Nutritional Support in the Perioperative Period

Topic 17

Module 17.1

Metabolic Responses to Surgical Stress

Mattias Soop, MD PhD
Consultant Surgeon, Reader in Surgery
Irving National Intestinal Failure Unit
Salford Royal Hospital and University of Manchester
Manchester, United Kingdom

Olle Ljungqvist, MD PhD
Professor of Surgery
Faculty of Medicine and Health
School of Health and Medical Sciences
Department of Surgery
Örebro University
Örebro, Sweden

Learning Objectives

- Understand how the body reacts to injury and surgery;
- Insights to stressors in surgical care;
- Have knowledge about how metabolic changes in surgery are related to surgical complications;
- Have knowledge about protein catabolism;
- Have knowledge about insulin resistance in surgery;
- Have knowledge about ways to reduce the catabolic response to elective surgery and how this affects recovery;
- Have knowledge about treatments that may impact on the metabolic response to elective surgery;
- Know about patients with special metabolic problems.

Contents

Key Messages

- Various stressors delay recovery and cause complications in surgery, many of them iatrogenic;
- Surgery and injury initiate a series of reactions causing catabolism;
- Insulin resistance is key to the metabolic response to surgery;
- Insulin resistance is closely related to many surgical complications and to postoperative fatigue and delayed recovery;
- Several simple treatments in the perioperative period can help reduce the catabolic reactions and thus enhance recovery and reduce complications;
- Fasting overnight is obsolete and patients should be given clear fluids to drink until 2 hours before anaesthesia, preferably a carbohydrate rich drink.

1. Aims of Perioperative Care

1.1. Obstacles to Recovery

The aim of perioperative care is to have the patient return to normal functions as fast and smoothly as possible. This commonly involves return of normal gastrointestinal function with the patient being able to eat and drink in a normal way and have the bowels moving. It also involves controlling pain to allow normal movement and ambulation. However, these functions are often disturbed with prevailing postoperative ileus, distension of the abdomen, pain from the wound, nausea and immobility. Much of this distress comes from unnecessary use of tubes and drains and overuse of intravenous fluids as will be discussed in this module.

1.2. Stressors in Surgery

Various different stressors are influencing postoperative patients as shown in **Fig. 1**. These stressors have different backgrounds and they often interact. Importantly, many stressors are iatrogenic; many traditional elements of care have been shown to disturb homeostasis with little benefit. Many of these treatments have poor supportive evidence, but remain in use simply because of institutional or national traditions.
Because of the widespread differences in perioperative care among countries around the world, and the often very slow uptake of novel concepts and treatments, there is a wide variety not only in care but also in outcomes. One example of this is in colorectal surgery where in many countries a traditional care pathway is still in place rendering more stress to the body than is actually needed. This will be discussed in module 17.3 where the principles of Enhanced Recovery After Surgery – ERAS – will be presented in detail. What is important already at this point is the fact that because of the variation in care the nutritional treatment, which it is possible to deliver, will vary greatly. To accommodate these differences the module 17.2 Nutritional Goals will cover nutritional treatment in

situations of more traditional care and in patients with complications in whom it is difficult or even impossible to employ the concepts of ERAS.

