Journal of Parenteral and Enteral Nutrition
Volume XX Number X
Month 2012 1-10

DOI: 10.1177/0148607112445580
http://jpen.sagepub.com
hosted at
http://online.sagepub.com

Jonathan E. Rhoads Lecture 2011: Insulin Resistance and Enhanced Recovery After Surgery

Olle Ljungqvist, MD, PhD

Abstract

This lecture reviews the current understanding of how insulin resistance, as a marker of the metabolic stress, is involved in recovery after major surgery. Insulin resistance develops as a graded response related to the magnitude of the operation. It lasts for weeks after medium-size surgery and affects all parts of body metabolism. Although hyperglycemia develops, muscle and fat uptake is reduced and other non-insulin-sensitive cells have an increase in glucose uptake as a result of the elevated glucose levels. Reduced glucose uptake and storage in muscle along with loss of lean body mass help explain reduced muscle function that will impair mobilization. The increased uptake of glucose in non-insulin-sensitive cells is involved in the development of several of the most common postoperative complications, including infections and cardiovascular problems. Many of the perioperative treatments in use are outdated, and modern care involves a multimodal approach with several treatments, such as preoperative carbohydrate treatment instead of overnight fasting, continuous epidural anesthesia for postoperative pain care, early feeding, and mobilization, all of which affect insulin by reducing the stress and enhancing recovery. Most of the previous mandatory catabolic responses to surgery can be avoided, resulting in substantially faster recovery and fewer complications. Methods to implement these modern treatments have been developed and used in Europe, resulting in improved care and shorter length of stay. (*JPEN J Parenter Enteral Nutr.* XXXX;xx:xx-xx)

Keywords

enhanced recovery; insulin resistance; postoperative nutrition; preoperative carbohydrates; surgery

Historical Reflection

In one of the first studies found on PubMed, Rhoads et al in 1946 studied the effect of preoperative force feeding of patients with poor nutrition status and high surgical risk.[1] The authors fed patients for 5 days preoperatively with a ≥0.8-g/kg nitrogen diet and achieved improved nitrogen balance, better postoperative outcome with regard to mobilization, and improved cardiovascular stability in a standardized tilt test. These early experiments showed that nutrition is important and that metabolic preparation is feasible and effective. What is striking about this study from 65 years ago is that the subject of study remains the same today: focus on muscle, protein, and postoperative function along with metabolic preparation before surgery to improve outcomes. So, the issues from the early days remain, but today we have new insights and possibilities. Our understanding of metabolic changes to surgical stress has increased, and this has helped us develop new ways of addressing problems facing surgeons for many decades.

Why Insulin Resistance and Enhanced Recovery?

Elective surgery is a treatment involving a deliberate injury to the body to remove disease or to repair organs. In response to any injury, the body sets off a series of reactions, including rapid neuroendocrine responses, setting of stress hormones, and activation of the cytokine and immune reactions.[2] These reactions lead to several changes in all parts of body metabolism, mobilizing substrates from all depots, and a general catabolic situation is established. In elective surgery, these metabolic changes can be reversed by the use of insulin.[3] However, in the postoperative situation, several-fold higher levels of insulin are needed to achieve the same metabolic effects as preoperatively, indicating a state of postoperative insulin resistance. Interestingly, when targeting and achieving

From Örebro University Hospital & Karolinska Institutet, Örebro, Sweden.

Financial disclosure: This work has been supported by the Swedish Research Council, Söderberg Foundation, Stockholm City Council, funds from the Karolinska Insitutet, and Nutricia Research.

The author has served in an advisory position for Fresenius Kabi, a German company in medical nutrition, and is currently serving as an adviser for Nutricia, a Dutch company in medical nutrition. The author patented a drink formula containing carbohydrates that is licensed to and commercialized by Nutritica. This patent expired in 2011. On behalf of the ERAS Society, the author started a commercial company, Encare AB, Sweden, that engages in change management.

Received for publication February 16, 2012; accepted for publication March 26, 2012.

Corresponding Author: Olle Ljungqvist, MD, PhD, Professor of Surgery, Nutrition & Metabolism, Department of Surgery, Örebro University Hospital & Karolinska Institutet, Örebro University Hospital, SE-710 85, Örebro, Sweden; e-mail: olle.ljungqvist@ki.se.

normal glucose levels with the insulin infusion, free fatty acid levels, urea excretion, and substrate oxidation are all normalized.[3] This shows that insulin resistance is present in all main parts of metabolism but also that insulin resistance can be counteracted in a synergistic way when achieving normoglycemia using insulin. This study was carried out in patients undergoing major abdominal surgery, and in more extreme stress, the situation may be different. Nevertheless, in major elective surgery, treating postoperative insulin resistance has been shown to normalize insulin action and the main components of metabolism. This is important, as will be outlined below.

Just as Dr Rhoads and his colleagues realized many years ago, we can influence elements in our perioperative care that will affect the outcome and recovery of the patient. Although feeding the undernourished patient was perhaps the most obvious nutrition treatment in those days, today we know that many perioperative care elements will have effects on metabolism directly or indirectly.

But to set the scenario right, we need to begin by defining the clinical goals for recovery in our postoperative patients. In general, we want the patient to recover to his or her preoperative function. This means in simple clinical terms that we want the return of bowel function, meaning both being able to eat and to have the bowels moving. Patients should be in control of pain using oral analgesics and be mobile to the extent they were before the operation. And of course, we want to avoid any complications. Once all these factors are achieved, the patient is actually ready to be discharged (see Table 1).

Insulin is the main anabolic hormone in the body and essential in governing all parts of metabolism. In doing so, insulin is also part of the regulation of the return of many functions in postoperative recovery outlined above, and insulin resistance is also important for the development of postoperative complications. In addition, many of the perioperative treatments have direct or indirect effects on insulin action. In recent years, several studies have shown that insulin resistance is a major key to the understanding of recovery after surgery[4] but also for the development of complications.[5] This recent study showed that the degree of insulin resistance when the patient was leaving the operating table was related to the risk of complications, particularly infectious complications.

