).*

Introduction

Patients undergoing major surgery are exposed to metabolic and endocrine alterations in carbohydrate, protein, and insulin metabolism, often summarized as the catabolic response. Preventing stress in an effort to minimize this catabolic response to surgery represents

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one key mechanism on which perioperative programs such as the Enhanced Recovery After Surgery (ERAS) concept are based.

This narrative describes the pathophysiology, clinical relevance, and treatment of perioperative catabolism.

The catabolic response to surgery: pathophysiology and clinical relevance

Pathophysiology

Glucose metabolism

Characteristic features of glucose metabolism are increased rates of glucose production combined with decreased peripheral glucose utilization, which result in hyperglycemia.

The magnitude of hyperglycemia depends on the severity of surgical tissue trauma.

In fasting non-diabetic patients undergoing elective intraperitoneal operations, blood glucose levels typically increase to 7-10 $mmol \cdot L^{-1}$. During cardiac surgery, glycemia frequently exceeds 10 $mmol \cdot L^{-1}$ in non-diabetic patients and 15 $mmol \cdot L^{-1}$ in diabetic patients.[1]

This hyerglycemia is further aggravated by the intravenous administration of drugs diluted in dextrose (antibiotics, catecholamines, and nitroglycerin), blood products containing large amounts of glucose, and nutritional support. Importantly, an infusion of 5% dextrose 100 mL (= 5 g of glucose) doubles the circulating glucose in a 70-kg non-diabetic patient.[2]

Although the effect of surgical technique on perioperative catabolism has not been well studied, laparoscopic procedures may have less impact on glucose metabolism than the open approach. Patients undergoing laparoscopic colon resection showed better glucose utilization when compared with laparotomy, possibly mediated through the reduction of tissue trauma, mitigation of inflammatory responses, and the preservation of insulin sensitivity.[3,4]

The choice of anesthetic drugs also affects glucose homeostasis. In contrast to propofol, high doses of opioids,[1] and neuraxial techniques, inhalational agents have been shown to accentuate the hyperglycemic response to surgery.[5,6]

The administration of corticosteroids for the prevention of postoperative nausea and vomiting, even in small doses, further exacerbates hyperglycemia in non-diabetic patients.[7,8]

Unexpectedly large numbers of patients show abnormal glucose homeostasis before surgery. In a prospective study in 500 patients presenting for elective procedures, 26% of previously undiagnosed patients showed blood glucose levels in the impaired-fasting glucose or diabetic range.[9,10]

Protein catabolism

Typical features of protein catabolism are stimulated rates of protein breakdown and amino acid oxidation which lead to a net loss of body protein.[11-13]

Metabolically healthy patients lose 40-80 g of nitrogen after elective abdominal surgery, equivalent to 1.2-2.4 kg of wet skeletal muscle.[14] Patients with burns or sepsis experience daily losses of up to 800 g of muscle mass. Protein loss in type 2 diabetic patients after colorectal cancer surgery has been shown to be 50% greater than in non-diabetics.[15]

Muscle wasting occurs early and rapidly during the first week of critical illness and is more severe among patients with multi-organ failure.[12] Significant muscle weakness and physical disability can persist for more than five years after injury and critical illness.[16,17]

There is no evidence to suggest that the magnitude of catabolic changes in elderly patients differs from those in younger adults. Age, however, may be associated with reduced muscle mass and a decreased capacity to utilize nutrients. Older patients may, therefore, be more vulnerable to protein catabolism.[18]

While older inhaled anesthetics, such as halothane, decrease protein breakdown and synthesis in humans, the impact of modern agents (desflurane, sevoflurane) on protein metabolism is unknown. Intravenous anesthetics (fentanyl, midazolam, propofol) have been shown to have no influence.[19-21]

Insulin resistance

Insulin resistance can be defined as any condition whereby a normal concentration of insulin produces a subnormal biological response.