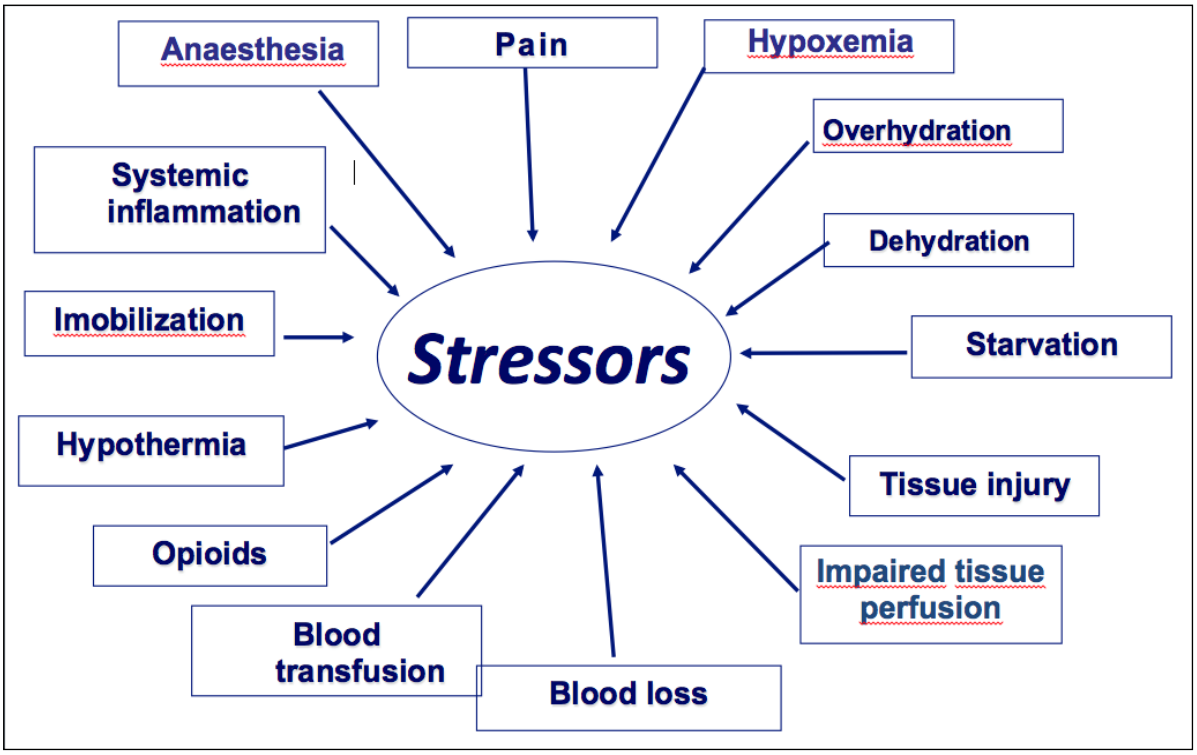

Fig. 1 Stressors in Surgery. A number of different factors contributes to the stress of surgery. Many of them are results of treatments given, many of them based on traditions rather than scientific evidence.

2. The Metabolic Response to Injury

Injury and surgery immediately spark a series of stress responses in the body. The most important reactions involve the release of stress hormones and cytokines. The magnitude of these reactions is related to the amount of stress inflicted. With greater stress, increasingly strong reactions cause more marked catabolic reactions. Central to all these reactions and the subsequent metabolic state is the loss of the normal anabolic actions of insulin, i.e. the development of insulin resistance (**Fig. 2**)(1). Excessive catabolic reactions are generally not beneficial for the body, and a state of catabolism with continuous breakdown of muscle tissue and loss of energy stores prolongs the time to recovery. Hence a key aspect of enhancing recovery after surgery is related to minimising the negative metabolic effects by reducing the catabolic responses and have the patient return to balanced metabolism as quickly as possible. Key to this process is the maintenance of proper energy and protein balance. Thus, nutrition in perioperative care is central for recovery.

