Why metabolism matters in elective orthopedic surgery

A review

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Like any surgical procedure or traumatic injury, orthopedic surgery evokes a series of stress responses in the body. Our understanding of the nature and the importance of these responses for postoperative metabolism—and subsequently function and outcome after surgery—has improved in recent years. This field of surgical research is growing rapidly. Recent studies have shown that the metabolic response to stress, and in particular the development of resistance to insulin and hyperglycemia, has been a hitherto unknown but major cause of postoperative complications and delayed recovery even in patients without diabetes (Thorell et al. 1999, van den Berghe et al. 2001). Here we review some of the recent developments in our understanding of the role of metabolism and examine them in the context of the patient undergoing elective orthopedic surgery. Our current knowledge of how best to counteract these disadvantageous responses is also summarized.

Postoperative insulin resistance

Many of the metabolic changes that occur in response to injury can be explained from a theoretical standpoint by a reduction in the action of insulin. This phenomenon is often called posttraumatic insulin resistance. The term insulin resistance is most often associated with diabetes, but an acute state of severe insulin resistance has been shown to occur after major surgery such as orthopedic and abdominal surgery (Nygren et al. 1998, Soop et al. 2001) . Recent studies have shown that the changes in glucose metabolism in the newly operated patient are very similar to those found in patients with untreated type 2 diabetes (Ljungqvist and Nygren 2000). This explains why the postoperative patient, who was metabolically healthy before the operation, develops hyperglycemia lasting several days or weeks after surgery.

Postoperative insulin resistance leads to an increase in glucose production—mainly from the liver—and at the same time to a reduction in glucose uptake in peripheral tissues, mainly skeletal muscle. Both of these changes in glucose metabolism cause hyperglycemia. In addition, the postoperative patient has a defective glycogen synthase activity for up to 1 month postoperatively (Henriksen et al. 2003), and this may in part explain the reduced muscle strength that can prevail for a long period of time after a major operation.

Generally speaking, studies on surgical patients have shown that the degree of insulin resistance that develops after surgery depends on the magnitude of the surgery performed. While smaller procedures such as inguinal hernias or laparoscopic cholcystectomies lead to a reduction in insulin sensitivity by about 15–20%, an open cholecystectomy causes a 50% reduction and a major colorectal procedure can cause a drop of about 75% relative to preoperative levels (Thorell et al. 1999). Independently from the type of surgery carried out, the perioperative blood loss also influences the degree of insulin

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resistance that develops postoperatively. In contrast, preoperative insulin sensitivity, sex, or age has not been shown to have any influence on this metabolic change.

For the orthopedic surgeon, it is important to realize that patients undergoing elective total hip replacement develop marked insulin resistance within minutes of their operation, resulting in a 40% reduction in the ability of insulin to facilitate glucose uptake relative to the preoperative state (Soop et al. 2001). It is likely that this marked degree of insulin resistance will remain for at least a couple of weeks. Studies from uncomplicated open cholecystectomies with a similar degree of insulin resistance have shown that it takes 2–3 weeks for this metabolic derangement to normalize

The resistance to the normal actions of insulin after an operation is not restricted to glucose metabolism, but also affects protein and fat metabolism. Insulin is the most potent inhibitor of protein breakdown in normal physiology, and this important regulatory role of insulin is also impaired in postoperative insulin resistance (Inculet et al. 1986). Insulin interacts with other hormones, and this action is also disturbed after injury. Thus, both IGF-I (Bang et al. 1998) and cortisol activity (Nygren et al. 1998a) are influenced by lack of insulin action in surgical stress. Lastly, insulin resistance also appears to enhance the inflammatory response (Hansen et al. 2003).