Much of the impairment of insulin function can be explained by the stress-induced increase of so-called counter-regulatory hormones (cortisol, glucagon, catecholamines). These hormones exert catabolic effects, either directly or indirectly, by inhibiting insulin secretion and/or counteracting its peripheral action. The relationship shown between the time course of perioperative interleukin-6 plasma concentrations and insulin resistance suggests that inflammatory mediators (cytokines) are also involved.[22] The impairment of tissue insulin sensitivity is particularly severe in skeletal muscle, quantitatively the most important organ for insulin-mediated glucose uptake.[23]

The magnitude of whole-body insulin resistance is most pronounced on the day after surgery (up to 70% reduction)

and lasts for about three weeks after uncomplicated elective abdominal operations. It has been linked primarily to the invasiveness of surgery.[24,25] Other factors may also contribute, such as the duration of trauma,[26] bed rest and immobilization,[27] type of anesthesia and analgesia,[28,29] nutrition and preoperative fasting,[30,31] blood loss,[25] physical status, and post-surgery rehabilitation.[32]

Clinical relevance

Glucose metabolism

Even moderate increases in blood glucose are associated with adverse outcomes. Patients with cardiovascular, infectious, and neurological problems are particularly sensitive to changes in glycemia.[33-37] In critically ill patients, mortality is positively correlated with increasing glucose levels > 5 mmol·L^{-1},[38] and in patients undergoing cardiovascular procedures, hyperglycemia was associated with increased mortality and organ dysfunction.[39] Patients with fasting glucose levels > 7 mmol·L^{-1} or random blood glucose levels > 11.1 mmol·L^{-1} on general surgical wards had an 18-fold increase in in-hospital mortality, a longer stay, and a greater risk of infection.[33]

Acute changes in glucose levels may facilitate the development of post-traumatic chronic pain. In a chronic post-ischemia pain animal model, hyperglycemia occurred at the time of injury, and strict glycemic control reduced mechanical and cold allodynia.[40]

Marked fluctuations in blood glucose may be harmful, independent of the absolute mean glucose level.[41-43] There is no consistent definition of glycemic variability, and several metrics, e.g., the coefficient of variation of blood glucose levels or the glycemic lability index, have been used in critical illness.[41,44] It is also unclear whether variations within the normal glycemic range or periods of significant hypo- and hyperglycemia are problematic.

There is recent evidence to suggest that the quality of preoperative glycemic control is clinically important. Elevated levels of hemoglobin A1c, an indicator of glucose control in the preceding three months, were found to be predictive of complications after abdominal and cardiac surgery.[45-48]

In non-cardiac non-vascular patients, preoperative blood glucose levels > 11.1 mmol·L^{-1} were associated with a 2.1-fold higher risk in 30-day all-cause mortality and a four-fold higher risk of 30-day cardiovascular mortality.[49] In a large cohort of 61,536 consecutive elective non-cardiac surgery patients, poor preoperative glycemic control was related to adverse in-hospital outcomes and one-year mortality.[50]

Protein catabolism

Because protein represents structural and functional components, erosion of lean tissue delays wound healing, compromises immune function, and diminishes muscle strength after surgery.[51,52] The ensuing muscle weakness prolongs mechanical ventilation, inhibits coughing, and impedes mobilization, thereby causing morbidity and complicating convalescence.[53,54] The length of time for return of normal physiologic function after discharge from the hospital is related to the extent of lean body loss during hospitalization.[54]

Significant mortality occurs after critically ill patients are discharged from the intensive care unit (ICU) and hospital.[16] Many of these deaths are ascribed to the loss of muscle mass, inadequate physical activity, muscle weakness, and the inability to mobilize.

Insulin resistance

Studies performed in a small number of patients over a six-year period in Sweden (1990-1996) report a correlation between the postoperative decrease in the patient's insulin sensitivity and length of hospital stay.[25] In a larger cardiac surgery patient population, intraoperative insulin resistance was associated with clinical outcome.[45] Independent of the patient's diabetic state, for every 20% decrease in insulin sensitivity, the risk of serious complications (mortality, myocardial failure, stroke, dialysis, and infection) more than doubled.[45] These findings support the assumption that, perioperatively, acute alterations in glucose homeostasis, i.e., the "diabetes of the injury", predict adverse events better than the presence or absence of diabetes mellitus itself.