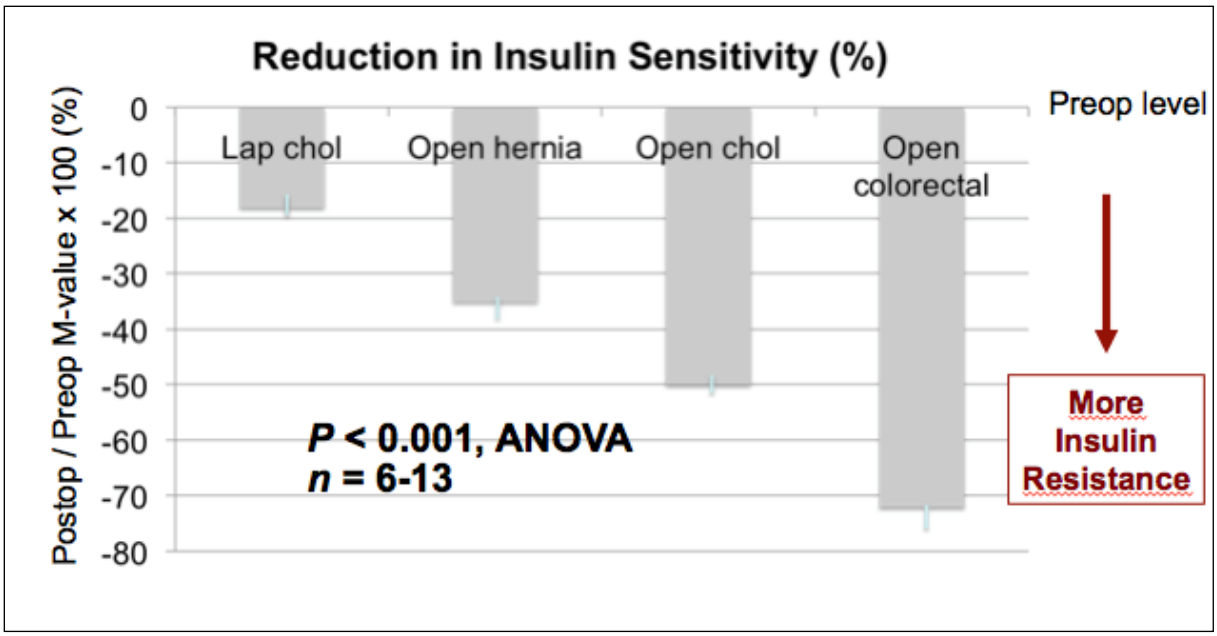

Fig. 2 Insulin resistance after surgery. The relative change in insulin sensitivity (postoperative / preoperative insulin sensitivity x 100, as determined using the hyperinsulinaemic normoglycaemic clamp technique) in relation to the magnitude of the surgical trauma (the size of the operation). From Thorell et al (1). (Lap and Open chol: laparoscopic and open cholecystectomy respectively.)

2.1 Insulin Actions under Normal Conditions

Insulin is the body's most important anabolic hormone. Insulin regulates glucose metabolism keeping it within very tight limits in health. Insulin ensures that glucose levels are normalised shortly after food intake by activating rapid glucose uptake and storage in muscle and fat, along with glucose loading of the liver as glycogen. This uptake is stimulated via specific glucose transporters, GLUT 4, that are activated by insulin. These transporters secure active and rapid uptake of glucose in these organs. Most other organs and cells have a transient increase of glucose uptake after carbohydrate intake. This uptake uses other transporters that act upon the prevailing glucose level. Since plasma glucose rises transiently after a meal, these organs also have a transient increase in uptake. This balance and interaction between these two different ways of regulating glucose uptake is important for daily glucose control, but is equally important for the development of some complications in surgery, as will be outlined below.

Insulin also controls protein metabolism, primarily by reducing protein breakdown in the muscle, but also by supporting protein synthesis in the presence of amino acids. Furthermore, insulin controls fat metabolism by stimulating formation of triglycerides and blocking their breakdown.

As outlined above, in insulin sensitive cells, primarily muscle and fat, insulin acts via specific receptors on the cell surface. Inside these insulin-sensitive cells, specific signalling pathways are activated securing anabolic reactions such as glycogen synthesis and storage and protein synthesis in muscle or the blocking of lipolysis in fat cells.

