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REVIEW ARTICLE/BRIEF REVIEW

Physiologic considerations of Enhanced Recovery After Surgery (ERAS) programs: implications of the stress response

Considérations physiologiques sur les programmes de Récupération rapide après la chirurgie (RRAC): implications de la réponse au stress

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Abstract

Purpose *Enhanced Recovery After Surgery (ERAS) programs have increasingly attracted the attention of clinicians who are intent on minimizing postoperative morbidity, decreasing variability in surgical care, and containing hospital costs. The purpose of this review is to discuss the relevant pathophysiology of the surgical stress response and its associated mechanisms that regulate important metabolic changes.*

Principal findings *The combination of hormonal release and various inflammatory responses inherent in the stress response to surgery contributes to a state of insulin resistance that represents one of the main pathogenic factors modulating perioperative outcome. The consequence of a decrease in insulin sensitivity is a significant change in protein and glucose metabolism characterized by an increase in the production of endogenous hepatic glucose, a decrease in the uptake of peripheral glucose, and an increase in the breakdown of protein. Muscle is the main tissue for uptake of insulin-mediated glucose, and consequent with the reduced activation of a specific glucose transporter protein (GLUT 4), glucose cannot be transported into the muscle cells. Consequently, breakdown of muscle protein, also related to insulin resistance, occurs to supply amino acids for gluconeogenesis, thus leading to the overall loss of lean muscle tissue. Besides the metabolic changes associated with the surgical insult, pain, relative perioperative starvation, and poor mobilization further contribute to a loss of insulin sensitivity and an increased catabolic state. Many of the ERAS elements that are implemented, including perioperative feeding, epidural analgesia, and minimally invasive surgery, modulate the stress response, promote insulin sensitivity, and attenuate the breakdown of protein.*

Conclusions *The implementation of a targeted ERAS program has been shown to modulate perioperative insulin sensitivity, thus improving postoperative outcomes and accelerating the return of baseline function.*

Résumé

Objectif *Les programmes de Récupération rapide après la chirurgie (RRAC) attirent de plus en plus l'attention des cliniciens qui cherchent à minimiser la morbidité postopératoire, réduire la variabilité des soins chirurgicaux et contenir les dépenses hospitalières. L'objectif de cette analyse est de discuter de la physiopathologie pertinente de la réponse au stress chirurgical et de ses mécanismes associés qui régulent d'importants changements métaboliques.*

Constatations principales *L'association d'une libération hormonale et de différentes réponses inflammatoires inhérentes au cours de la réponse au stress chirurgical contribue à un état de résistance à l'insuline qui représente l'un des principaux facteurs pathogéniques modulant l'évolution périopératoire du patient. La baisse de sensibilité à l'insuline a pour conséquence une modification significative du métabolisme des protéines et du glucose, caractérisée par une augmentation de la production de glucose hépatique endogène, une diminution de la capture du glucose périphérique et une augmentation du catabolisme des protéines. Le muscle est le principal tissu où a lieu la*

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capture du glucose à médiation insulinique et, du fait d'une moindre activation de la protéine transporteur spécifique du glucose (GLUT 4), ce dernier ne peut pas être transporté dans les cellules musculaires. Par conséquent, une dégradation des protéines du muscle (également liée à la résistance à l'insuline) a lieu pour fournir la néoglucogenèse en acides aminés, ce qui conduit à une fonte globale de la masse musculaire maigre. À côté des modifications métaboliques associées à l'agression chirurgicale, la douleur, le jeûne relatif périopératoire et l'absence de mobilisation contribuent encore plus à la perte de la sensibilité à l'insuline et à un accroissement du catabolisme. De nombreux éléments de la RRAC mis en œuvre, dont l'alimentation périopératoire, l'analgésie péridurale et la chirurgie très peu invasive, modulent la réponse au stress, facilitent la sensibilité à l'insuline et atténuent le catabolisme protéique.