In the late 1990s, Henrik Kehlet, a surgeon from Denmark, introduced the concept of a multimodal approach to recovery after surgery, called fast-track surgery,[6] and using this model published a report of 17 patients discharged with a median postoperative stay of 2 days after open colonic resections.[7] At that time, the postoperative stay was around 10 days in most modern institutions (and still remains so in many institutions around the world), so this caused quite a sensation when it was published. Kehlet and his work was a major source of inspiration for a group of surgeons in northern Europe who decided to start a collaboration to further explore the possibilities of improving outcomes and recovery after surgery using insights to metabolism and nutrition as a platform for further improvements. We were pleased to find Dr Kehlet involved in the initiation and early work of this group, called the Enhanced Recovery After Surgery (ERAS) study group (see the Acknowledgments). We intentionally renamed the concept *ERAS* to focus on recovery instead of speed per se. The term *ERAS* is now an accepted term for multimodal perioperative care programs resulting in fast recovery.

Table 1. Targets for Postoperative Recovery and Discharge Criteria

Goal	Specifics
Return of bowel function	Being able to eat Bowels moving
In control of pain	Using oral analgesics
Mobilized	To the extent preoperatively
No complications	In need of medial treatment (in hospital)

The study group focused initially on colonic resections and, based on Kehlet's initial protocol, refined and updated it to a consensus review published in 2005[8] describing a protocol for evidence-based perioperative care. This has since further developed into consensus protocols for also rectal surgery,[9] and protocols used in liver surgery in the group have also been presented.[10] This work is now being extended into other domains of surgery, including upper gastrointestinal (GI) surgery, gynecology, and urology, and the principles of these concepts have been published in many surgical domains as reviewed by Kehlet and Wilmore.[11] Certain features are common to these protocols, particularly the way they act: by reducing the stress reactions caused by the surgery and supporting the return of key functions (ie, GI function and mobilization).

From a traditional care situation, the evidence in the literature shows that many of these old routines need to be abandoned (Table 2). This means many of the traditional care elements, many of them causing major discomfort for the patient, should be abandoned for the better of the patient. For the complete list of the evidence behind the most recent protocol update and the evidence behind it, see Lassen at al[9]; for upcoming updates and protocol and general information, please see the website of the ERAS Society for Perioperative Care, a newly started nonprofit professional society (www.erassociety.org).

The use of ERAS protocols has been shown to have marked effects not only on general recovery after surgery but also in reducing complications. A meta-analysis from 2010, based on 6 studies from 4 countries where the ERAS group employed at least 4 ERAS elements in the care protocol compared with traditional care, showed a mean reduction in length of stay of 2.5 days.[12] Perhaps more important was the finding of a reduction of complications by about 50%. Obviously, such improvements have marked implications for the patients, staff, hospital organization, and the costs of care. Indeed, a report from New

Table 2. Changes From Traditional Care to Evidence-Based Perioperative Care Practice in Enhanced Recovery After Surgery Protocols for Colonic Resections[9]

Changes for the Surgeon	Changes for the Anesthetist
No routine bowel cleansing	Carbohydrate treatment instead of overnight fasting
Drink and food the day of surgery	No long-acting sedation for premedication
Avoid abdominal drains	Mid-thoracic epidural anesthesia
Early removal of urinary catheter	Balanced fluids
Remove intravenous fluid day 1 after surgery	Use vasopressors to control hypotension
Prepare for early discharge	No or short-acting opioids

Zealand showed that even when employing a very ambitious program to start an ERAS program with travels across the world for the ERAS team and full-time staff employed, the average saving per patient was more than $5000 for the first 50 patients, mainly due to shorter length of stay and reducing costs for complications.[13]

How Insulin Resistance Is Affected by Perioperative Care Elements

A key objective in the recovery of the patient is to have gut function return as fast as possible. Securing energy intake is important because studies show that just allowing low glucose intake intravenously, such as 50 g in 2000 mL/d, results in marked insulin resistance.[14] Healthy volunteers treated this way for 3 days lost about 50% of their insulin sensitivity. Bed rest in this shorter time span caused no further resistance. However, long-term bed rest, shown by Biolo and his team,[15] results in a marked change in protein metabolism, significantly reducing protein synthesis. When combined with hypocaloric nutrition, protein breakdown is further enhanced. Protein balance is affected by insulin, and in particular, insulin has been shown to reduce protein breakdown, whereas protein synthesis in muscle is more affected by the availability of amino acids.[16] Other studies show that bed rest rapidly impairs aerobic capacity,[17] further impeding mobilization. Apart from bowel function and mobilization, avoiding pain is an important aim for recovery. One reason for this is that pain per se causes insulin resistance as shown by some elegant studies by Greisen et al.[18] So for all 3 aims of recovery, insulin resistance is an important component.

How Best to Define and Measure Insulin Resistance?

How best to define insulin resistance? The initial studies of insulin resistance focused on glucose metabolism,[19] and this remains the cornerstone of all recent studies as well. However, other studies have shown that not only glucose metabolism but also protein[20] and fat metabolism[21] are affected, so insulin resistance affects all parts of metabolism.[3] A more appropriate and broader definition of postoperative insulin resistance is as follows: below-normal insulin effect of insulin for glucose, protein, and/or fat metabolism in the postoperative phase.

How best to measure insulin resistance? Determinations of insulin sensitivity or resistance should be performed in situations when insulin can be expected to be active. At basal levels in the fasted state, insulin levels remain at about 5–12 µU/mL in plasma (variations depending on methods used), and at this level, insulin has minimal effects on glucose and protein metabolism. Glucose is supplied by endogenous production at a rate of about 2 mg/kg/min, and glucose uptake is at the same low level and minimally affected by insulin. However, as soon as nutrients are consumed, insulin is released to levels about 6–8 times the basal levels. At these levels, glucose production is shut off, and peripheral glucose uptake is enhanced about 3- to 4-fold.[22] This elevation in glucose uptake is seen only at the higher physiological levels of insulin, whereas half the elevation (3-fold increase from basal) has no effect on glucose uptake. In the early postoperative situation, it is the glucose uptake that is the main cause of insulin resistance. Because this mechanism is activated only at high physiological levels (meal levels) of insulin, it is necessary to use a method allowing studies of glucose metabolism at these levels. The change in glucose turnover at the low basal fasting levels represents at most 10%–15% of the total whole-body insulin resistance after surgery. 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 homeostatic model assessment (HOMA)[23] using these basal levels report results that are very different[24] from studies using the appropriate methods (ie, the hyperinsulinemic normoglycemic clamp).[25]

Insulin sensitivity in normal adult elective surgical patients varies by a factor of 7–8. However, as shown in Figure 1, the relative change after any given procedure group is more consistent.[4] The greater the operation, the more resistant the patient becomes. In addition, Figure 1 also shows that the surgical technique makes a major difference since laparoscopic techniques render minimal resistance, whereas the same procedure done using open techniques results in a 50% fall in sensitivity.