2.2 Insulin Resistance in Surgical Stress

With any major injury, such as major surgery, the actions of insulin are overwhelmed as a result of the release of the stress hormones (glucagon, catecholamines, cortisol and growth hormone) and the inflammatory reactions mediated by cytokines. In response to stress, amino acids, free fatty acids and glucose are released into the blood stream from various tissues. Substrate metabolism is changed and the body starts to consume fat more than glucose. Following major surgery, such as colorectal surgery, these reactions are reversible if the patient is treated with exogenous insulin. This was shown nicely in studies by Brandi et al who illustrated that if insulin is infused in sufficient amounts to normalize glucose levels, the rest of metabolism is also normalized (2). In these patients nutrition was provided as total parenteral nutrition during the course of the study. Thus, when nutrition is provided and insulin action is reinstated, protein breakdown is normalised, and free fatty acid levels and substrate oxidation return to normal. All occur once the effects of insulin on metabolism are reinstituted. From a clinical point of view it seems that infusion of sufficient insulin to normalise glucose levels can be used as a target end-point to achieve these reactions.

3. Complications after Surgery

3.1 Metabolism and Complications

Over the last 10 years it has become evident that changes in metabolism and excessive catabolism are involved in the development of many of the common complications occurring after surgery. A large study from Canada showed some years ago that insulin resistance is closely associated with the development of major complications (3). In this study insulin sensitivity was determined on the operating table at the end of surgery. The authors showed that with each stepwise reduction in insulin sensitivity (ie increasing insulin resistance) the risk of complications increased. This was particularly obvious for the development of infectious complications. As a result of insulin resistance, hyperglycaemia develops, and hyperglycaemia is one such cause of infectious complications. Other studies in elective surgical patients showed that patients with preoperatively elevated HbA1c, as a sign of disturbed glucose metabolism, also have higher postoperative glucose levels, and, associated with this, more complications (4). Studies in non-diabetics involving several thousand patients show a close association between the peak glucose level and morbidity, in particular medical complications such as infections, cardiovascular and renal problems, but also reoperations and even mortality (5). The development of surgical hyperglycaemia has many similarities to that described for hyperglycaemia in diabetic patients (**Table 1**) (6). However, while insulin resistance is progressive and slow in the development and progression of diabetes, in surgery insulin resistance is rapid in its onset but transient and has passed within weeks in most cases.

Table 1
Insulin resistance and glucose metabolism in diabetes type 2 and in the postoperative patient

Factor	Surgery	Diabetes type 2
Glucose level	Elevated	Elevated
Glucose production	Elevated	Elevated
Peripheral glucose uptake	Reduced	Reduced
GLUT 4 activation in muscle	Reduced	Reduced
Glycogen formation	Reduced	Reduced

Hence some of key characteristics of hyperglycaemia are an increase in glucose production, a relative reduction in glucose uptake in the periphery and the loss of activation of glucose transporters and glycogen storage in response to insulin stimulation in muscle and fat. The same changes also occur in type 2 diabetes. With insulin resistance the main mechanism for glucose uptake into the large potential depots in muscle and fat is blocked. This, along with the increase in glucose production contributes to the sustained elevation of glucose. Instead of glucose uptake into the normal depots, glucose uptake is markedly increased in the organs and cells that take up glucose in relation to the prevailing glucose level, including blood cells, renal cells, endothelial cells and neural cells. With glucose levels increased, these cells have no immediate mechanism to block glucose uptake in response to this rapidly developing stress. In addition, these cells have no storage capacity for glucose. This leaves glycolysis as the only metabolic pathway remaining for the elevated glucose inflow. When glycolysis is overloaded, this ultimately causes problems for these cells. With massive glucose inflow to the mitochondria the oxidative capacity is eventually overwhelmed and oxygen free radicals are produced. This in turn causes changes in cell metabolism that ultimately result in changes in gene expression and signalling. These reactions occur in many cells such as the endothelium, kidney, nerve and blood cells. These are also the key cells involved in many of the most common complications such as cardiovascular complications, renal failure, neuropathy and infection. While the details of these mechanisms have been explored in more depth in diabetic complications, there are several similarities between the type of complications developing in diabetes (6) and those seen in surgical stress (5).