The question is: how does this influence the postoperative course and recovery of the orthopedic patient? There are three major effects where insulin resistance may impair recovery from surgery, including orthopedic operations. Firstly, insulin resistance is the direct underlying cause of hyperglycemia and this has been shown to be a risk factor in many common postoperative complications (van den Berghe et al. 2001). Secondly, insulin is one of the main anabolic hormones in the body and when resistance sets in, muscle protein losses increase (Crowe et al. 1984, Yuill et al. 2005). Thirdly, when glucose uptake and storage is reduced in muscle and proteins are lost, these two factors will reduce muscle strength (Henriksen et al. 2003).

Furthermore, some authors have reported prolonged bone healing in diabetic patients compared to non-diabetic patients (Cozen 1972, Loder 1988), and defective and delayed bone healing has been shown in a variety of diabetic-healing animal models characterized by hyperglycemia and low insulin levels (Macey et al. 1989, Topping et al. 1994, Funk et al. 2000). It has also been reported that systemic insulin treatment reverses this impaired bone healing (Macey et al. 1989, Follak et al. 2004). However, these studies do not discriminate between a direct effect of insulin on the bone and indirect systemic effects on skeletal metabolism. The importance of systemic alterations in the metabolic state after surgery, e.g. the effect of postoperative insulin resistance on bone metabolism and fracture healing, has not yet been evaluated in clinical studies.

Hyperglycemia—a recently described risk factor in surgery

In a large randomized trial in Belgium, of mainly surgical intensive care patients who were ventilated overnight, it was clearly demonstrated that the loss of normal insulin action to maintain normoglycemia was associated with markedly increased morbidity and mortality (van den Berghe et al. 2001). More than 1,500 consecutive patients were randomized to receive either intensive insulin treatment to normalize glucose levels to 6 mmol/L, or treatment with insulin only if their blood glucose levels exceeded 12 mmol/L. The study showed a remarkable effect on outcome by normalizing the action of insulin on glucose. Patients with intensive insulin therapy had 43% lower mortality in intensive care as a result of a 40–50% reduction in the frequencies of sepsis, ventilator support, kidney failure, and polyneuropathy.

The mechanisms of action of intensive insulin therapy in critical illness are not yet known. A recent post hoc analysis from the large material in the Belgian insulin trial has revealed some tentative explanations as to why hyperglycemia may be a common cause of many of these complications. As mentioned above, the reduction in insulin-induced glucose uptake in cells dependent on insulin (mainly muscle and fat) is one of the causes of the elevated glucose levels. However, many cells take up glucose in proportion to the plasma level of glucose, and independently of insulin. The organs involved—for example the liver, nervous tissue, and blood cells—will increase their uptake of glucose when hyperglycemia develops. This leads to

excess glucose metabolism through glycolysis, the Krebs's cycle, and into the mitochondrial oxidative chain. When these metabolic pathways become overloaded, increased amounts of oxygen free radicals form and these and other end-products affect gene expression of cytokines (Brownlee 2005).

The study from Belgium has been repeated in slightly different clinical settings and with slightly different protocols, but with essentially similar results. Thus, for the severely stressed postoperative patient in critical care, combating insulin resistance is an essential aspect of patient care. Interestingly, a recent study from the US showed that in relative terms, the effectiveness of controlling insulin resistance with insulin may be most effective in patients with lower-severity illness, as measured by APACHE II scores (Krinsley 2004). This category of patients would include any major surgical procedure, including major orthopedic operations.

Endocrine and inflammatory responses to injury and surgery

It has long been known that long bone fractures cause stress reactions in the body. Just as in any injury or surgical procedure, the body reacts with the release of stress hormones such as cortisol, catecholamines, and glucagon. These hormones are released quite quickly (within minutes to half an hour) and rapidly cause major alterations in metabolism by mobilizing substrates from all energy stores—including glucose from glycogen, fat from fat deposits, and protein mainly from muscle. All of these hormones also counteract the actions of insulin. Thus, each one of them alone, and even more so in combination, causes insulin resistance.

At the same time, the inflammatory system is also activated in injury. Thus, cytokines are released, among which tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) have been identified as being particularly involved in the metabolic responses. It has been shown that there is a correlation between the degree of release of IL-6 and the degree of insulin resistance after elective surgery (Thorell et al. 1996b). Interestingly, when insulin is treated to control glycemia in critically ill surgical patients, CRP levels are reduced, suggesting a feedback loop by insulin on the inflammatory response.