After a medium-size upper abdominal procedure, such as open cholecystectomy, insulin resistance remains for about 2–3 weeks even in uncomplicated postoperative patients. Further analysis has shown that insulin resistance is an independent predictor of length of stay. Along with the type of surgery and blood loss during surgery, this parameter explains more than 70% of the variation in length of stay.[4]

When examining the details of the change in glucose metabolism in the postoperative insulin resistant state, it was found that the driving forces behind hyperglycemia were both

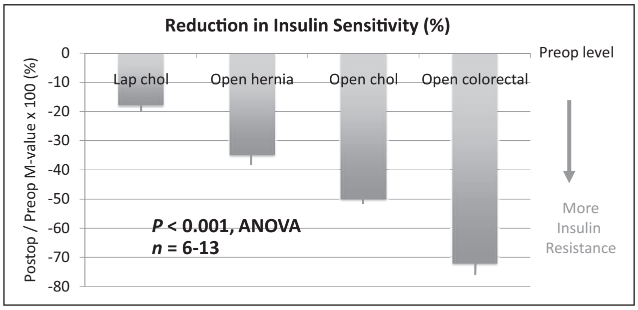

Figure 1. The relative change ((M-value after surgery/M-value after surgery) × 100) in insulin sensitivity after different surgical procedures and surgical approaches (open vs laparsocopic cholecystectomy). The lower the sensitvitiy, the greater the resistance to insulin as determined using the hyperinsulinemic normoglycemic clamp under a similar type of general anesthesia. Lap, laparosocopic; Chol, cholecystectomy. n = 6–13 per group, means ± SEM; differences between groups $P < .001$, analysis of variance. Adapted from Thorell et al.[4]

an increase in glucose production and a reduction in glucose uptake in the periphery. At the cellular level, muscle is the main tissue for insulin-mediated glucose uptake. In muscle, there is a reduced activation of the specific glucose transporting protein, GLUT 4, after surgery.[26] This is likely to be caused by reduced activation of the insulin signaling system in the cells, including PI-3 kinase.[27] At the same time, glycogen formation is reduced in the postoperative insulin-resistant state.[28] Thus, the overall change in glucose metabolism that develops very fast in surgery holds many similarities to that found in patients with type 2 diabetes (Table 2).

How can insulin resistance be involved in postoperative recovery? In insulin-resistant states, there will be less effective facilitating glucose transport into the muscle cell, and less glycogen is stored as well. At the same time, there will loss of protein from the muscle, rendering overall loss of lean body mass. These 2 factors in combination, less energy and less structural protein, result in lower muscle function and less capacity to mobilize. In addition, studies in patients with burns have also shown that insulin has an important anabolic role for wound healing.[29]

Insulin Resistance and Complications

Many of the most common complications developing in surgery are similar to those occurring in diabetes; the difference is that they develop within days in surgery and often after a much longer time in diabetes (Table 3). It is also noteworthy to find that the cells involved in many of the complications are not dependent directly on insulin for their glucose uptake. These cells include immune cells involved in infections, endothelial cells for cardiovascular complications, and neural cells for neuropathies. These cells take up glucose mainly depending on the prevailing glucose level in the plasma (and interstitial fluids). These cells have no storage capacity for glucose, so the only pathway for glucose once inside the cells is through glycolysis. Brownlee[31] very nicely showed how these cells, when overloaded with too much inflow of glucose, eventually start producing oxygen free radicals, leading to changes in gene expression in many cells, causing further enhancement of inflammation, which in turn causes further insulin resistance in a vicious cycle. Similar findings are now being unraveled also in surgical insulin-resistant states. Recent studies from muscle[32] and adipose tissue[33] show increased inflammatory signaling developing during surgery. Many of the recent findings of changes after surgery are in line with changes reported in diabetes,[31] including signs of reactive oxygen species (ROS) overproduction and protein kinase C (PKC) activation, causing further inflammation.

Table 3. Changes in Glucose Metabolism in Postoperative Patients and in Patients With Type 2 Diabetes[30]

	Postoperative	Type 2 Diabetes
Hyperglycemia	++	++
Whole-body insulin sensitivity	–	– –
Glucose production	+	++
Peripheral glucose uptake	– –	– –
GLUT 4 translocation	–	–
Glycogen formation	–	–

+ indicates increase, – indicates decrease.

Since the first study by van den Berghe et al[34] from 2001 showing reduced mortality in surgical intensive care unit (ICU) patients when lowering glucose to normal levels as opposed to allowing hyperglycemia, the interest in glucose control has been very high. The reduced mortality was associated with avoiding subsequent developments of complications when glucose was under control. The action taken was to secure reinstatement of insulin action (ie, treating insulin resistance). This lowered a range of complications, including infections, renal failure, polyneuropathy, and the need for assisted ventilation. Subsequent studies in the medical ICU were less clear, and a large multicenter trial in more severely stressed mixed ICU patients reported increased mortality when using strict glucose control.[35] Interestingly, in trauma and postsurgical patients, the subgroup of patients in that trial who were the closest to the patients in the first van den Berghe trial showed a similar trend for lowering mortality as well. This suggests that in surgical patients, controlling glucose by treating insulin resistance is beneficial by avoiding the development of complications. This is very different from using insulin to treat insulin resistance in a severely stressed septic medical patient with the complication already present. This may very well help explain some of the differences between the results in various ICU trials of glucose control.