Studies have shown that the main pathways for insulin signalling are disturbed after surgical stress and that this blocks the normal anabolic actions of insulin in muscle cells (7, 8). This is also true for fat cells where pathways of insulin are disturbed, while pathways promoting inflammation are enhanced (9). Studies have shown that this activation inside fat cells constitutes an important mechanism by which the inflammatory response is enhanced. This is often referred to as secondary activation. Muscle is also affected by surgical stress, and fatigue is a very common postoperative problem. This fatigue can be

explained by a combination of disturbed intracellular glucose metabolism and protein catabolism causing muscle protein breakdown, and at the same time limitations of available energy in the form of glucose and/or glycogen. The heart is another muscle that is vulnerable to stress and metabolic disturbances and insulin resistant states. Insulin has also been shown to be a key hormone for tissue healing, and hence a state of insulin resistance is accompanied by lower healing capacity (10).
Many of the complications in surgical stress are similar to those occurring in patients with diabetes (**Table 2**).

Table 2
Patterns of complications in diabetes and postoperative patients

Cells involved	Surgery (Occurring within days)	Diabetes type 2 (Develop over months & years)
Blood / immune cells	Infections	Infections
Renal	Renal failure	Renal failure
Endothelial	Cardiovascular	Cardiovascular
Nerve	Polyneuropathy	Polyneuropathy
Muscle	Fatigue	Fatigue

Thus, it is not only the changes occurring in postoperative glucose metabolism that are similar to those found in diabetes. The pattern of complications, and the affected cells are also the same in many instances. While in diabetes the disease progresses slowly, and complications usually develop over months and years, the change in surgery-induced glucose metabolism is established within minutes, and the complications usually occur within the first week of surgery.

3.2 Treating Insulin Resistance

Randomised studies of postoperative and trauma patients have shown that controlling glucose levels with insulin impacts on outcome by reducing the development of some of the more common complications in the surgical ICU (11, 12, 16). In addition, observational studies in patients undergoing colorectal surgery and treated in surgical wards where a lower glucose level was maintained had fewer complications than those with only slightly higher levels (by approximately 1 mmol/l (~20 mg/dL)) (4). In addition, there is a close relationship between the peak glucose level postoperatively and later developments of complications as mentioned above (5). While there is little doubt that higher glucose levels are associated with worse outcomes in surgery, the debate about when and how to treat them remains under debate. This is especially true for hyperglycaemia on the surgical ward where nursing is much less intense compared to the ICU. In this environment the use of

iv insulin to run a tight glucose control regime is most often not possible due to lack of personnel.
Recently, the focus in postoperative metabolism has been on glucose. However, there is an abundant literature from earlier years showing that negative protein balance is also detrimental for recovery after surgery. Protein balance is also under strong influence of insulin. Hence, in insulin resistant states, protein balance becomes negative, mainly because of increased protein breakdown in muscle, but also because of lack of amino acid supply. The main effect of insulin here is in reducing protein breakdown in muscle, while protein synthesis is mainly stimulated by insulin in the presence of amino acids (13). In stress-induced insulin resistance, treatment with insulin can counteract protein losses (2, 14) and support tissue healing (15). Smaller experimental studies in man clearly suggest that retaining insulin action is a key to anabolism and is likely to play a role in avoiding complications after surgery. This notion has been supported in a large, single centre randomized trial of patients after, mainly thoracic, surgery (11). These patients were given a combination of enteral and parenteral nutrition, and when given insulin to normalize glucose to 4.5 – 6.0 mmol/l (80-110 mg/dL), the authors reported a marked reduction in complications that affected cells sensitive to hyperglycaemia, and a marked reduction in mortality.
However, in one of the first large multicentre follow-up trials of patients under greater stress a similar treatment resulted in the opposite effect, with a slightly but significantly higher mortality (16). These seemingly conflicting findings are likely to be explained by some key differences between the Leuven and the Australasian trials. The Australasian, and several subsequent trials, included mainly patients with medical disease and established complications such as sepsis and organ failure (12). The initial Leuven trial included postoperative patients without established complications (11). Thus, intensive insulin treatment may be most effective when used to prevent further morbidity. This notion is supported by the finding in the Australasian trial of a numerically lower mortality in the treated group in the subgroup of major trauma (who were generally without prior morbidity) (n=886, P=0.07) (16).
For the patient recovering from surgical injury, the Leuven and the Australasian trials support the notion that controlling glucose is of benefit in preventing further morbidity. The several ICU trials that followed may not be as relevant for the discussion about glycaemia in the postoperative patient, since they contained a high proportion of medical patients with established complications and organ failure, with higher levels of stress and who were overall more severely ill, as indicated by scores and higher mortality rates. An in-depth discussion about glucose control in ICU is found in the LLL programme on Nutrition in the ICU.
For the surgical patient, a very practical and useful way to control glucose levels postoperatively is to follow the ERAS protocol, where many of the elements employed in the programme reduce the metabolic stress, including insulin resistance (17, 18).

