Modulating postoperative insulin resistance by preoperative carbohydrate loading

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The concept of preoperative overnight fasting was challenged and proved to have no benefits over allowing patients to drink clear fluids up until 2 h before surgery. This led to changes in the guidelines for preoperative fasting in many countries around the world. This concept has more recently been developed further. Mounting evidence indicates that instead of being operated in the traditional overnight fasted state, undergoing surgery in the carbohydrate-fed state has many clinical benefits. Many of these clinical effects can be related to reduced postoperative insulin resistance by preoperative carbohydrate loading. This article summarises the present understanding of the mechanisms behind the positive clinical effects and gives an overview of the information available regarding the clinical effects of this treatment. Finally, the article summarises the most recently published national guidelines on preoperative fasting routines where preoperative carbohydrates are recommended for use before a major surgery. These are to be considered for all patients allowed to drink clear fluids and undergoing elective surgery.

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little scientific backing and, when challenged, proved not to be any safer than allowing patients to drink clear fluids up until 2 h before anaesthesia and surgery. This rendered several national anaesthesia societies to change the policies and produce new and substantially more liberal guidelines. Canada was the first to change and was later followed by Norway, the UK and the USA. When instituting these changes, follow-ups were also carried out and showed that there was no increase in complications with the new guidelines, while patient comfort was improved. In particular, the discomfort of thirst, scored as one of the most important preoperative discomfort by patients, was improved.

The physiology of overnight fasting

Most people sleep during the night as a natural part of normal life. Once awake, most people have something to drink and eat. When any nutrients are consumed, insulin is released to store these nutrients. As soon as this happens, the metabolic state is changed drastically. When the nutrients are absorbed, glucose levels rise and the insulin, released in response, causes a series of rapid metabolic changes. In brief, glucose metabolism is a complete reversal from the fasted state. Gluconeogenesis is completely shut off and no glucose is released from the liver. Instead, glucose absorbed is just stored as glycogen in the liver. In the muscle, the other main tissue affected by insulin, specific glucose transporters, GLUT4, are activated by insulin to greatly enhance the uptake of glucose. The cells change from fat consumption to glycosysis, and a major proportion of the glucose taken up is stored as glycogen. Fat cells no longer release fat and lipolysis is stopped. If a carbohydrate load is given alone, protein breakdown will be stopped in the muscle, and if the meal also contains proteins, protein synthesis in muscle will also be stimulated. Energy consumption changes from fat to carbohydrates.

This insulin-dominated metabolism lasts for about 4 h after each meal. Since it is common to have meals at intervals lesser than 4 h, this metabolic state remains throughout the day since every meal yields this response to secure that the body makes use of the nutrients consumed. It is only during the night that the effect of insulin fades away and metabolism is governed by other hormones. Just the fact that insulin drops to low basal levels has a marked impact on metabolism. However, this transition to a fasted state and later to starvation metabolism, should food be withheld for a longer period of time, is supported not only by several other hormones including glucagon and cortisol but also through complex interactions with the growth hormone and the insulin-like growth factor 1 system (IGF-1). It is beyond the scope of this article to go into detail about this physiology. For the purposes of this article, it is important to be reminded about the basic and fundamental differences between the overnight fasted and the fed state, since this change impacts on the postoperative metabolism.

In summary, the metabolic setting with the routines of overnight fasting, and even with the more liberal guidelines initially proposed, rendered the patient in a fasted state of metabolism because the fluids recommended (water, coffee, tea and some juices) contained no or only minimal calories, and hence do not cause a release of insulin. Without this release of insulin, it is not possible to have the change in metabolism brought about.