In less stressed studies, such as in consecutive patients with colorectal cancer, data suggest that glucose metabolism is highly relevant when explaining developments of common postoperative complications.[36,37] In patients with a normal HbA1c as opposed to an elevated level and lower glucose levels during the postoperative course, the risk of complications, dominated by infections, is lower. The patients with elevated HbA1c before the operation had no known diabetes, and probably the derangement in glucose metabolism was because of the cancer disease for which they had surgery. Another finding was that elevations in glucose were associated with higher CRP levels, indicating again an association with the inflammatory responses. This study was performed in an advanced ERAS environment where both groups of patients consumed an average of 1500 kcal/d spontaneously using hospital food complemented with some nutrition supplements. The glucose values given were the averages of 5 taken throughout the day and thus mostly postabsorptive glucose levels.

The most convincing evidence to date of the role of insulin resistance in surgical complications is a recent study from Montreal where almost 300 patients undergoing thoracic surgery were studied using the clamp method while being operated on.[5] Sato et al[5] reported that the risk of complications, particularly serious infections, was proportional to the degree of insulin resistance when the patient left the operating table. This finding was independent of several other factors, including the presence of diabetes. The fact that hyperglycemia impairs several key functions of the immune system is well known since many years from studies both in surgery and in diabetes.[38]

Although it is clear that hyperglycemia and insulin resistance have a negative impact on outcomes in surgery, many seemingly basic questions still remain. For instance, it is still not clear which glucose level, taken at which time and in which situation, is the most predictive for risk or should be the target for treatment. Hence, we have no clear guidance whether the basal glucose level is the important one. If so, how long should we wait after turning off intravenous (IV) infusions of nutrients or after enteral or oral feeding? A very recent study in colorectal patients indicates that even small elevations of peak glucose levels increase the risk of complications.[37] Although these questions do seem basic, getting the right answers to them still remains an important challenge.

Enhanced Recovery Protocols: Integration and Protection Against Insulin Resistance

ERAS protocols are standardized integrated care protocols adjusted to the patient's journey to minimize the stress reactions to surgery and support the return of functions. The protocols are based on available evidence in the literature.[9] A very important component of the ERAS philosophy is to keep up a continuous audit and follow up the outcomes but also the compliance to the protocol items in the protocol. This is important because all elements of the protocol have been shown to have a direct impact on the outcome. Many of the care protocol items have direct or indirect effects on insulin resistance (see below).

The following example shows how metabolism and function, as well as the different elements, interact. In the preoperative phase, we can choose to minimize the developments of insulin resistance using 2 simple and readily available treatments: preoperative carbohydrate treatment instead of overnight fasting and epidural anesthesia. These treatments will also affect the postoperative phase and treatments given at that stage of the patient's journey.

Preoperative Carbohydrates

Overnight fasting is probably the best-known medical "rule" worldwide. It was first proposed after the first anesthesia death reported in 1848.[39] The main reason behind the proposal was to ensure an empty stomach at the time of anesthesia. To secure this, it was felt that an overnight fast would be sufficient. However, it was not until in the 20th century that it became the standard preparation for elective surgery[40] when an author of a textbook simply stated this a rule. From then on, most authors did the same, until the entire idea of overnight fasting was questioned, proven unnecessary, and finally changed.[41] Overnight fasting causes discomfort such as thirst, hunger, headaches, and anxiety, and intake of clear fluids taken up until 2 hours before anesthesia does not increase the gastric volumes.[42,43] On the contrary, intake of clear fluids stimulates the stomach to empty and has often been reported to reduce residual gastric volumes. The risks associated with aspiration are related to the patient's comorbidity rather than the time of fasting, with the exception of patients with slow gastric emptying. Intake of clear fluids is now recommended up until 2 hours before anesthesia and surgery. Intake of water, tea, coffee, and some juices has been shown to reduce thirst and sometimes hunger and headaches. However, clear fluids have little if any effect on body metabolism, and with the fasting routines applied, the body is set to undergo stress in a fasted state. For most people in any other situation, this would be an unnatural way to prepare for stress. This certainly applies for normal workdays but also for sports. Some early animal experiments in hemorrhagic stress and endotoxemia several years ago set us off to question if the fasted state was good or bad (reviewed in Ljungqvist[44]). In short, these studies showed that in hemorrhage, glucose had a life-saving role in fed rats with glycogen stores available. In acute hemorrhage, glucose was rapidly released to secure plasma refill by osmotic means, shifting water from cells to the extracellular space. Fasted rats succumbed to the same bleeding. They also had a more pronounced endocrine stress response. Also, in endoxemic stress, fed rats had a survival advantage over those withheld food overnight.

Body metabolism has natural diurnal variations (for a very didactic description of normal human metabolism, see Frayn[45]). In the morning shortly after waking up, most people have breakfast, usually a mixed meal. This elicits the release of insulin. Insulin has many effects on body metabolism, and among many other actions, insulin will not only secure the storage of nutrients but also change the oxidation from fat to carbohydrates, while also activating glucose transport into muscle and fat and glycogen and fat storage as well as protein anabolism. All of the above are reversed by stress, and many of the reactions are also affected by the overnight fast (although this is perfectly normal).

The most obvious way to change metabolism from the overnight fasted state to the fed state was to give a carbohydrate load. This was initially done using IV glucose at a high concentration (20% glucose) and dose (5 mg/kg/min)[46] and later using a mixture of complex carbohydrates as an oral drink[47] that showed to improve preoperative well-being while also emptying fast enough to be safe for clinical use. Later studies showed that intake of this drink completely reversed the setting of overnight fasting while stimulating glucose uptake, shutting down gluconeogenesis, and thus setting the patient to a much more anabolic state than the fasted state before the onset of the surgical stress.[28,48] This elevation of insulin sensitivity is believed to carry through to the postoperative situation, where several studies in major surgery have shown that the preoperative carbohydrate treatment results in substantially less postoperative insulin resistance (for reviews, see Ljungqvist[25] and Nygren et al[49]). Recent studies from China showed that this treatment has direct effects on intracellular muscle signaling pathways.[27] Preoperative carbohydrates result in postoperative higher activation of PI-3 kinase. This is a key intracellular signal activating, among other things, the glucose transporter GLUT4. Early studies indicated that GLUT4 activation is reduced after surgery.[26] In addition, the same Chinese study also showed that tyrosine protein kinase activity, a key anabolic signaling pathway, was maintained at a higher level after surgery in patients given preoperative carbohydrates. This helps explain the intracellular mechanisms behind some earlier findings of improved anabolic status with this treatment. Yuill et al[50] showed improved muscle mass, Crowe et al[51] showed less nitrogen losses, and Henriksen et al[52] reported improved vastus muscle strength postoperatively from the addition of a preoperative carbohydrate treatment compared with fasting or placebo. The finding of improved strength was associated with higher glycogen synthase activity, and the difference between groups was present as late as a month after surgery. Another effect reported for preoperative carbohydrate treatment is less immune depression after surgery as indicated by improved HLA-DR expression of monocytes.[53]