Anticatabolic strategies

The clinically important question is whether the catabolic stress response is a mere reflection of the severity of the underlying disease or whether the complications associated with catabolism can be reduced by its prevention or treatment. Hence, a number of strategies have been designed to minimize catabolic illness and, ideally, enhance outcome.[55]

Such therapies include the administration of endocrine (growth hormone,[56,57] insulin,[58] glucagon-like peptide-1,[59] steroids) or other agents (ß-blocker),[60] glycemic control,[61] various types of anesthesia (epidural anesthesia, intravenous opioids),[28,62] as well as nutritional support, in particular the provision of specific nutrients such as polyols (xylitol, sorbitol), fructose,[63-65] and amino acids

(glutamine, arginine, branched chain amino acids,[66-68] α-ketoanalogues).[69]

Due to lack of effectiveness (branched chain amino acids, glutamine,[70] α-ketoanalogues, intravenous opioids), unavailability in North America (polyols, fructose), cost and side effects (growth hormone, steroids, xylitol),[71,72] only two treatment modalities are presently used in clinical practice – glycemic control and nutritional support.

Glycemic control

Pioneering observational studies conducted in diabetic patients undergoing open heart surgery in Portland, Oregon, USA, showed reduced morbidity and mortality with improved glycemic management.[73] In 2001, the Leuven-I study showed superior outcomes with maintenance of normoglycemia, i.e., a mean blood glucose of 4.4-6.1 $mmol \cdot L^{-1}$.[61]

In critically ill patients, predominantly after cardiac procedures, mortality decreased by 50%. Besides saving lives, normoglycemia reduced the risk of infection, acute renal failure, liver dysfunction, peripheral neuropathy, muscle weakness, and anemia.

Several limitations of this unblinded trial raised concerns about the wider applicability of the study; these included the early administration of a relatively large amount of calories within the first 24 hr of admission, an unusually high mortality rate in the control group, and a treatment effect exceeding that of previous ICU studies. More importantly, recent large randomized clinical trials were unable to reproduce these benefits.[74-78]

The Leuven-II trial[75] and the VISEP study,[76] both using the Leuven insulin protocol and achieving mild hyperglycemia, reported a frequency of severe hypoglycemic episodes (< 2.2 $mmol \cdot L^{-1}$) in 18.7% and 17% of their respective study populations. In the NICE-SUGAR study, 74% of patients receiving intensive therapy had an episode of mild hypoglycemia, while in 7%, the hypoglycemia was severe.[74] *Post hoc* analysis showed that hypoglycemia was associated with mortality.[77] The Glucontrol trial was stopped prematurely because of a high rate of unintended protocol violations and a 9% incidence of hypoglycemia.[78]

A review of the effect of glycemic control on the incidence of surgical site infections was inconclusive because of the small number of studies ($n = 5$), the heterogeneity in patient populations, the definitions of outcome measures, and the fact that glycemic targets were different and/or were not achieved.[79]

A meta-analysis of studies performed in cardiac surgery suggested a lower mortality and risk of arrhythmias with tight perioperative glycemic control.[80] In contrast, more recent studies in cardiac patients failed to show any benefit but reported an increased incidence of hypoglycemia.[81-84] All these studies were small and some were retrospective.

Hence, to date, the optimal glucose level for enhancing clinical outcomes is unknown.

This uncertainty is reflected by the diversity of published recommendations concerning glycemic control in critically ill and surgical patients (Table).[85-89]

It is particularly interesting that most "glycemic control studies" after Leuven-I were unable to establish and preserve a normal blood glucose level.[74,76,78] Therefore, the conclusions that studies failing to reach this target reported regarding the clinical benefits of normoglycemia are questionable. While most associations still recommend treatment of random glucose levels > 10 $mmol \cdot L^{-1}$ (Table), a large clinical trial is warranted to identify the ideal blood glucose concentration during and after major surgery.