4. Special Metabolic Risk Groups

4.1 The Malnourished Patient

The malnourished patient is at particular risk of complications and slower recovery (19). From a metabolic point of view these patients have substantially smaller reserves of energy and protein and they are also likely to have reduced lower immune function. It is therefore

important to identify patients who are malnourished or at risk of becoming malnourished. It is advisable to inform the patient of the importance of eating normal food up until the night before surgery and also to be liberal in providing nutritional supplements during the period before the operation (20). In more extreme and complicated cases, enteral and/or parenteral nutrition is often indicated as outlined in module 17.2.

4.2 The Patient with Diabetes

The patient with diabetes is another who has higher risks of complications. These patients are at risk of being catabolic from the very start if their diabetes is not under control. In addition, diabetic patients become even more insulin resistant after surgery. Several reports indicate that it is the peak glucose value that is related to major adverse outcomes after surgery (5), and some suggest that diabetic patients more often reach higher glucose levels after surgery than non-diabetics (21). Studies have shown that patients with diabetes under good control empty a preoperative carbohydrate drink at the same rate from the stomach as healthy volunteers. This was true for patients both on oral medication and those on insulin. The glucose level rose higher and stayed elevated longer than in the healthy controls, but from a safety point of view these patients may also be able to prepare for surgery this way if concurrently given their usual morning medication (22).

4.3 The Patient with Cancer

Patients with cancer coming for surgery often have disturbed glucose metabolism, even if they have not been diagnosed with diabetes. This is illustrated in a study in colorectal cancer patients, showing that every fourth patient coming for colorectal surgery without known diabetes had an elevated HbA1c indicating glucose intolerance (4). This is not all that surprising since cancer is known to cause insulin resistance. What was not known was that the patients with an elevated preoperative HbA1c also had a higher glucose level after surgery. In addition, they displayed higher CRP levels and developed more complications, in particular infectious complications.
The surgeon usually meets the patient a few weeks before the patient is to receive the operation. Many of the patients will have radiation or chemotherapy, but most of them will have surgery planned for as soon as possible. In most units the operation can be done within a few weeks. This still allows the patient to prepare metabolically and for the surgeon to institute appropriate treatments to ensure that the patient is in the best metabolic and nutritional status by the time of the operation. See further guidance in module 17.2.

5. Measures that Disturb Homeostasis

5.1 Preoperative Fasting

Preoperative fasting was first proposed in 1848 after the first anaesthetic death was reported (25), and became one of the best known medical rules during the last century (26). There is now overwhelming evidence for more liberal fasting guidelines, with intake of clear fluids permitted up until 2 hours before the onset of anaesthesia and surgery (27-31). Nevertheless, the old overnight fasting routine is still practiced in many countries. In addition to causing unnecessary discomfort for the patients, the fasted state of metabolism coming in to surgical stress has been shown not to be optimal (32). Instead of fasting,