Combining Feeding With Pre- and Postoperative Epidural Anesthesia

By placing an epidural with local anesthetics in the mid-thoracic region (Th 6–9) and activating it before the onset of the operation, the release of 2 key stress hormones, epinephrine and cortisol, is markedly reduced.[54] These 2 hormones are well known to cause insulin resistance, and when blocked, postoperative insulin resistance was reduced by almost 50%. Using this mechanism to reduce insulin resistance and at the same time also employing preoperative insulin stimulation by using preoperative carbohydrates was tested by Soop et al.[55] Combining these 2 treatments along with immediate postoperative complete enteral feeding resulted in an almost complete abolishment of insulin resistance. During the course of the first few days of complete feeding, glucose levels remained within normal fasting levels while no insulin was given (or required). Another metabolic effect of the combinations of treatments was the maintenance of complete nitrogen balance. This study shows that it is possible to almost completely avoid postoperative insulin resistance, and in this situation obviously, the need for any additional insulin to control glucose may not be needed. This is very useful in the postoperative phase at the wards where insulin treatment to control glucose may be difficult to maintain with appropriate levels of safety.

There are other reasons for success of the above protocol. The epidural block, maintained the first few days after surgery, also serves effectively to control pain while avoiding the use of opiates. The use of epidurals has been shown to have a marked effect on GI motility, with a meta-analysis indicating 2 days faster recovery of motility using epidurals vs opiate-based analgesia.[56] This is another key to making enteral feeding work early after surgery. Furthermore, any nutrient consumed while less resistant to insulin will be used in a more anabolic or normal way. Again, the preoperative carbohydrate and the epidural work together for better metabolic effects. Last, pain control is important not only for patient comfort but also to avoid insulin resistance, as shown by Greisen et al.[18]

Minimizing Insulin Resistance and Supporting Anabolism

Although the above example is just one of many illustrating how a multimodal approach is useful to control and support the enhancement of recovery after surgery, several other factors are involved. These include patient information and patients' active participation in their own recovery, the use of the right premedication (if used at all), surgical techniques, avoiding hypothermia, fluid balance during and after surgery, and immediate mobilization (for references, see Lassen et al[9]). Many of these have direct or indirect effects on metabolism, as alluded to above. Some new developments may well prove to be included in the next generation of recommendations. These include some reevaluation of the concept in the setting of minimally invasive surgery, as it is slowly but gradually making its way into more complex surgical procedures. Laparoscopic surgery markedly reduces insulin resistance, as shown many years ago.[57] Restoring gut function is another key area, where chewing gum is showing to be a novel approach.[58] This will have indirect effects on insulin resistance by supporting the return of intake of food and nutrients. Similarly, maintaining fluid balance is another key area often overlooked, both in terms of gut function[59] but also for avoiding complications.[60,61]

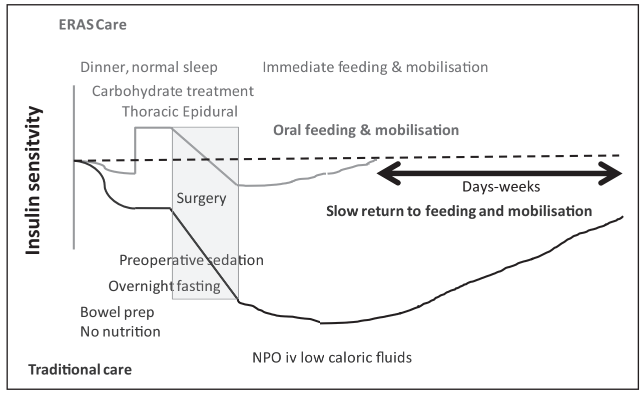

Figure 2. An illustration of how enhanced recovery after surgery (ERAS) care (blue line and text) differs from traditional care pathways (red line and text) and their relative estimated effects on insulin sensitivity. The graph is based on a series of studies comparing the effects of various treatments in the perioperative care period on insulin sensitivity.[14,15,18,47,53,62,63] These effects were combined in relative terms and added to each other. Although the data behind the graph are based on studies, the combination of the data is an estimate of the development and should be viewed as just that and not as a scientific experiment. NPO, nil per os.

Making the Patients' Journey While Maintaining Metabolic Control

From the above discussions, we can review the patients' journey in the traditional care pathway and compare that with the ERAS protocol using insulin sensitivity (or resistance) as the marker of the metabolic stress. Figure 2 gives an arbitrary (and not strictly scientific) illustration of how different treatments in traditional vs ERAS care affect insulin sensitivity. The figure shows that the ERAS protocol allows the patient to maintain insulin sensitivity throughout the perioperative phase by using treatments that will avoid the development of insulin resistance. Avoiding fasting, using an epidural, and controlling pain and mobilizing after surgery will minimize the development of insulin resistance. By stimulating insulin pre- and postoperatively using carbohydrates and feeding, respectively, again insulin activity is kept more normal.

ERAS and Outcomes

Although numerous studies show very good clinical results in the literature, many of these findings are slow to find their way into daily clinical practice. Sometimes it is clear what should be done, and clinicians are well aware of what should be done, but it is still not done. A very good example of how hard it can be to have simple yet markedly effective treatments introduced into practice was given by Dr Levy (Brown University),[64] who presented a keynote lecture at the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) Clinical Week in 2007. In his lecture, he presented a study from Germany where intensive care specialists were asked if they use low tidal volume ventilation in their patients. This type of ventilation was shown to reduce mortality and has no extra cost, and it can easily be used on any modern ventilator. Ninety-two percent of the responders replied they did use this mode of ventilation. However, the authors surveyed the actual setting of the ventilators and found that only 4% were set the right way. This illustrates that even if we do know what should be done and may think we are doing the right thing, it is only when we actually check what is being done that we know for sure. Therefore, to make an ERAS protocol work in real-life medical practice, you need to have full control over what is actually being done in detail with every patient.