According to conventional protocols, blood glucose is frequently monitored, and insulin is titrated to a glycemic range. These "insulin sliding scales" are reactive, allow hyperglycemia to occur before therapy is initiated, take hours to be effective, and sometimes fail to establish target glycemia.[61,90]

In the critically ill, many regimens have evolved into algorithms requiring difficult and, at times, impractical calculations. Unless computerized, they are time-consuming and error prone. The interaction between glucose homeostasis and the neuroendocrine/inflammatory consequences of surgery is so complex that optimal glucose control cannot be achieved by occasional blood glucose measurements followed by reactive adjustments of insulin administration. Using a preemptive infusion of large doses of insulin, together with glucose infused at a variable rate to maintain a blood glucose of 4.0-6.0 $mmol \cdot L^{-1}$ (glucose insulin administration while maintaining normoglycemia = GIN therapy), it was possible to preserve consistent normoglycemia during open heart and major abdominal cancer surgery.[91]

While maintenance of normoglycemia and avoidance of large variations in glycemia are metabolically important, insulin *per se* possesses non-metabolic properties with potential benefits for surgical patients, especially those with cardiovascular disease. Protocols using supraphysiological doses of insulin in patients undergoing coronary artery bypass grafting showed anti-inflammatory and cardioprotective effects, as reflected by lower tumour necrosis factor α, interleukin 6, interleukin 8, and troponin levels.[92] These immunological changes were associated with a decreased requirement for inotropic support[93] and echocardiographic signs[94] of improved global myocardial function.[93]

Table Guidelines advocated by various medical organizations for adult glycemic control

	Cardiac Surgery	Critical Care	Non-cardiac Surgery
European Association for the Study of Diabetes (2013)[86]	individualized	individualized	individualized
Canadian Diabetes Association (2013)[87]	-	8-10.0 mmol·L^{-1}	5-10.0 mmol·L^{-1}
Surviving Sepsis Campaign (2012)[88]	-	6.1-10.0 mmol·L^{-1}	-
Society of Thoracic Surgeons (2009)[85]	< 10.0 mmol·L^{-1}	< 10.0 mmol·L^{-1} (if ICU stay < 3 days) < 8.3 mmol·L^{-1} (if ICU stay > 3 days)	-
American Diabetes Association & Association of Endocrinologists (2014)[89]	< 7.8 mmol·L^{-1} (fasting) < 10.0 mmol·L^{-1} (random)	7.8-10.0 mmol·L^{-1}	-
Canadian Clinical Practice Guidelines (2013)[163]	-	7-9.0 mmol·L^{-1}	
SCCM/ASPEN Guidelines (2009)[164]	-	6.1-8.3 mmol·L^{-1}	

ICU = intensive care unit; SCCM/ASPEN = Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition

Nutrition

Critical illness and the immediate period after abdominal surgery are characterized by semistarvation due to anorexia and/or restricted oral food intake. Unless amino acids and calories are provided in amounts sufficient to match ongoing demands, rapid net loss of lean tissue ensues. Hence, the primary goal of nutrition support is to attenuate protein wasting by optimizing nutrient delivery within the constraints of organ function.

The provision of hyper-, iso-, or hypocaloric amounts of energy, with or without protein, is a therapeutic modality that has traditionally been used to achieve this goal in surgical patients. Hyperalimentation, i.e., the administration of large hypercaloric amounts of energy and amino acids, is the only traditional strategy to induce anabolism after surgery.[95,96] Overfeeding, however, has been abandoned in clinical practice because of serious adverse effects (hyperglycemia,[39,97-99] respiratory distress,[100] liver dysfunction).[101,102] The provision of isocaloric amounts of glucose and amino acids improves nitrogen balance[95] and attenuates protein losses after surgery, but it fails to produce a positive nitrogen balance, i.e., anabolism.[95,103] Meta-analyses in surgical patients concluded that concepts of hyper- and isocaloric intravenous feeding have no overall clinical benefit and, in fact, may even be harmful, i.e. increase the rate of infectious complications and cardiovascular morbidity.[104,105]