Impact of the setting of metabolism at the onset of stress

As far back as in the 1940s, animal studies indicated that the response to a given injury was influenced by the metabolic state of the animal and that even shorter time periods with different intakes alter these reactions. The fact that a poor nutritional status and major weight loss before elective surgery impacts on the outcome in surgery had already been demonstrated by then, but the fact that shorter periods of nutritional manipulations also have an impact on surgery was novel at that time. Later studies by Järhult showed that, in haemorrhage, the availability of glycogen for release as glucose was directly related to the capacity to respond to haemorrhage in studies in cats. Later studies in rats showed that even a short period of food deprivation, 6 h, or more obviously 24 h, impacted on the survival following haemorrhage in rats. The mechanism behind the survival benefit in the fed state was directly related to the capacity to release glucose from glycogen in the liver and to mount a state of hyperglycaemia, causing a state of hyperosmolality in the extracellular space. The extracellular hyperglycaemic hyperosmolality caused fluid transfer from the larger reserves of water in the cells to the extracellular compartment, including plasma. This capacity for plasma refill was vital for survival.
In the follow-up studies, it became obvious that the pattern of stress reactions was governed by the nutritional state of the animal right at the onset of stress. Hence, the endocrine response was more stressful in the fasted rat \(^{11}\), and even if glucose was infused right after the start of the haemorrhage, many of the endocrine responses seen in fasted animals still remained, suggesting that it was not the development of the further level of stress that determined the reactions but rather the state of metabolism right at the onset of the insult. \(^{12,13}\) These observations were not only limited to the stress of haemorrhage, but also there were similar findings in other models of stress including endotoxaemia. \(^{14}\)

Animal studies indicated that there was a clear advantage in being stressed in a fed rather than a fasted state. In particular, the studies indicated that the availability of glycogen seemed to be a key factor. Although the metabolism in rats is many times faster than in humans and a short fasting period overnight causes weight loss in rodents, the time frame for glycogen consumption and the change of metabolism is fairly similar to humans. Hence, the loss of glycogen and the simultaneous change in metabolism from a fed to a fasted state changed the reactions to a given stress, and even shorter periods of fasting proved harmful for the animal. These findings prompted the question if having patients fasted overnight (and often much longer) before the stress of elective surgery was actually the best way to prepare for surgery, or if setting the body metabolism to a fed state would be beneficial. In particular, the change ongoing in glucose and carbohydrate metabolism seemed to be key and also a useful study target in metabolism.

The first study to investigate the role of preoperative carbohydrate feeding studied the effects of intravenous infusions of a concentrated glucose solution (20% glucose given at a rate of 5 mg kg\(^{-1}\) min\(^{-1}\)). \(^{15}\) It was shown that this treatment resulted in less protein losses. Around the same time, Allison and co-workers showed in two articles that treatment of stressed surgical and trauma patients with insulin was beneficial \(^{16,17}\) and Hallberg showed mortality benefits in pancreatitis in patients when glucose was controlled by insulin. \(^{18}\) These early studies all showed that insulin resistance was a key factor for outcomes in surgical stress.

Methods to study insulin resistance in surgery

From the experiments carried out in animal research and the findings in the literature supporting a key role for glucose metabolism for stress reactions, it was decided to start investigating postoperative insulin resistance and to study this parameter as an outcome variable potentially indicating the level of metabolic stress. The gold standard to study insulin sensitivity and its change to insulin resistance is the hyperinsulinaemic normoglycaemic clamp. \(^{19,20}\) Since the variation in insulin sensitivity is large in normal healthy people (in our experience, at least sevenfold), it was clear that it was the relative change in insulin sensitivity induced by the operation that was the best and most reliable measure to use. \(^{21}\)

The drawback with the clamp method is that it is cumbersome to use compared with some of the other methods that have been proposed and used to study postoperative insulin resistance. The latter includes determining insulin and glucose in the basal state and the homeostasis model assessment (HOMA) method. \(^{22}\) The problem with all of these alternative methods is that they perform the measurements in a situation when insulin is normally not active, that is, at the basal state. While there may well be a correlation that is significant between the HOMA and clamp methods in some situations, this does not mean that they can be interchangeable. In fact, they cannot, because they measure insulin and glucose at completely different physiological situations. HOMA is based on measures in the basal fasted state, while the clamp method studies insulin at levels when it is active, that is, the carbohydrate-fed state. While the clamp method consistently finds insulin resistance even after minor surgery, this may be much more difficult to detect using the HOMA method. This is important to remember when reviewing the literature on this topic because the very low sensitivity of the HOMA method may often lead to findings that suggest no insulin resistance developing after surgery when there is, in fact, a substantial change.