Conclusions *La mise en œuvre d'un programme ciblé de RRAC a démontré qu'il modulait la sensibilité périopératoire à l'insuline, améliorant ainsi les aboutissements postopératoires et accélérant le retour au fonctionnement initial.*

As over 35 million operations are performed annually in North America, a considerable portion of health care funding is directed towards improving surgical outcome.[1] With a better understanding of the pathophysiology of the surgical stress response and greater interdisciplinary collaboration between health care providers, considerable attention has been focused on how to improve the quality of surgical care, reduce perioperative morbidity, accelerate the recovery process, and better utilize health resources. A common goal in the development and implementation of an Enhanced Recovery After Surgery (ERAS) program has been the need to understand and identify the factors that keep patients in hospital longer than necessary and delay their return to baseline function.[2] When compared with traditional care, the ERAS programs represent a major change in the process of care, as each ERAS component addresses a specific physiologic target.

In an attempt to elucidate a common physiological mechanism that characterizes many of the elements of the ERAS program, this article discusses how all of the elements must be integrated in order to facilitate clinical improvement. The literature search for this article is based on experimental and clinical works identified using MEDLINE® and the Cochrane Library. The key words used for searching included "fast-track", "enhanced recovery", "insulin resistance", "multimodal analgesia", and "perioperative care".

The intensity of the surgical stress response

Surgery represents a major trauma to the body triggering a cascade of events that are broadly referred to as the stress response. This response is characterized by an increased release in neuroendocrine hormones and activation of the immune system via the upregulation of various cytokines. The combination of both a systemic inflammatory response and hypothalamic-sympathetic stimulation acts on target organs, including the brain, heart, muscle, and liver. This series of reactions leads to metabolic changes, thus mobilizing substrates to supply energy to these vital organs. The constellation of the stress response's components includes anxiety, pain, tissue damage, ileus, tachycardia and other hemodynamic disturbances, cognitive dysfunction, hypoxia, disruption of sleep patterns, hypothermia, acidosis, hyperglycemia, loss of body mass, impaired homeostasis, and even altered fibrinolysis.[3] It is also evident that preoperative morbid conditions, such as heart and lung disease, diabetes, obesity, and cancer, decrease physiological reserves, thus exacerbating the stress response and further contributing to poor postoperative recovery.

Overall, the magnitude of the inflammatory response is consistent with the degree of surgical insult. An obvious clinical example is the use of endoscopic surgical techniques when compared with open procedures. Outcomes associated with laparoscopic techniques are generally well established to have less pain and shorter hospitalization; this has been shown with cholecystectomy.[4] Indeed, for cholecystectomy, the laparoscopic approach has been associated with a marked decrease in the inflammatory response.[4] This has also been seen with laparoscopic hysterectomy where a recent study showed a decrease in circulating interleukin (IL)-6 and C-reactive protein (CRP) compared with open hysterectomy.[5]

The severity of the inflammatory response to a standardized surgical insult has been shown to be widely variable, with human studies using a cardiopulmonary bypass model attributing such variability to genetic polymorphism.[6] Patients with higher pro-inflammatory responses were shown to be prone to a greater incidence of postoperative complications.[7] These genomic findings have yet to be adequately studied in abdominal surgery.

Central to the physiological changes characterized by the inflammatory response is the relatively acute development of insulin resistance. A correlation was shown between high circulating values of CRP, a marker of the inflammatory response, and poor preoperative insulin sensitivity in patients scheduled for cardiac surgery.[8] These same subjects became hyperglycemic after cardiac surgery and required very high doses of exogenous insulin in an attempt to target euglycemia.

It is now recognized that chronic tissue inflammation is an important cause of obesity-induced insulin resistance. The accumulation of increased numbers of adipose tissue macrophages that release cytokines (including tissue necrosis factor-α, IL-1ß) can act through paracrine mechanisms to inhibit insulin's action directly at its target cells or leak into the systemic circulation to cause insulin resistance via endocrine effects.[9] While the systemic inflammatory response is essential for many beneficial aspects of wound healing, an exaggerated inflammatory response has been associated with adverse perioperative outcomes.

Insulin resistance as a main pathogenic factor

The combination of catecholamine release and impaired immune function, hallmarks of the surgical stress response, can contribute to a state of insulin resistance that represents the most important pathogenic factor modulating the perioperative outcome.