Postoperative insulin resistance and protein metabolism

After surgery, the normal anabolic action of insulin is hindered. This results in increased lipolysis, with increased levels of free fatty acids that are oxidized to a greater extent. In addition—and perhaps more importantly—protein balance becomes negative, and breakdown of muscle protein is increased. This results in loss of muscle protein and subsequent reduction in lean body mass, which is also found after total hip replacement (THR) (Hedstrom et al. 1999). It has been shown that post-surgical patients and trauma patients are able to retain protein to a much greater extent if insulin is given as part of the feeding therapy (Hinton et al. 1971, Woolfson et al. 1979, Inculet et al. 1986, Ferrando et al. 1999). This again highlights the key role of insulin in post-injury metabolism.

Postoperative insulin resistance and muscle function

Two main factors stemming from insulin resistance are involved in the reduction in muscle function after surgery. One is the loss of muscle mass due to negative protein balance, as discussed above. In addition, the disturbance in glucose metabolism in muscle will cause further disturbances to muscle function. The main target organ for insulin-stimulated glucose uptake is muscle. Insulin resistance results in two main problems in muscle metabolism—reduced glucose uptake and a reduced capacity to store glucose as glycogen. Both of these changes set in within minutes of the injury or operation, and both remain for several weeks or even months. Reduced capacity of glycogen synthase activity has been found in the vastus lateral muscle one month after major abdominal surgery (Henriksen et al. 2003).

These two factors, the loss of muscle protein and the reduced capacity to store glycogen, probably contribute to the postoperative fatigue in patients undergoing surgery.

How to counteract insulin resistance

There are two principal strategies to counteract insulin resistance: to minimize its development by preventive measures, or to treat it once it occurs.

There are ways of preventing the development of postoperative insulin resistance. Mid-thoracic

epidural anaesthesia and analgesia, inserted at a vertebral level above the innervation of the adrenal glands (i.e. above Th8) will markedly reduce the release of catecholamines and cortisol, reducing the development of insulin resistance by about 40% compared to general anaesthesia alone (Uchida et al. 1988). Postoperative EDA provides the most effective pain control after both general and orthopedic surgery. Minimization of pain represents the second measure that will minimize insulin resistance (Greisen et al. 2001). A third way involves the surgical technique, at least for abdominal surgery (Thorell et al. 1996a). Thus, a laparoscopic minimally invasive technique has been shown to reduce insulin resistance by half compared to conventional subcostal techniques of open surgery (Thorell et al. 1996a). Lastly, avoiding preoperative fasting and preparing the patient metabolically instead has also been shown to reduce insulin resistance (Ljungqvist et al. 2002).

The overnight fasting routine was suggested well over 150 years ago, to ensure an empty stomach before ether or chloroform anesthesia. This routine is still in place in many countries despite clear evidence that it is unnecessary for most elective patients. Many national anesthetic societies have also changed their recommendations over the last 15 years or so, and now recommend that patients may drink clear fluids up until 2–3 hours before anesthesia (Ljungqvist and Soreide 2003). This recommendation is based on the fact that the discomfort of thirst is avoided. Moreover, it has recently been shown that the overnight fasted state of metabolism is not the optimal way to prepare the metabolism of the body for surgery. Instead, a carbohydrate load that is sufficient to result in a release of insulin comparable to that after a normal meal has been shown to have several positive effects on metabolism, in particular by reducing insulin resistance.