setting off daytime metabolism with a carbohydrate load has been shown to have several positive effects on outcomes after elective surgery. Many of these effects can be associated with the effect on insulin action and insulin sensitivity that a carbohydrate load can have.
The normal diurnal rhythm of metabolism can be separated into two major entities, daytime metabolism that starts with breakfast, and night-time metabolism that prevails during the later phases of the night. Insulin is a key regulator of both. When we eat breakfast insulin is released and activates several mechanisms to ensure that the body stores the nutrients just consumed. Digestion is slow and takes a few hours. Therefore, the effects of insulin remain for 4-5 hours, and are usually still active by the time the next meal is consumed. During the day, metabolism is dominated by storage and anabolism, all under the influence of insulin. It is only during the late night when the interval between meals is prolonged that the effects of insulin wane. At this point other hormones are activated, mainly glucagon and cortisol. They are both anti-insulinergic and catabolic and set metabolism into breakdown mode. This is the situation with which the body comes into surgery if in an overnight fasted state.
A 20% glucose infusion intravenously overnight at a rate of 5 mg/kg/min or intake of 200-400 ml of a carbohydrate rich drink at a concentration of around 12% have been used to break the overnight fasted state. At these concentrations, daytime metabolism is set. This treatment initiates the activation of glucose uptake in insulin sensitive organs (mainly muscle and fat) and breaks the overnight fasted and catabolic state before the onset of the operation (33).
Intake of a carbohydrate-rich drink also enhances insulin sensitivity. This is probably one of the main reasons for the postoperative effect of substantially lower insulin resistance with the use of the preoperative carbohydrate loading. The carbohydrate load has effects mainly on the peripheral uptake of glucose in the first day or two (34, 35), while later the effect of a carbohydrate load is mainly to reduce endogenous glucose production (36). Both these effects will lower glucose levels in the postoperative phase (49). Interestingly, some of the effects remain for a very long time after surgery. This was shown in a study in which glycogen storage capacity was reduced in fasted patients for up to a month after elective colorectal surgery, while this was much improved with only a preoperative carbohydrate load (37). The mechanism behind these effects on glucose and protein has recently become clearer with studies showing that the insulin signalling pathways for the major anabolic effects in muscle cells are better preserved with carbohydrate loading compared to placebo (8). The effect is likely to be due to the stimulation of these pathways by the carbohydrate load before the onset of stress.
A recent study employing skeletal muscle biopsies before and after major surgery has further elucidated potential mechanisms both of insulin resistance and preoperative carbohydrate treatment (50). In this study, postoperative insulin resistance was associated with muscle inflammatory responses, and with impaired inhibition of FOXO1-mediated pyruvate dehydrogenase kinase-4 mRNA and protein expression after surgery. The net effect was a reduction in glucose oxidation, resulting in impaired glucose uptake in muscle. Preoperative carbohydrate supplementation attenuated postoperative insulin sensitivity by limiting muscle inflammation and improving insulin’s ability to inhibit pyruvate dehydrogenase kinase-4 activity (50).
Setting metabolism to an anabolic state before surgery using preoperative carbohydrates has several clinically relevant effects. With this preparation, protein metabolism is better maintained (38, 39), lean body mass is retained (40) and postoperative muscle function is

better maintained (37, 39). It is not just the skeletal muscle that is affected by metabolism and carbohydrate loading, since so also is the cardiac muscle. Hence, several reports have shown that the heart functions better when carbohydrate loading is used than after surgery performed in the fasted state (41-43). A recent Cochrane analysis reported roughly 1.5 days shorter hospital stay after major abdominal surgery with preoperative carbohydrates (44). This effect could not be shown for other forms of surgery, but this conclusion was based on fewer studies and ones of lesser overall quality.