The low sensitivity of the cell to insulin, thus defining insulin resistance, indicates an abnormal biological response to a normal concentration of insulin. As insulin controls glucose, fat, and protein metabolism, a change in insulin sensitivity impacts the whole of metabolism. As a consequence of surgical trauma, there is an alteration in glucose metabolism with increased hepatic glucose production and decreased peripheral uptake – both contribute to hyperglycemia.[10] Although muscle is the principal tissue for uptake of insulin-mediated glucose, with the reduced activation of a specific glucose transporter protein (GLUT 4), glucose transport into the muscle cells is significantly reduced (Fig. 1).

Breakdown of muscle protein is mediated by the reduced effect of intracellular insulin, with loss of muscle mass amounting to almost 50-70 g of protein per day. Therefore, hyperglycemia and breakdown of muscle protein are the two main metabolic consequences of the surgical stress response[11] (Table 1).

The direct relationship between an increase in the production of endogenous glucose and a breakdown of protein shown after surgery is characterized by an increased breakdown of whole body proteins into amino acids and shown to be directly responsible for the increased production of endogenous hepatic glucose.[12] As there is a strong association between these two metabolic alterations and postoperative complications, it is plausible to assume that insulin resistance can represent the main pathogenic mechanism.

Upon closer analysis, tissues that either mediate the injury or serve as the injury target in perioperative complications are not dependent on insulin *per se* for their glucose uptake. For example, immune cells involved in infections, endothelial cells in cardiovascular complications, and neural cells in neurological complications, have no specific glucose transport mechanisms. Instead, the uptake of glucose in these tissues is concentration dependent. As a result, there is an accumulation of glucose that can be used by the cells, partly for glycolysis, with the rest leading to the production of oxygen radicals and subsequent inflammation (Table 2). Many of these changes are similar to those observed in diabetic patients where an increased breakdown in protein is commonly reported after surgery.[13]

In diabetic subjects, a negative correlation has been shown between the degree of insulin resistance and the balance of whole-body protein. Similarly, a 50% greater postoperative loss of whole-body protein was reported in insulin-resistant patients compared with normal patients.[14] Even when supplemental nutrition is administered to these patients, it is usually poorly directed towards the synthesis

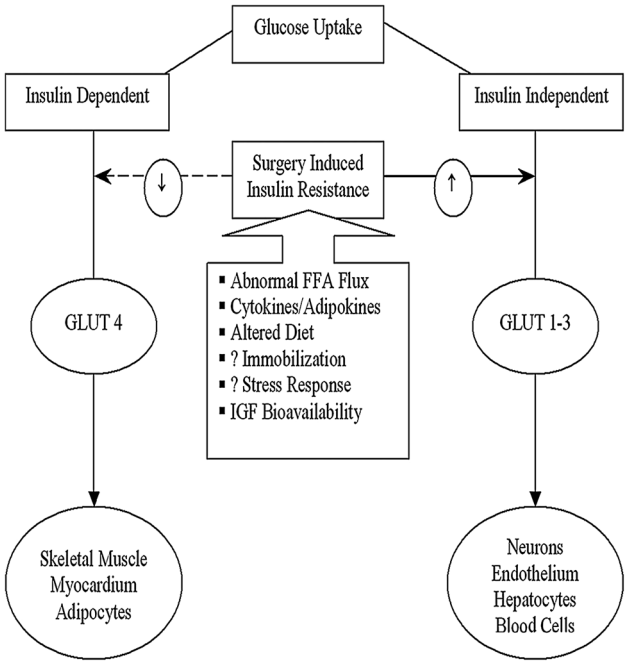

Fig. 1 Physiology of glucose uptake and the biochemical alterations contributing to perioperative insulin resistance. FFA = free fatty acid; GLUT1-4 = glucose transporters; IGF = insulin-like growth factor

Table 1 Nitrogen Loss* From Various Physiologic Insults

• Minor surgery	40 g
• Gastrointestinal tract surgery	100-150 g
• Sepsis	200 g
• Burns	300 g