For this reason, the ERAS study group set out about 10 years ago to measure the use of every element in the protocol agreed upon and store them in a database for comparisons between the units but also to support the implementation of the ERAS protocol in each unit involved. This proved to be most useful and showed that the different units did quite differently,[65] that improved results could be achieved rather quickly,[66] and that a protocol alone was not enough to be successful and improve results.[67] Using the experience from this multicenter collaboration and the expertise of CBO Kwaaliteetsintitut in the Netherlands, a training program using an ERAS database was set up, and several hospitals in the Netherlands participated in this program and successfully changed and improved practice.[68,69]

Single-center studies also showed that indeed, the better the compliance to the protocol elements, the better the outcomes. Gustafsson et al[70] showed that with the improvement of compliance from below 50% to above 90%, length of stay was brought down from 9.4 to 6 days and complications from 45% to 19% in 940 mixed colorectal cancer surgery patients. Discharge earlier was not associated with more readmissions. On the contrary, readmissions came down from 11% to 2%, showing that patients actually recovered faster. Further analysis showed that the 2 independent factors determining outcomes were carbohydrate treatment and avoiding overload of fluids. As a sign, again, of the interaction between different elements, carbohydrate treatment was associated with less IV fluid needs. A meta-analysis of 6 randomized trials with at least 4 elements of the ERAS protocol on the treatment group reported similar findings. It showed that length of stay after colonic resections was reduced by 2.5 days and complications reduced by 50%.[12]

Concluding Remarks

Although surgery and perioperative care are constantly developing, it is often a very slow process to implement new care modalities into daily routines. Traditional care is associated with marked metabolic reactions with major catabolism rendering massive insulin resistance and protein losses, and in this setting, major complications and prolonged recovery are not uncommon. Today it is possible, using modern multimodal care principles, to avoid almost all of the negative sides of the metabolic responses and insulin resistance and render the patient in an anabolic state very fast even after major surgery. The employment of ERAS principles has been shown to markedly improve outcomes by reducing complications and speed up return of functions. An important mechanism behind these improvements is the understanding and control of metabolism. As much as surgeons like to believe that it is only the surgical skills that make the difference, recent insights have taught us that metabolic control is another important factor to recognize. With these insights, I feel that it is fair to say that metabolism and nutrition are back in the surgical arena today. The main challenge ahead is how to support units to employ modern perioperative care pathways for the further improvement of surgical care.

Author's Note

It is a great honor for me to receive the Jonathan E. Rhoades lecture award. The work initiated by Dr Rhoades, which has been continued and further developed by many of his coworkers, has been a great inspiration and source of knowledge for me in my work from the very early days of my interest in surgical nutrition and metabolism.

Acknowledgments

I wish to acknowledge all those who meant so much to me during the years, especially my teachers in clinical science and research from the Karolinska Institutet and Hospital Professors Suad Efendic for introducing me to the world of diabetes research and insulin resistance, as well as Gunnar Nylander, Bertil Hamberger, and James Ware for bringing me into the field of surgical stress and metabolism. I also thank my great group of collaborators—my long-term companions Anders Thorell and Jonas Nygren, but also the talented juniors Mattias Soop, Jonatan Hausel, Monika Svanfeldt, Ulf Gustafsson, and old friends like Folke Hammarqvist, Olav Royaackers, and Jan Wernerman at the Karolinska Insitutet. I want to thank my U.S. collaborators, especially K. Sree Nair, Mayo Clinic, for long-term support, and also Laurie Goodyear and Edward Horton at the Joslin Diabetes Center for great collaborations. Finally, I thank the ERAS study group—Ken Fearon, Edinburgh, U.K., with whom I coinitiated the group, and the collaborators Arthur Revhaug and Krsitoffer Lassen (Tromsö, Norway), Martin von Meyenfeldt and Cornelius deJong (Maastricht, the Netherlands), Henrik Kehlet (Copenhagen, Denmark), D. Lobo and K. Varadhan (Nottingham, U.K.), and Claudia Spies and Aarne Feldheiser (Berlin, Germany)—for excellent friendship and spirit and the greatness of knowing how to collaborate. I thank the A.S.P.E.N. committee for the privilege to present at this very special occasion.

References

1. Ljungqvist O, Fearon K, Little RA. Nutrition in surgery and trauma. In: Gibney MJ, Marinos E, Ljungqvist O, Dowsett J, eds. *Clinical Nutrition*. Oxford, UK: Blackwell; 2005:312-323.
2. Ljungqvist O, Fearon K, Little RA. Clinical nutrition. In: Gibney MJ, Elia M, Ljungqvist O, Dowsett J, eds. *The Human Nutrition Textbook Series*. Oxford, UK: Blackwell Science; 2005.
3. Brandi LS, Frediani M, Oleggini M, et al. Insulin resistance after surgery: normalization by insulin treatment. *Clin Sci (Lond)*. 1990;79(5):443-450.
4. Thorell A, Nygren J, Ljungqvist O. Insulin resistance: a marker of surgical stress. *Curr Opin Clin Nutr Metab Care*. 1999;2(1):69-78.
5. Sato H, Carvalho G, Sato T, Lattermann R, Matsukawa T, Schricker T. The association of preoperative glycemic control, intraoperative insulin sensitivity, and outcomes after cardiac surgery. *J Clin Endocrinol Metab*. 2010;95(9):4338-4344.
6. Kehlet H. Multimodal approach to control postoperative pathophysiology and rehabilitation. *Br J Anaesth*. 1997;78(5):606-617.
7. Kehlet H, Mogensen T. Hospital stay of 2 days after open sigmoidectomy with a multimodal rehabilitation programme. *Br J Surg*. 1999;86(2):227-230.
8. Fearon KC, Ljungqvist O, Von Meyenfeldt M, et al. Enhanced recovery after surgery: a consensus review of clinical care for patients undergoing colonic resection. *Clin Nutr*. 2005;24(3):466-477.
9. Lassen K, Soop M, Nygren J, et al. Consensus review of optimal perioperative care in colorectal surgery: Enhanced Recovery After Surgery (ERAS) group recommendations. *Arch Surg*. 2009;144(10):961-969.
10. Ljungqvist O, Braga M, Fearon K. Perioperative nutrition. In: *Basics in Clinical Nutrition*. 4th ed. Publishing House Galén, Prague, Czech Republic; 2011:437-444.
11. Kehlet H, Wilmore DW. Evidence-based surgical care and the evolution of fast-track surgery. *Ann Surg*. 2008;248(2):189-198.
12. Varadhan KK, Neal KR, Dejong CHC, Fearon KCH, Ljungqvist O, Loboet DN. The Enhanced Recovery After Surgery (ERAS) pathway for patients undergoing major elective open colorectal surgery: a meta-analysis of randomized trials. *Clin Nutr*. 2010;29(4):434-440.
13. Volkert D, Saeglitz C, Gueldenzoph H, Sieber CC, Stehle P. Undiagnosed malnutrition and nutrition-related problems in geriatric patients. *J Nutr Health Aging*. 2010;14(5):387-392.
14. Svanfeldt M, Thorell A, Brismar K, Nygren J, Ljungqvist O. Effects of 3 days of 'postoperative' low caloric feeding with or without bed rest on insulin sensitivity in healthy subjects. *Clin Nutr*. 2003;22(1):31-38.
15. Biolo G, Ciocchi B, Stulle M, et al. Calorie restriction accelerates the catabolism of lean body mass during 2 wk of bed rest. *Am J Clin Nutr*. 2007;86(2):366-372.
16. Nygren J, Nair KS. Differential regulation of protein dynamics in splanchnic and skeletal muscle beds by insulin and amino acids in healthy human subjects. *Diabetes*. 2003;52(6):1377-1385.
17. Marco J, Barba R, Zapatero A, et al. Prevalence of the notification of malnutrition in the departments of internal medicine and its prognostic implications. *Clin Nutr*. 2011;30(4):450-454.