In North America, provision of hypocaloric glucose at a dose below the patient's actual energy requirement is still being used to "feed" patients after elective abdominal surgery. Nevertheless, the anticatabolic properties of hypocaloric glucose observed in healthy fasting subjects do not apply to patients after surgical trauma. A glucose infusion of 150-200 g·day^{-1}, administered either alone[95,106-108] or with amino acids,[95,106] has no impact on nitrogen balance after surgery. Despite its inability to prevent protein catabolism, perioperative hypocaloric nutrition may have clinical benefits, such as a reduced infectious complications and length of hospitalization.[109]

Although little is known about the clinical advantage of early enteral nutrition after elective major surgery, some protocols, including ERAS programs advocate early recommencement of oral food intake. According to the results of one clinical trial, patients receiving preoperative carbohydrates and complete enteral feeding immediately after colorectal surgery remained normoglycemic and maintained a positive protein balance.[110] Early enteral nutrition after major rectal cancer surgery has been shown to be safe and associated with less ileus and anastomotic leakage.[111] More recent studies focused on the effects of immune-enhancing nutrients, such as n-3 fatty acids, arginine, and nucleotides. One meta-analysis using preoperative immunonutrition reported a decrease in total complications and infections when compared with no or standard therapy.[112] Another study failed to show the superiority of preoperative immunonutrition over the use of standard oral supplements.[113] In selected surgical cancer populations (head and neck, pancreas), perioperative immunonutrition may be beneficial.[114-116]

Some methodological problems, encountered in earlier reports, may explain the limited effectiveness of hypocaloric nutritional concepts in surgical patients. These include the disregard of type and quality of analgesia, lack of individualization of nutrition support,

inadequate assessment of catabolism before surgery, underestimation of preoperative starvation and disregard of hyperglycemia.

Anesthesia and analgesia

Neuraxial anesthesia

Segmental blockade of nociceptive signals at the spinal cord level provides the most effective pain relief after intraperitoneal procedures. Apart from optimal pain control, neuraxial blockade has anticatabolic effects that may contribute to better outcome.[117]

Epidural and intrathecal administration of local anesthetics prevents or blunts the neuroendocrine stress response, which results in improved insulin sensitivity with a positive influence on glucose and protein catabolism.[118] By attenuating insulin resistance and facilitating exogenous glucose utilization, neuraxial techniques reduce the amount of energy that is required to maintain protein balance. If the energy load of parenteral feeding can be decreased, use can be made of peripheral veins and hyperglycemia can be avoided. Epidural analgesia together with the perioperative infusion of hypocaloric glucose (200 $g \cdot day^{-1}$) has been shown to minimize the oxidative loss of protein after colorectal surgery, thereby saving muscle mass at a rate of 100 $g \cdot day^{-1}$.[119] The extent of protein sparing was greater than that previously achieved with other pharmacological and nutritional interventions, including growth hormone, glutamine, and total parenteral nutrition.[56,66,120] In addition, patients receiving epidural analgesia could be rendered anabolic by supplementing hypocaloric glucose with amino acids.[121]

Opioids

High-dose opioid anesthesia attenuates most of the endocrine and metabolic responses to surgery, but it is used rarely for procedures of short and intermediate duration.[122] Newer short-acting narcotics, such as sufentanil, alfentanil, and remifentanil, prevent intraoperative catabolism, also when used at a smaller dose. Postoperative catabolic changes, however, are either unaffected or even more pronounced.[28]

Individualization of nutritional support

Nutrition is typically prescribed on the basis of body weight and/or estimations of the patient's energy expenditure (EE). Use of body weight as the sole reference does not account for variations in body fat and lean tissue, the main determinant of whole-body energy consumption.[123] The Harris-Benedict equation is a formula commonly used to predict EE in surgical patients;[124] however, marked differences between measured and calculated EE have been reported, with measured amounts from 50-150% of the predicted EE value.[125-127] Indirect calorimetry allows direct measurement of the patient's EE and prompt adjustment to individual nutritional needs.