Human studies on insulin resistance in elective surgery

The early studies showed that the degree of insulin resistance was determined by the magnitude of the stress (i.e., the level of surgical insult), while factors such as preoperative insulin sensitivity and
gender had no influence. Further, measuring insulin sensitivity with the clamp before and after the operation in a standardised way gave very reproducible results. Further studies showed that in the early phase after surgery, the resistance was mostly located in the periphery, that is, mainly in the muscle, while, a few days later, the resistance was much more prominent in the liver as well. In the periphery, the muscle is the key organ sensitive to insulin. In the muscle, it has been shown that there is a rapid reduction in the activation of specific glucose-transporting proteins after surgery. Normally, these proteins, called GLUT 4, are rapidly activated after glucose challenges, resulting in insulin stimulation. After surgery, however, GLUT 4 activation does not occur to the same extent, explaining the block or hindrance to glucose uptake in muscle. Furthermore, inside the muscle cell, there is a reduction in glycogen synthase activity that has been reported to last for at least a month. These changes in muscle cause glucose to be turned away from muscle and stored in this tissue after surgery. Instead, there is likely to be an increase in glucose uptake in the cells that are not sensitive to insulin, where glucose uptake is governed by the prevailing glucose concentration in plasma and the extracellular space. This increased flow of glucose into these cells (nerves, renal and blood cells), which virtually have no protection against massive glucose inflow or any storage capacity, may, in turn, cause marked changes in their metabolism. Excess glucose can enter these cells only through glycolysis, and in case of excess glycolysis, oxygen free radicals are generated in the mitochondria. These radicals, in turn, may cause marked changes in metabolism further upstream and also in gene expression. These theories have been outlined by Brownlee for diabetes, and many of these events seem to apply also for surgically induced insulin resistance.

Interestingly, very recent data show that inside the muscle, gene expression is altered as a result of surgical stress, and there seems to be an up-regulation of genes for inflammation while a lesser up-regulation was obvious for genes involved in the insulin-regulated pathway. There are at least two important systems mediating insulin resistance. While it has been shown in many studies in healthy volunteers that stress hormones such as adrenaline, cortisol, glucagon and growth hormone can all cause insulin resistance, they need not necessarily be present for insulin resistance to develop. In addition, there is a clear indication that the release of cytokines play a role in the development of insulin resistance.

Postoperative insulin resistance affects not only glucose metabolism, which is also the most studied part of metabolism, but also when combining the clamp method with tracers for amino acids or other methods for metabolic studies. It has become evident that the metabolism of the entire body is affected by surgery. Insulin resistance, as determined using the clamp methods, is indeed a good reflection of the overall metabolic change. Brandi and co-workers very elegantly showed this. In a postoperative situation, insulin was infused to bring down glucose to normal levels while also feeding the patients. While there were clear indications of protein catabolism, stressed fat and glucose metabolism when total parenteral nutrition (TPN) was given alone, once they achieved normoglycaemia using insulin, the entire body metabolism normalised. This seems to work at least for patients within reasonable limits of stress while for the patients suffering the greater extremes of stress, insulin treatment seem to have no effect.

Preoperative carbohydrates and postoperative metabolism

The first study to test any effect on postoperative insulin resistance by preoperative carbohydrates used an overnight intravenous infusion of glucose at a high rate (5 mg kg$^{-1}$ min$^{-1}$). The total amount of glucose given was about 300 g in 1500 ml. This treatment reduced postoperative insulin resistance by about 50%. While this had the desired metabolic effect, the infusion of the 20% glucose solution was not always well tolerated when given in a large but peripheral vein. This concentration was needed to avoid fluid overload and disturbing sleep the night before surgery. The rather high osmolality of 20% glucose solution caused irritation and, in some cases, pain, and was found not to be an ideal mode of administration. For these reasons and in line with the developments in the preparative fasting routines that were beginning to take place around the same time, a drink containing carbohydrates to be taken shortly before the operation was developed.