18. Greisen J, Juhl CB, Grøfte T, et al. Acute pain induces insulin resistance in humans. *Anesthesiology*. 2001;95(3):578-584.
19. DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am J Physiol*. 1979;237(3):E214-E223.
20. Svanfeldt M, Thorell A, Hausel J, et al. Randomized clinical trial of the effect of preoperative oral carbohydrate treatment on postoperative whole-body protein and glucose kinetics. *Br J Surg*. 2007;94(11):1342-1350.
21. Felländer G, Nordenström J, Tjäder I, Bolinder J, Arner P. Lipolysis during abdominal surgery. *J Clin Endocrinol Metab*. 1994;78(1):150-155.
22. Nygren J, Thorell A, Efendic S, Nair KS, Ljungqvist O. Site of insulin resistance after surgery: the contribution of hypocaloric nutrition and bed rest. *Clin Sci (Lond)*. 1997;93(2):137-146.
23. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. *Diabetes Care*. 2004;27(6):1487-1495.
24. Mathur S, Plank LD, McCall JL, et al. Randomized controlled trial of preoperative oral carbohydrate treatment in major abdominal surgery. *Br J Surg*. 2010;97(4):485-494.
25. Ljungqvist O. Modulating postoperative insulin resistance by preoperative carbohydrate loading. *Best Pract Res*. 2009;23:401-409.
26. Thorell A, Nygren J, Hirshman MF, et al. Surgery-induced insulin resistance in human patients: relation to glucose transport and utilization. *Am J Physiol*. 1999;276(4, pt 1):E754-E761.
27. Wang ZG, Wang Q, Wang WJ, Qin HL. Randomized clinical trial to compare the effects of preoperative oral carbohydrate versus placebo on insulin resistance after colorectal surgery. *Br J Surg*. 2010;97(3):317-327.
28. Ljungqvist O, Nygren J, Thorell A, Brodin U, Efendic S. Preoperative nutrition: elective surgery in the fed or the overnight fasted state. *Clin Nutr*. 2001;20(suppl 1):167-171.
29. Pierre EJ, Barrow RE, Hawkins HK, et al. Effects of insulin on wound healing. *J Trauma*. 1998;44(2):342-345.
30. Ljungqvist O, Nygren J, Thorell A. Modulation of post-operative insulin resistance by pre-operative carbohydrate loading. *Proc Nutr Soc*. 2002;61(3):329-336.
31. Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. *Diabetes*. 2005;54(6):1615-1625.
32. Witasp A, Nordfors L, Schalling M, Nygren J, Ljungqvist O, Thorell A. Increased expression of inflammatory pathway genes in skeletal muscle during surgery. *Clin Nutr*. 2009;28(3):291-298.
33. Witasp A, Nordfors L, Schalling M, Nygren J, Ljungqvist O, Thorell A. Expression of inflammatory and insulin signaling genes in adipose tissue in response to elective surgery. *J Clin Endocrinol Metabol*. 2010;95(7):3460-3469.
34. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patients. *N Engl J Med*. 2001;345(19):1359-1367.
35. NICE-SUGAR Study Investigators. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med*. 2009;360(13):1283-1297.
36. Gustafsson UO, Thorell A, Soop M, Ljungqvist O, Nygren J. Haemoglobin A1c as a predictor of postoperative hyperglycaemia and complications after major colorectal surgery. *Br J Surg*. 2009;96(11):1358-1364.
37. Jackson RS, Amdur RL, White JC, Macsata RA. Hyperglycemia is associated with increased risk of morbidity and mortality after colectomy for cancer. *J Am Coll Surg*. 2012;214(1):68-80.
38. Kahaodiar L, McCowen K, Bistrian B. Perioperative hyperglycemia, infection or risk? *Curr Opin Clin Nutr Metab Care*. 1999;2:79-82.
39. Fatal applications of chloroform. Section on Legal Medicine. *Edinburgh Med Surg J*. 1848;69.
40. Maltby JR. Fasting from midnight—the history behind the dogma. *Best Pract Res Clin Anaesthesiol*. 2006;20(3):363-378.
41. Maltby JR. New guidelines for preoperative fasting. *Can J Anaesth*. 1993;40(5, pt 2):R113-R121.
42. Brady M, Kinn S, O'Rourke K, Randhawa N, Stuart P. Preoperative fasting for preventing perioperative complications in children. *Cochrane Database Syst Rev*. 2005;(2):CD005285.
43. Brady M, Kinn S, Stuart P. Preoperative fasting for adults to prevent perioperative complications. *Cochrane Database Syst Rev*. 2003;(4):CD004423.
44. Ljungqvist O. To fast or not to fast? Metabolic preparation for elective surgery. *Scand J Nutr*. 2004;48(2):77-82.
45. Frayn KN. *Metabolic Regulation: A Human Perspective*. London: Portland Press; 1996.
46. Ljungqvist O, Thorell A, Gutniak M, Häggmark T, Efendic S. Glucose infusion instead of preoperative fasting reduces postoperative insulin resistance. *J Am Coll Surg*. 1994;178(4):329-336.
47. Nygren J, Thorell A, Jacobsson H. Preoperative gastric emptying: effects of anxiety and oral carbohydrate administration. *Ann Surg*. 1995;222(6):728-734.
48. Svanfeldt M, Thorell A, Hausel J, Soop M, Rooyackers O, Nygren J. Effect of "preoperative" oral carbohydrate treatment on insulin action: a randomized cross-over unblinded study in healthy subjects. *Clin Nutr*. 2005;24:815-821.
49. Nygren J, Thorell A, Ljungqvist O. Preoperative oral carbohydrate nutrition: an update. *Curr Opin Clin Nutr Metab Care*. 2001;4(4):255-259.
50. Yuill KA, Richardson RA, Davidson HI, Garden OJ, Parks RW. The administration of an oral carbohydrate-containing fluid prior to major elective upper-gastrointestinal surgery preserves skeletal muscle mass postoperatively: a randomised clinical trial. *Clin Nutr*. 2005;24(1):32-37.
51. Crowe PJ, Dennison A, Royle GT. The effect of pre-operative glucose loading on postoperative nitrogen metabolism. *Br J Surg*. 1984;71(8):635-637.
52. Henriksen MG, Hessov I, Dela F, Hansen HV, Haraldsted V, Rodt SA. Effects of preoperative oral carbohydrates and peptides on postoperative endocrine response, mobilization, nutrition and muscle function in abdominal surgery. *Acta Anaesthesiol Scand*. 2003;47(2):191-199.
53. Melis GC, van Leeuwen PA, von Blomberg-van der Flier BM, et al. A carbohydrate-rich beverage prior to surgery prevents surgery-induced immunodepression: a randomized, controlled, clinical trial. *JPEN J Parenter Enteral Nutr*. 2006;30(1):21-26.
54. Uchida I, Asoh T, Shirasaka C, Tsuji H. Effect of epidural analgesia on postoperative insulin resistance as evaluated by insulin clamp technique. *Br J Surg*. 1988;75(6):557-562.
55. Soop M, Carlson GL, Hopkinson J, et al. Randomized clinical trial of the effects of immediate enteral nutrition on metabolic responses to major colorectal surgery in an enhanced recovery protocol. *Br J Surg*. 2004;91:1138-1145.
56. Jørgensen H, Wetterslev J, Møiniche S, Dahl JB. Epidural local anaesthetics versus opioid-based analgesic regimens on postoperative gastrointestinal paralysis, PONV and pain after abdominal surgery. *Cochrane Database Syst Rev*. 2000;(4):CD001893.
57. Thorell A, Nygren J, Essén P, et al. The metabolic response to cholecystectomy: insulin resistance after open compared with laparoscopic operation. *Eur J Surg*. 1996;162(3):187-191.
58. Fitzgerald JE, Ahmed I. Systematic review and meta-analysis of chewing-gum therapy in the reduction of postoperative paralytic ileus following gastrointestinal surgery. *World J Surg*. 2009;33(12):2557-2566.
59. Lobo DN, Bostock KA, Neal KR, Perkins AC, Rowlands BJ, Allison SP. Effect of salt and water balance on recovery of gastrointestinal function after elective colonic resection: a randomised controlled trial. *Lancet*. 2002;359(9320):1812-1818.
60. Brandstrup B, Tønnesen H, Beier-Holgersen R, et al. Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens: a randomized assessor-blinded multicenter trial. *Ann Surg*. 2003;238(5):641-648.
61. Varadhan KK, Lobo DN. A meta-analysis of randomised controlled trials of intravenous fluid therapy in major elective open abdominal surgery: getting the balance right. *Proc Nutr Soc*. 2010;69(4):488-498.
62. Nygren J, Soop M, Thorell A, Efendic S, Nair KS, Ljungqvist O. Preoperative oral carbohydrate administration reduces postoperative insulin resistance. *Clin Nutr*. 1998;17(2):65-71.