* 1 g of nitrogen is 30 g hydrated lean tissue

Table 2 Events occurring in tissues unprotected from glucose uptake

Uncontrolled inflow of glucose
• No glucose storage
• Excessive glycolysis
• Production of oxygen radicals
• Inhibition of glycolysis and the Krebs cycle
• Altered gene expression
• Enhanced inflammatory responses

of proteins.[14] The clinical implications of the perioperative state of insulin resistance have been shown in a recent large study in patients undergoing cardiac surgery. In a study by Sato *et al.* in 273 patients scheduled for on-bypass cardiac surgery, the authors used the hyperinsulinemic-normoglycemic clamp technique to assess the degree of intraoperative insulin resistance and its impact on postoperative morbidity. Their study results showed that the risk of complications (e.g., serious infections) was proportional to the degree of intraoperative insulin resistance.[15] This finding was independent of several other factors, including the presence of diabetes.

Measuring insulin resistance

In a response to surgery, the body's intrinsic endocrine and inflammatory responses all result in mobilization of metabolic substrates from their storage areas – thus defining the catabolic state. This state can be reversed with insulin, which is the only fully anabolic hormone. As opposed to the preoperative period where there is equilibrium between the anabolic and catabolic functions, in the postoperative state, very high concentrations of insulin are required to achieve the same metabolic effect as in the normal non-injured state, thus indicating a state of insulin resistance. The administration of high doses of insulin has been successful in attempting to normalize this catabolic state.[16]

Several methods to measure insulin resistance have been proposed; however, the hyperinsulinemic-normoglycemic clamp (HNC) technique represents the gold standard procedure[17] whereby insulin is infused at a constant rate to obtain a steady-state insulin concentration above the fasting level. Based on frequent measurements of plasma glucose levels, glucose is intravenously infused at variable rates to maintain normoglycemia (4-6 mmol·L^{-1}). Given that endogenous glucose production is completely suppressed, the glucose infusion rate (under steady-state conditions) is reflective of glucose disposal, and therefore, is an indicator of peripheral insulin resistance: the greater the glucose infusion rate the more sensitive the body is to insulin and *vice versa*.[17]

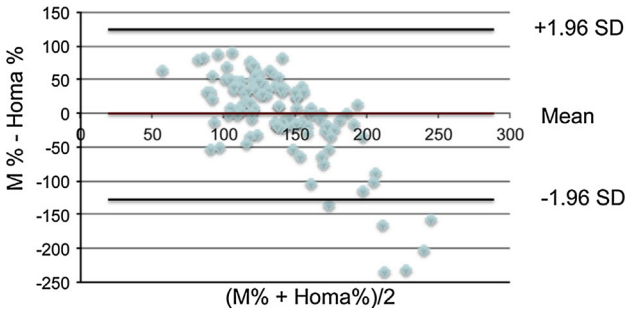

Fig. 2 The degree of agreement between the methods for the relative change in insulin sensitivity after surgery using Bland-Altman analysis. The relative change for both methods was 39% with a mean of difference of 0. There was a large range for the two standard deviation "limits of agreement" of 125%. In addition, there was a proportional error where a low degree of insulin resistance was underestimated by homeostatic model assessment (HOMA) and a high degree of resistance was overestimated (Modified with permission[18])

The homeostatic model assessment (HOMA), another measurement based on the concentration of fasting serum insulin and plasma glucose, has also been proposed; however, this is not a reliable technique after surgery as it measures glucose and insulin concentration in the fasted state when insulin release is relatively quiescent[18] (Fig. 2). In fact, in the fasted state, the basal insulin levels are low and have minimal effect on protein and glucose metabolism. In contrast, after an infusion of glucose or ingestion of carbohydrates, the concentration of insulin increases four to sixfold and facilitates glucose uptake by the cell.[19] For an accurate determination of the sensitivity of insulin in regulating the uptake of glucose, it has to be measured when the circulating concentrations of insulin are at relatively high physiological levels. During the early postoperative period, circulating glucose concentrations are high because of impairment in the uptake of peripheral glucose. Because this mechanism is activated only at high physiological levels of insulin, it is necessary to use a method that allows studies of glucose metabolism at these levels. The HNC is then more reliable than the HOMA and provides a real picture of the state of insulin resistance. Therefore, determinations of insulin resistance using basal glucose and insulin levels will not detect whole-body insulin resistance appropriately in surgical patients. Methods such as HOMA[20] that use these basal levels report results that are very different from studies using the appropriate methods (i.e., the HNC).[18,21]