A preoperative carbohydrate-rich drink had to contain sufficient carbohydrates to achieve a rise in insulin to levels known to change metabolism from a fasted to a fed state, meaning levels seen at a meal. At the same time, the fluid had to pass the stomach fast enough to ensure that it was perfectly safe to use in the preoperative situation. To achieve insulin release, a certain concentration of carbohydrates in the
drink is an important factor since sports drinks containing around 6–7% carbohydrates do not elicit insulin release. However, it was found that a concentration twice as high had the desired effect on insulin release. Gastric emptying is influenced by several factors. For clear fluids such as a carbohydrate drink, osmolality is one such key factor. Hence, the drink was developed to contain about 12% carbohydrates using complex carbohydrates to secure a low osmolality. This drink proved to have all the desired effects in clinical trials\textsuperscript{35} and showed to be possible to test in broader patient groups. Since these early tests\textsuperscript{36}, this drink has been tested in well over 2000 patients in clinical studies, and in more than 2 million patients in daily clinical practice without any adverse events reported. The drink was subsequently showed to have effects very similar to the intravenous treatment as regards insulin resistance.\textsuperscript{37} This formula has been the most used mode of administration of carbohydrates before surgery.

During the morning of surgery, an overnight fast will set the patient to a lower level of insulin sensitivity compared with if the patient has had breakfast or taken the carbohydrate drink\textsuperscript{38,39} Taking a load of 50 g of the carbohydrates causes a sharp increase of approximately 50% in whole body insulin sensitivity. There is a marked increase in glucose uptake and sharp decline in glucose production. After intake of the carbohydrate drink, the body metabolism is in a carbohydrate-storing state, as expected. When the injury of surgery occurs, there are mediators released to act in the opposite direction, shutting off glucose uptake in muscle and increasing glucose production. These two components together make up the insulin resistance. If the patient is pretreated with carbohydrates, the starting point for these two reactions are much more anabolic and hence the stress results in a less catabolic end setting compared with if the patient already has a starting point towards the catabolic state by being fasted overnight. This is likely to be the main mechanism of action of the drink, resulting in a roughly 50% less pronounced insulin resistance as shown in several types of surgeries.\textsuperscript{25,34,37,40–42} It also clear that insulin resistance develops very quickly during surgery as indicated by glucose and insulin levels measured during ongoing surgery\textsuperscript{36} and that several bodily reactions to the operation differ from the start of the operation, depending on whether carbohydrates have been given or not. This is similar to the findings in animals, as discussed earlier. At the same time, there are studies indicating that the effects of preoperative carbohydrate loading can be remarkably long lasting. Henriksen et al. showed that even up to 1 month after surgery, there was greater activity in glycogen synthase in muscle (biopsies from the vastus lateralis muscle) in the preoperatively carbohydrate-loaded patients.\textsuperscript{27} This finding was associated with improved muscle strength in the same group.

In further studies of the metabolic effects of carbohydrate loading, it has been demonstrated that protein metabolism, as shown in the very early work by Crowe et al.\textsuperscript{15}, is positively affected by this treatment. Urea losses are minimised\textsuperscript{15}, and protein breakdown reduced.\textsuperscript{43} All of these findings can be closely associated with insulin resistance and the effects that preoperative glucose/carbohydrate loading will have on metabolism after surgery.

When combining the preoperative carbohydrates with epidural anaesthesia, also shown to reduce insulin resistance\textsuperscript{44}, Soop et al. showed that insulin resistance could be almost completely abolished after major colorectal surgery.\textsuperscript{45} During complete enteral feeding, glucose levels were maintained at or below 6 mmol\,l\textsuperscript{-1} without any need of additional insulin. At the same time, the protein balance was maintained. This shows that it is possible to avoid the major catabolism that otherwise occurs after major surgery.