63. Svanfeldt M, Nygren J, Ljungqvist O, Thorell A. Three days of postoperative hypocaloric feeding with or without immobilization cause marked insulin resistance in healthy volunteers. *Clin Nutr*. 2000;19(suppl 1):126.
64. Levy M M, Keynote lecture, A.S.P.E.N. Nutrition Week Congress, 2007.
65. Nygren J, Hausel J, Kehlet H, et al. A comparison in five European centres of case mix, clinical management and outcomes following either conventional or fast-track perioperative care in colorectal surgery. *Clin Nutr*. 2005;24(3):455-461.
66. Nygren J, Soop M, Thorell A, et al. An enhanced-recovery protocol improves outcome after colorectal resection already during the first year: a single-center experience in 168 consecutive patients. *Dis Colon Rectum*. 2009;52(5):978-985.
67. Maessen J, Dejong CH, Hausel J, et al. A protocol is not enough to implement an enhanced recovery programme for colorectal resection. *Br J Surg*. 2007;94(2):224-231.
68. Jottard K, Hoff C, Maessen J, et al. Life and death of the nasogastric tube in elective colonic surgery in the Netherlands. *Clin Nutr*. 2009;28(1):26-28.
69. Maessen JM, Dejong CH, Kessels AG, et al. To eat or not to eat: facilitating early oral intake after elective colonic surgery in the Netherlands. *Clin Nutr*. 2009;28(1):29-33.
70. Gustafsson UO, Hausel J, Thorell A, Ljungqvist O, Soop M, Nygren J; Enhanced Recovery After Surgery Study Group. Adherence to the enhanced recovery after surgery protocol and outcomes after colorectal cancer surgery. *Arch Surg*. 2011;146(5):571-577.