Assessment of catabolism before surgery

In order to evaluate the efficacy of nutritional support, the patient's baseline catabolic state must be quantified because sarcopenia is related to postoperative morbidity and mortality.[128,129] A significant association exists between the degree of preoperative catabolism and the anabolic effect of nutrition, with catabolic patients benefitting the most.[121] These more recent observations support the previous substantiation of superior outcomes in perioperatively fed malnourished patients.[130]

Many clinical and biochemical indices have been used to characterize the nutritional status of surgical patients, but all techniques have limitations.[131-133] Anthropometric and body composition measurements need to be treated with caution in subjects who are dehydrated and/or have edema or ascites.[131] Serum proteins are pathophysiological markers influenced by factors other than malnutrition or catabolism.[131,134]

Protein economy in surgical patients was often expressed as nitrogen balance, i.e. the difference between the body's total nitrogen intake and its total nitrogen loss; however, retention of nitrogen within the body and underestimation of nitrogen excretion in urine and other routes (feces, skin, and wound secretion) invariably lead to false positive values.[135,136]

Novel tracer methods using metabolic substrates (glucose, amino acids) labelled with stable isotopes (^{2}H, ^{13}C, ^{15}N) are considered the technique of choice for the global assessment of catabolism in humans and its relation to protein and energy intake.[137]

They provide a dynamic picture about the kinetics of glucose and amino acids on the whole body (protein breakdown, oxidation and synthesis, glucose production and utilization) and the organ-tissue level.[138-140]

Preoperative fasting

Elective surgery has routinely been performed after overnight fasting to minimize the risk of aspiration. Under certain conditions, such as a high risk of aspiration or preoperative bowel preparation, fasting periods are long enough to deplete hepatic glycogen stores and, thereby, increase the demand for amino acids for gluconeogenesis rather than tissue repair.[141-145] Animal studies have shown

that coping with stress is improved when the animals enter the trauma fed, not fasting.[142] Overnight treatment with glucose prevents postoperative decrease in insulin sensitivity[30,146] and early loss of protein after gastrointestinal surgery[147-149] and augments voluntary muscle function.[150] Clinical studies conducted in small patient populations reported better outcomes with preoperative nutrition[112,130,151-154] and emphasize that avoidance of fasting makes patients less susceptible to complications and may decrease hospital length of stay.[27,154-156] In contrast, the results of a larger randomized controlled trial showed no significant benefit.[157]

A recent meta-analysis, however, suggests that preoperative administration of oral carbohydrates accelerates recovery after major abdominal surgery.[158] The current ERAS guidelines, therefore, recommend the routine use of preoperative carbohydrate drinks.[159]

Hyperglycemia

Hyperglycemia *per se* has been shown to exacerbate protein catabolism during critical illness and, therefore, may blunt the anabolic response to feeding strategies that include glucose. In severely burned patients, net muscle protein catabolism increased proportionally with the level of blood glucose.[160] After major surgery for cancer, hyperglycemia induced by parenteral nutrition was associated with muscle protein catabolism, while maintenance of normoglycemia restored a neutral protein balance.[161]

Similar observations were made more recently in patients receiving intensive care, particularly during the early stages of critical illness.[162]

Conclusion

In conclusion, more and more evidence suggests that reversal of the catabolic responses to surgery may be associated with better outcomes. It appears that there is significant potential for perioperative physicians to optimize surgical recovery by preserving glucose homeostasis and providing optimal pain control and perioperative nutrition.

Key points

- Hyperglycemia, protein loss, and insulin resistance are important characteristics of the so-called catabolic response to surgery. All these features are associated with adverse outcomes.
- The optimal glucose concentration for improving clinical outcomes is unknown. Most associations recommend treatment of random blood glucose > 10 mmol·L^{-1}.
- Glucose insulin administration, while maintaining normoglycemia (GIN) therapy, allows for maintenance of perioperative normoglycemia, even in patients undergoing major surgery. Furthermore, GIN reduces glycemic variability, allows for feeding while avoiding glucotoxicity, and has anti-inflammatory, cardioprotective, and inotropic effects.
- Neuraxial anesthesia blunts the neuroendocrine stress response and results in improved insulin sensitivity with a positive influence on glucose and protein catabolism.
- The avoidance of preoperative fasting with oral carbohydrate administration accelerates recovery after major abdominal surgery.
- Enhanced Recovery After Surgery programs advocate early enteral feeding after colorectal surgery with potential clinical benefits.

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