Perioperative elements that contribute to insulin resistance

Some preoperative conditions, such as cancer,[22] morbid obesity,[23] metabolic syndrome,[24] diabetes,[25] and

sarcopenia[26] – the latter defined as the loss of muscle mass and coordination resulting from the process of aging – have been characterized by a hyperinflammatory state and low insulin sensitivity. The following intraoperative elements have been identified as contributing to the establishment of the postoperative state of insulin resistance: fasting and starvation, pain, and bed rest and fatigue.

Fasting and starvation

In order to maintain adequate circulating glucose concentrations during fasting as well as to compensate for the depleted stores of liver glycogen, fat and protein become the principal metabolic substrates providing energy to the vital organs. This change in substrate utilization is mediated by hormones such as glucagon and epinephrine. The fasting serum insulin levels are usually quite low, and the insulin which is available is unable to function effectively due to inhibition by the elevated levels of the abovementioned catabolic hormones. The implications of preoperative fasting on the metabolic response to surgery assume that the body has sufficient reserves to provide at a period of substantially increased energy requirements. Data from animals have shown that fasting not only causes a greater endocrine response to hemorrhagic stress but also results in lower survival compared with non-fasted animals.[27,28]

The transition to a non-fasted state with a meal or exogenous glucose administration elicits a significant insulin response and also blocks endogenous glucose production. Insulin changes the principal source of metabolism from fat to carbohydrates, thus maintaining protein stores and activating glucose transport into muscle. This anabolic state protects the body from surgical stress by reducing the level of insulin resistance induced by the catabolic hormones (glucagon, catecholamines) which characterize the postoperative period.

Pain

Pain from the surgical wound elicits its own inflammatory and metabolic responses, serving to augment even further the noxious pathways already described. Descending inhibitory sympathetic pathways modulate the transmission of nociceptive inputs at the level of the spinal cord. Responses to these nociceptive stimuli activate the hypothalamic-pituitary-adrenal axis and cause additional sympathetic stimulation as well as the systemic release of pro-inflammatory cytokines, which themselves are a major determinant of postoperative insulin resistance.[29]

Although it is difficult to separate the stress response elicited by pain itself from that which is a direct result of the trauma of the surgical incision, it is clear that pain stimuli themselves can initiate a response. This has been shown in an elegant study by Griesen *et al*. who produced an experimental model of a sustained painful stimulus on the abdominal wall without surgical incision and were able to measure a distinct endocrine, metabolic, and inflammatory response.[30] Furthermore, the metabolic changes were compatible with a state of insulin resistance, the latter being confirmed by using the HNC technique. The rate of disappearance of isotopically labelled glucose decreased by 16%, and the rate of glucose infusion necessary to maintain the target glucose-plasma concentration (5.5 $mmol \cdot L^{-1}$) decreased by 22%.

In this context, any intervention aimed at relieving pain would be expected to decrease (or potentially abolish altogether) insulin resistance. However, it would make sense if deafferentation of nociceptive pathways is initiated at the level of the periphery or before reaching the central nervous system. Neural blockade (epidural or spinal) with local anesthetics initiated before surgery and continued after surgery has shown to decrease the level of intra and postoperative insulin resistance.[31] This is probably related to the attenuation of hormonal response (cortisol and epinephrine) and, to a lesser degree, inflammatory response. No impact on insulin resistance has been shown by systemic opioids, while available data are lacking on the use of nonsteroidal anti-inflammatory drugs (NSAIDs), beta-blockers, alpha-2 agonists, or intravenous lidocaine. The effect of epidural analgesia, besides the normalization of glucose metabolism, is quite evident on protein breakdown and amino acid oxidation.[32] The addition of nutrients, either carbohydrates alone or carbohydrates with amino acids, in conjunction with epidural analgesia normalizes postoperative protein balance and insulin resistance.[33-35]