5.2 Pain Control

An important part of the catabolic response is mediated by the release of the adrenal hormones cortisol and catecholamines. The release of these hormones can effectively be blocked by the use of epidural anaesthesia (45). The placement of the epidural should be such that it covers the dermatomes around T10 to achieve this effect, preferably at the level of T8-9. Importantly, it is crucial to activate the epidural before the onset of surgery to avoid the release of these potent catabolic hormones.
The epidural has several effects and one that is related to the metabolic aspects of enhanced recovery is pain relief. Pain itself causes insulin resistance (46). Avoiding pain is a key feature during the postoperative phase, and the epidural plays a key role.

5.3 Multimodal Metabolic Approach

Combining epidural anaesthesia and analgesia with carbohydrate loading reduce insulin resistance in two different ways (as outlined above), and a combined effect can be achieved. This combination allowed complete enteral feeding immediately after major colorectal surgery which could be continued for several days without any need for insulin, and still glucose levels were kept within the normal range (at approximately 6 mmol/l (110 mg/dL)) (**Fig. 3**). This was possible because the two treatments almost completely blocked the development of insulin resistance. The patient in a balanced metabolic state is able to take care of glucose control with endogenous insulin release (47). This is clinically important since rigorous glucose control otherwise often requires intravenous insulin with the entailing need for continual adjustments, and this is difficult to manage on regular surgical wards. A recent study in over 900 consecutive patients undergoing elective colorectal cancer surgery showed that compliance with the evidence-based ERAS protocol is key to improved outcomes (48). Thus, if fewer than 50% of the key perioperative treatment elements were adhered to then the length of stay was several days longer and complications more than 100% more common, than in patients who had been treated according to the protocol at levels of 90% concordance. Many of these treatments that have strong scientific evidence in their support also affect metabolism directly or indirectly. Hence maintaining metabolic stability and homeostasis is key to recovery, and nutrition is obviously a key factor in achieving this.

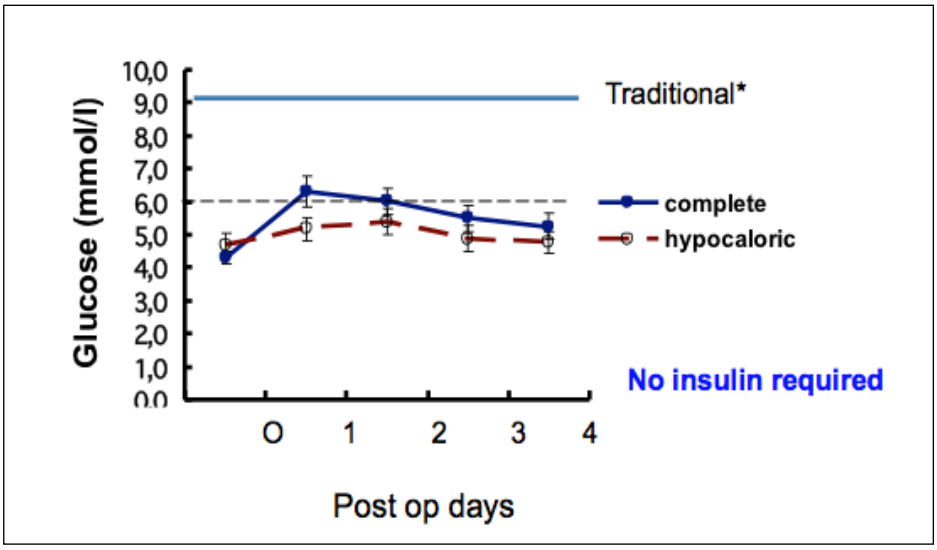

Fig. 3 Glucose after major colorectal surgery using a multimodal approach to metabolic control. Combining mid-thoracic epidural analgesia with preoperative carbohydrates while providing complete enteral nutrition (blue line) or hypocaloric glucose achieves the same level of glucose control without any need for insulin. From Soop et al (47).

6. Summary

This module describes the metabolic responses to surgical stress and how this impacts on outcomes. It also covers proposals for treatments that support anabolism and faster recovery after surgery by providing the optimal metabolic setting for postoperative nutrition.

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