By providing a load of carbohydrates prior to surgery, the patient will be in a fed state instead of a 16–18 h preoperative fasted state. The carbohydrate load is given to trigger a release of insulin similar to the amounts found after a normal meal such as breakfast. If intravenous administration is chosen, provision of a 20% glucose solution at rate of about 5 mg/kg/min is required in order to achieve sufficient insulin release. Lower concentrations, such as the commonly used 5% solutions, will not cause any significant insulin response. A more physiological and simple mode of administration of preoperative carbohydrates is as a carbohydrate-rich beverage. Thus, a hypo-osmolar 12.5% carbohydrate mixture given orally 2–3 hours before the operation (which is still in accordance with modern fasting guidelines) has been shown to be safe; the evidence for this comes from large materials (at least 1,000 patients) in clinical studies (Ljungqvist et al. 2002) and also in many more patients from clinical practice (Ljungqvist et al. 2002).

This change in preoperative metabolism has been shown to be associated with several effects on postoperative metabolism. Perhaps most importantly, it has been shown to reduce insulin resistance by about 50% in different types of surgery, including elective THR (Nygren et al. 1998b, Soop et al. 2001).

In one study, insulin and glucose were given from a couple of hours before the operation for THR and up until about 3 hours postoperatively (Nygren et al. 1998a). This was compared to patients who underwent no such treatment before the operation. In both groups, insulin resistance was measured immediately after the operation. The treatment group had no change in insulin sensitivity at all, while a 40% reduction was found in the control group. In addition, substrate metabolism was unaffected in the insulin- and glucose-treated group, which was similar to the results in a third group of matched controls who did not undergo surgery but were given the same insulin and glucose infusion over the same period of time. One likely explanation for these findings was that the treatment group had no elevation in cortisol postoperatively and also had a higher level of free IGF-I. Both of these endocrine factors support normal anabolic metabolism. So, in essence this study shows that it is possible—although somewhat cumbersome and perhaps not clinically practicable—to completely avoid some of the essential parts of the metabolic stress reactions. Almost the same result can be gained with the use of an oral drink, as shown in a similar patient population undergoing THR (Soop et al. 2001).

Preoperative carbohydrate treatment has been shown to counteract both of the main driving forces behind hyperglycemia, and thus results in lower

glucose production and improved glucose uptake (Soop et al. 2001, 2004b). In a study in which precautions were taken to avoid insulin resistance by the use of continuous epidural and preoperative carbohydrates (resulting in substantially less insulin resistance compared to the situation without such treatment), it was possible to feed these patients without any insulin and still retain glucose levels at normal levels (< 6 mmol/L) (Soop et al. 2004a).

Reducing insulin resistance using preoperative carbohydrate treatment has also been shown to improve protein metabolism. Thus, preoperative intravenous carbohydrate treatment using a 20% glucose intravenous overnight infusion was found to reduce nitrogen losses (Crowe et al. 1984), and preoperative oral carbohydrate treatment has been found to reduce the loss of lean body mass by half after major upper abdominal surgery (as measured by mid-arm circumference) (Yuill et al. 2005). Preoperative oral carbohydrate treatment also reduced postoperative large muscle fatigue up to one month after major colorectal surgery (Henriksen et al. 2003). All of these improvements can be associated with a reduction in insulin resistance and suggest improved recovery. A meta-analysis of 3 smaller prospective studies (52 patients in total) showed a reduction in length of hospital stay (Ljungqvist et al. 2001). These studies were not initially designed to measure length of stay, but data were available for a retrospective analysis.

In summary, insulin resistance that develops after orthopedic surgery represents a common underlying mechanism for metabolic derangements. In particular, the development of hyperglycemia has been shown to be deleterious by causing many common postoperative complications. Insulin resistance can be avoided using epidural analgesia, minimally invasive surgical technique, optimal pain control, and preoperative carbohydrate treatment. If hyperglycemia develops despite these preventive measures, for example in emergency surgery, it should be counteracted using intensive insulin therapy to establish normoglycemia and to minimize the risk of developing common hyperglycemia-associated complications. Prevention and treatment of insulin resistance has been shown to have a marked effect on morbidity, mortality, and recovery after surgery.

OL is the owner of a patent licensed to Royal Numico NV, a commercial company in the Netherlands that produces and sells a preoperative carbohydrate beverage based on this patent.

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