Bed rest and fatigue

Confining patients to bed for a prolonged period of time initiates a series of metabolic responses that can be deleterious if not corrected. Bed rest causes a decrease in functional capacity, cardiac stroke volume, and cardiac output. Peak oxygen consumption decreases at a rate of 1% for every two days of bed rest. In addition, both muscle weakness and atrophy begin after only one day of bed rest, with the extent being greater in older people. Insulin sensitivity begins to decrease within as little as two days of bed rest; this is accompanied by a drop in the synthesis of muscle protein.[36-38]

The impact of insulin resistance on organ function and related morbidity

Although not definitively proven, it is possible that the occurrence of reduced insulin sensitivity before surgery,

coupled with both the intra- and postoperative establishment of insulin resistance, impacts several organs via inflammatory pathways.

The gut is particularly sensitive to inflammatory mediators that are initiated by surgical manipulation. The changes in blood flow that it induces, along with the liberation of various gut peptides, can lead to disturbances of gut motility and absorption and ultimately result in ileus.[39]

Generalized fatigue is a frequent feature of the postoperative period. A complex inter-relationship has been shown between the degree of the inflammatory response (and intensity of surgery), the presence of cancer, as well as a patient's nutritional intake.[40] Patients not only feel tired but also require relatively more energy to accomplish the basic tasks of activities of daily living. In a recent study, only 40% of patients having had laparoscopic colectomy returned to their preoperative functional walking capacity at eight weeks following surgery.[41] Loss of functional capacity can occur even in patients undergoing day surgery. In a study of patients who underwent laparoscopic cholecystectomy, a procedure whereby patients are usually discharged home a few hours after surgery, 30% had not returned to baseline function at four weeks after surgery.[42]

The importance of glucose control on postoperative morbidity has been shown in recent studies. Patients undergoing colorectal surgery with elevated HbA1c (glycosylated hemoglobin) and no history of diabetes had a higher rate of postoperative infections.[43-45] Also, elevated glucose levels on both the day of surgery and the first postoperative day were associated with a higher incidence of complications and increased levels of CRP, indicating an association with the inflammatory response.[46] Postoperative complications following cardiac surgery, particularly serious infections, have been shown to be directly proportional to the degree of insulin resistance, as assessed using the HNC at the end of cardiac surgery.[15]

Minimizing insulin resistance with ERAS programs

Since the pathophysiological nature of the surgical stress response is multifactorial, therapeutic interventions should logically be aimed at the different components implicated in the genesis and propagation of insulin resistance. Treating postoperative insulin resistance will normalize insulin action and the main components of metabolism. Since the ultimate aim of an ERAS program is to facilitate recovery and minimize the rate of complications, there is emerging evidence that implementation of several strategies may modulate perioperative insulin resistance. No specific metabolic mechanism is known for other ERAS elements.

Preoperative optimization

In the last 30 years, major improvements in preoperative cardiorespiratory optimization have occurred. The result has been a significant reduction in both preoperative cancellations and perioperative mortality. Nevertheless, in the same period of time, we have seen an increase in patient comorbidities, many of which are related to what is considered a "modern lifestyle", including obesity, diabetes, hypertension, and some cancers. The culmination of these comorbidities represents an ongoing challenge to perioperative physicians, as all these factors are associated with significant postoperative complications. In addition, there has been an increase in the number of elderly patients and in operations for cancer.

In spite of major advances in surgical techniques and perioperative care, including anesthesia and analgesia techniques, the incidence of postoperative complications following major abdominal surgery remains as high as 30%.[47] This implies that factors besides surgical and anesthesia care (e.g., patient-related factors) impact quality of recovery. Some of these patient-related factors can be assessed with various risk assessment indices such as VO_2 peak (i.e., highest value of oxygen uptake attained during high intensity exercise testing), HbA1c, CRP, and albumin.