Preoperative carbohydrates and clinical outcomes

Given the clear dampening of the metabolic stress responses by preoperative carbohydrates, it seems reasonable to expect clinical benefits as well. Further, there are, indeed, a series of improvements reported from this preparation. Patient wellbeing is improved. The entire change in fasting guidelines came about to reduce the discomforts preoperatively, primarily thirst. This is clearly improved when water or any drink is given. However, there are other preoperative discomforts apart from thirst that arise from fasting, and several of them are reduced when carbohydrates are given. These include hunger and anxiety\textsuperscript{46}, and others have reported less preoperative nausea and vomiting.\textsuperscript{46} Further, postoperative subjective wellbeing may be affected by preoperative carbohydrate loading. Hausel et al. reported less postoperative nausea and vomiting after laparoscopic cholecystectomy\textsuperscript{47} as did Faria et al.\textsuperscript{48} while Bisgaard found no difference between groups.\textsuperscript{46}
Muscle function is improved. While it was shown that preoperative carbohydrates improved protein metabolism following surgery, as outlined above, this also transforms into less losses of muscle mass\textsuperscript{49} and improved muscle strength.\textsuperscript{27} This is likely to contribute to the improved muscle function recently reported in Enhanced Recovery After Surgery (ERAS) protocols where preoperative carbohydrates are an essential part.\textsuperscript{50,51} About 25 years ago, studies targeted at supporting the heart muscle in cardiac surgery showed substantially improved results when glycogen loading of the heart was performed using intravenous (IV) glucose either alone, with fat or in combination with potassium and insulin (GIK).\textsuperscript{52–54} A recent study in American Society of Anaesthesiology (ASA III–IV) patients undergoing cardiac surgery confirmed these protective effects during surgery from preoperative carbohydrate loading.\textsuperscript{55} The positive effects reported were less need for inotropic support and fewer arrhythmias.

There is one study reporting that the depression of the immune system that occurs in response to surgery is avoided with preoperative carbohydrate loading.\textsuperscript{56} Although this is very preliminary, the findings also suggest the immune system may be affected by metabolic changes occurring on a daily basis and that they may be of importance for reactions to surgical stress. There are a few reports on the length of stay. Ljungqvist et al. showed in a meta-analysis of three small studies that preoperative carbohydrate loading resulted in shorter length of stay\textsuperscript{57} and Noblett et al.\textsuperscript{58} confirmed shorter time until fit for discharge in a small but prospective randomised trial. In a larger study by Yuill et al., the authors reported a trend towards faster recovery but this was not statistically significant.\textsuperscript{49}

Current recommendations on preoperative fasting

In the guidelines on preoperative fasting produced during the past 6 years, preoperative oral carbohydrates are recommended. These include the German\textsuperscript{59} and Scandinavian\textsuperscript{60} guidelines for elective major surgery; the most recent ones from the UK\textsuperscript{61} recommend considering this treatment for all patients undergoing elective surgery. A group of patients sometimes mentioned as an exception to modern fasting guidelines are the patients with diabetes. It has been proposed that these patients have slower gastric emptying, but recent evidence suggest this has only marginal clinical relevance when it comes to the intake of clear fluids.\textsuperscript{62} Indeed, a recent study of gastric emptying in diabetics treated with oral medication or insulin show that there seems to be no difference in gastric emptying of a carbohydrate-rich preoperative drink compared with healthy volunteers.\textsuperscript{63} These patients were well controlled and take their regular morning medication along with the drink. It still remains to be investigated if patients with poor control of their diabetes can be allowed to take this treatment. Nevertheless, one study showed no increase in gastric volumes of diabetic patients taking the drink compared with those without diabetes or those taking placebo or fasting.\textsuperscript{55}

Perioperative care in major elective surgery has been undergoing marked changes in recent years. The introduction of comprehensive care programmes based on best-available practice has been constructed. These include the the ERAS\textsuperscript{51} protocol. These programmes have been shown to result in remarkable improvements in both recovery after surgery and complications.\textsuperscript{64} They target two specific aims: to minimise the metabolic stress of the operation and to support the function of vital organs. In these programmes, the inclusion of preoperative carbohydrates is a component that supports both these aims and, therefore, is one of the key treatments in the ERAS protocol.

Clinical practice points

- Preoperative fasting routines recommends intake of clear fluids up until 2 h and allows intake of solid food up until 6 h before elective surgery.
- The most recent updates of fasting guidelines in Europe recommend intake of a carbohydrate-rich clear drink up until 2 h before (in some guidelines: major) elective surgery to reduce postoperative metabolic derangements and improve patient wellbeing.
- Preoperative carbohydrate loading is a recommended treatment in the ERAS (Enhanced Recovery After Surgery) protocol.
Research agenda

- Studies on the effects of carbohydrate loading on postoperative fat metabolism are meagre and this field needs to be better explored.
- Studies on the effects of preoperative carbohydrate loading and length of stay or time until recovery have until now been done only in small study groups.

References