Based on some of these measures and knowing that a patient is at increased risk of complications, it seems very appropriate to prepare these individuals and optimize their physiological reserve before surgery. This is where the concept of preventative strategies inherent in *prehabilitation* programs has gained relevance, contrasting with *rehabilitation* where therapeutic interventions are implemented after the surgical insult has occurred. Prehabilitation can be defined as the process enabling patients to withstand the stress associated with surgery by augmenting physiological, nutritional, and emotional reserve in the preoperative period.[48]

Physical activity has been shown to be highly beneficial in many medical conditions, including diabetes, coronary artery disease, hypertension, rheumatoid arthritis, and some forms of cancer; however, disproportionately little research has been directed towards surgical patients. Physical activity in humans lowers the inflammatory response, as shown by lower levels of CRP.[49] At the present time, there is both a paucity of human studies as well as many conflicting results on the benefits of prehabilitation. This is likely due to the heterogeneity of the surgical models used and the fact that factors other than physical exercise, such as nutritional state and anxiety levels, may also play some

role in the postoperative processes involved with returning to full functional capacity after surgery. A pilot study followed by a recent randomized controlled trial using multimodal interventions in the three to four weeks prior to colorectal surgery for cancer showed significant improvement in functional capacity and mental health in over 80% of patients two months after surgery.[41,50] Of course, this field of research is in its relative infancy, and there is a need for a better understanding of the mechanisms initiated during prehabilitation that result in modulating functional capacity.

Perioperative feeding

With the previously outlined rationale in mind, it makes sense to prepare the body for surgery in a "fed" state where insulin levels are elevated, storage of substrates are made available, and insulin sensitivity is elevated in anticipation of the incoming surgical stress. There is considerable evidence that a preoperative carbohydrate drink increases insulin sensitivity before surgery and attenuates the development of insulin resistance in the postoperative state.[51,52] Complex carbohydrates appear to have a greater insulin secretion response, which has a pronounced effect on blocking gluconeogenesis. In addition, early postoperative oral feeding has been shown to be feasible in patients undergoing major surgery, and no side effects have been reported.[53]

The physiological advantage of feeding at a time of catabolic stress relates to the increased stimulation of insulin production that subsequently inhibits the breakdown of protein. This then facilitates incorporation of the amino acids – made available by the feeding – into protein synthesis.

The perioperative administration of insulin to maintain blood glucose at 6-8 $mmol \cdot L^{-1}$ has been shown to overcome postoperative insulin resistance and improve outcome.[54] Normoglycemia and protein balance can be maintained to some extent by large doses of insulin, indicating that insulin sensitivity is reduced (defined as an abnormal response to a normal concentration of insulin) throughout the period of intraoperative surgical stress, probably as a result of the raised inflammatory response that affects insulin target cells (myocytes, adipocytes, hepatocytes).[54] It remains to be seen whether other pharmacological or nutritional modalities could be introduced to minimize insulin resistance.

Minimally invasive surgery

The rationale behind minimizing traumatic surgical access (i.e., the surgical wound) is, in part, to reduce the activation of neurohumoral and inflammatory pathways that could adversely affect recovery. This effect can be achieved by reducing both access (i.e., incisional) trauma as well as internal trauma. Abdominal wall trauma can be reduced by limiting both the size and the orientation of the incision. By their very nature, endoscopic techniques limit the size of the incision. In addition, the trauma to the abdominal wall is better contained by splitting the muscle fibres instead of cutting them. Changing the incision from vertical to horizontal could also decrease pain as a result of having fewer dermatomes involved in transporting nociceptive signals to the central nervous system. In addition, the stimulation of inflammation can be reduced by minimizing manipulation of internal organs and direct trauma. Modern technology, such as ultrasonic cautery devices, reduces peritoneal injury and blood loss. The intraoperative cardiorespiratory and metabolic effects of pneumoperitoneum, almost universally used during endoscopic surgery, are significant, as shown by the pronounced elevation of circulating levels of cortisol and catecholamines.[4] Indeed, pneumoperitoneum in and of itself can cause a rise in this sympathetic response, which almost matches that elicited by laparotomy. The fact that the overall inflammatory response during laparoscopy is significantly attenuated may indicate an overall lesser degree of tissue damage.[4,5] This would explain, at least in part, the improved postoperative functional state following laparoscopy compared with conventional laparotomy. Thus, minimally invasive surgery remains an essential component of any ERAS program.

Maintaining physiologic homeostasis

Neuraxial blockade achieved with either epidural or spinal local anesthetic techniques has been shown to decrease perioperative insulin resistance and attenuate the increase in both blood glucose and postoperative protein catabolism.[31,34,54] The addition of nutritional supplementation while receiving postoperative neuraxial analgesia promotes protein synthesis and improves postoperative protein balance.[55] Maintaining a patient's normothermic state during surgery has been shown to attenuate the perioperative release of catecholamines[56] and decrease loss of body nitrogen.[57] Nevertheless, there are few data on the effect of active patient warming on minimizing the perioperative inflammatory response and insulin sensitivity – a potential area of future research.

Mobilization

Although the ERAS programs emphasize the importance of early mobilization, the degree of mobilization required in order to facilitate functional recovery is not known. This is particularly true as patients tend to lose muscle mass

rapidly after surgery and recovery can be delayed. Protocols differ between clinical care pathways as they include different types of exercise (i.e., in bed *vs* out of bed, and aerobic *vs* anaerobic) and exercises involving different muscle groups. A specific ERAS program does not usually specify the type of exercise to be conducted after surgery but encourages patients to increase the amount of exercise each day in order to reach predetermined goals. There is insufficient knowledge about the value of aerobic exercise in the immediate catabolic period, while it might be possible that resistance exercise could counteract the loss of muscle mass. Data from the oncology literature would suggest that physical exercise helps to overcome the fatigue during adjuvant therapy for breast cancer[58] and leads to lower mortality following colorectal cancer.[59] It goes without saying that adequate pain relief and minimal sedation facilitate mobilization, and therefore, integration of various elements is a necessity for better outcomes.

Future directions

Knowledge of the metabolic sequelae of surgery has led to a better understanding of the changes that occur when implementing a series of therapeutic modalities having a positive impact on physiological and clinical outcomes. Many of these components have been built into ERAS programs, although it is not clear how many of the individual elements are needed to achieve enhanced recovery.[60]

It is clear that the inflammatory and metabolic response triggers the establishment of insulin resistance which represents the major metabolic derangement leading to several clinical disturbances. Nevertheless, the connection between physiological and clinical outcomes is not always evident. Many aspects of the response to surgery still need to be explained, such as the mechanism of postoperative fatigue and the link between the inflammatory response and some features of the postoperative clinical course, e.g., sympathetic activation, ileus, postoperative sleep disorders, and cognitive dysfunction. Furthermore, the means to control visceral pain needs to be better elucidated. It is plausible that enhanced knowledge of these mechanisms would help to target the metabolic alterations with better therapeutic interventions. Pharmacological intervention with anti-inflammatory agents (steroids, lidocaine, NSAIDs, alpha-2 agonists), insulin sensitizers (metformin), and therapeutic supraphysiological insulin administration needs to receive better attention, as each of these might have benefits in modifying the inflammatory response and therefore modulate some of the postoperative insulin resistance. Patient variability in the severity of the inflammatory response, which could be genetic in origin, also deserves in-depth analysis. Ultimately, patients will reap the benefit of such advances in research that result in better clinical care and outcome.

Key points

- Surgery induces a state of insulin resistance.
- Pro-inflammatory mediators and catabolic hormones elicit metabolic changes that are characterized by hyperglycemia and protein catabolism.
- Metabolic changes lead to physiological disturbances that have an impact on recovery.
- Evidence-based modalities need to be integrated throughout the perioperative period to modify insulin resistance.
- Many aspects of ERAS programs that are based on known physiologic elements, can decrease both postoperative length of stay and rates of complications.

Conflicts of interest None declared.

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