Metabolic Adaptation to Overnight Starvation

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Background

The first anaesthetic death occurred in 1848, two years after the first general anaesthetic was performed. Fifteen-year-old Hannah Greener aspirated and died while under chloroform anaesthesia for a toenail removal. Following this tragedy, it was proposed that a prolonged period of fasting should precede anaesthesia to allow the stomach to be empty of its contents. This tradition of overnight fasting became one of the most well-known routines in medicine. It was only challenged in the late 1980s and was found to be based on very little scientific evidence, and proved to be no safer than allowing patients to drink clear fluids up until 2 hours preoperatively. When the anaesthesia guidelines changed, follow-up investigations were performed and found no increase in complications (aspiration) and improved patient wellbeing (discomfort of thirst). More recently, Enhanced Recovery After Surgery (ERAS) takes the preoperative fasting guidelines one step further by advocating for a carbohydrate-rich drink 2 hours before induction of anaesthesia with the aim of reducing postoperative insulin resistance and protein catabolism.

Metabolic Effects of Overnight Fasting

The human organism requires a constant supply of fuel to provide the energy to survive. This energy intake is supplied intermittently as meals over the course of the day, while during the night we naturally fast.
The body contains these fuel stores:

- Carbohydrate (400g) – glycogen in liver & muscle – lasts 12-24 hours
- Protein (10-12kgs, only 20-30% is available as fuel) – lasts +- 21 days
- Fat (10-15kgs) – lasts +- 55 days

The post absorptive state (after the last glucose from the previous meal has been completely absorbed) occurs during the overnight fast when the effect of insulin fades away and glucose begins to be released from the liver (and lesser extent kidney) by glycogenolysis (glycogen breakdown) and gluconeogenesis (glucose synthesis from non-carbohydrate sources – lactate, alanine [muscle] and glycerol [fat]). The stimulus for this glucose production is a lack of substrates, resulting in the glucose level lowering and a resultant decreased insulin/glucagon ratio as the insulin level drops.

Should food be withheld for a longer period, there is transition from the ‘fasted state’ to starvation metabolism. This process (discussed in more detail later) is supported by several other hormones, in addition to low basal levels of insulin, like glucagon and cortisol, but also through complex interactions with growth hormone and the insulin-like-growth factor 1 system (IGF-1). IGF-1 is an anabolic hormone with effects on glucose and protein metabolism like those of insulin. Even brief fasting or hypocaloric nutrition for a few days (a regimen often used after abdominal surgery) results in marked reduction in insulin sensitivity (insulin resistance). The reduction in insulin levels and the low insulin/glucagon ratio is followed by reduced IGF-1 activity by an increase in IGF binding protein-1 (IGFBP-1).

Should a meal (or carbohydrate load) then be absorbed, there is a rapid switch from glycogenolysis to glycogenesis (glycogen synthesis) and increased peripheral glucose uptake (mainly in muscle) due to increased insulin levels and insulin/glucagon ratio. The delivery of lactate from anaerobic glucose metabolism maintains gluconeogenesis, although glucose-6-phosphate during these conditions is directed into liver glycogen (the indirect pathway). This results in almost completely inhibited glucose release from the liver and a rapid switch from net catabolism to net anabolism. In addition, levels of IGFBP-1 decrease, and IGF-1 activity increases.

Starvation Metabolism

Absolute starvation ultimately leads to death. Metabolic adaption to starvation is the body’s way of delaying this endpoint for as long as possible and allows us to survive starvation for up to 2 months. Since liver glycogen is depleted within 24 hours, gluconeogenesis (at the expenses of muscle protein)

becomes the sole provider of glucose for tissues that depend on glucose for survival – i.e. the brain, renal medulla and erythrocytes. During prolonged starvation, metabolism adapts in order preserve the protein stores from rapid depletion. This process is characterized by a reduction in T3 levels which leads to a decrease in the metabolic rate and muscle proteolysis. Reduced insulin levels along with activation of the adrenergic system result in an increased lipolysis in adipose tissue so that fats become the principle energy source. Glycerol from triglycerides (TGs) enters the glycolytic pathway and free fatty acids (FFAs) are broken down to acetyl-coenzyme A (acetyl-CoA). Excess acetyl-CoA results in formation of ketone bodies (ketosis). Some FFAs can contribute to gluconeogenesis. During prolonged starvation, the brain, kidneys and muscle begin to utilize ketone bodies efficiently as a source of fuel. The liver, through gluconeogenesis, can effectively recycle lactate (from glycolysis in glucose-dependent tissues) which is driven by energy derived from FFA oxidation and minimizes protein oxidation.

When FFAs and ketones are available as fuel, important mechanisms for protein-sparing are initiated. This occurs through the inhibition of key enzymes by the high acetyl-CoA/CoA ratio - 1) reduced glycolysis by pyruvate dehydrogenase inhibition & 2) reduced oxidation of amino acids by inhibition of branch chain 2-oxo-acid dehydrogenase. In starvation, the kidney becomes a gluconeogenesis tissue by converting the excess hydrogen ions that the kidney excretes as ammonia (from glutamine and glutamate) into glucose.

In summary, about 10-15% of the body weight can be lost without severe functional derangement, while weight loss of 35-40% becomes life-threatening.

Metabolic Effects from Surgery

Humans respond to surgery (and trauma) with multiple neuroendocrine changes leading to catabolism of stored body fuels and retention of salt and water. This '*surgical stress response'* was first described in the late 1920s, among patients admitted to hospital with long bone fractures. They found dramatic increases in nitrogen, potassium, phosphate, sulphur and creatine urinary losses and concluded that these represented a systemic breakdown in skeletal muscle. Later experimental studies showed increased levels of adrenal cortical hormones in response to injury. Furthermore, severing afferent nerve pathways from the site of injury diminished this response.

Modern understanding of the surgical stress response is that it involves activation of the sympathetic nervous system, secretion of catabolic hormones (cortisol, glucagon, growth hormone and catecholamines) and local cytokine responses to tissue injury. This response is usually proportional to the degree of surgical trauma or injury incurred. The endocrine component includes activation of the hypothalamic-pituitary-adrenal axis with increased cortisol secretion, increased secretion of vasopressin and increased pancreatic secretion of glucagon; this response leads to a net increase in peripheral insulin resistance and catabolism of skeletal muscle. The degree of peripheral insulin resistance has been linked to the magnitude of the catabolic response. In contrast to the situation during fasting, the metabolic adaption to minimize loss of body mass (particularly muscle mass) does not occur. Furthermore, injured tissues and tissues where synthesis of acute-phase proteins occurs still rely on glucose as a substrate. In addition, increasing body metabolism results in more severe net loss of fat and protein stores, and these responses are not to any great extent influenced by the availability of exogenous substrates.

The stress response to surgery has likely developed as an evolutionary response, allowing injured animals to survive without food and with healing of their wounds. However, in the current highly controlled surgical environment, this response is associated with several deleterious effects, including organ dysfunction, hypercoagulation, immunosuppression, catabolism and impaired wound healing. Peripheral insulin resistance is associated with hyperglycaemia - a possible cause of postoperative complications and an independent predictor of length of hospital stay.

Metabolic Effects of Preoperative Carbohydrate Drink

Only recently has it been shown that intake of clear fluids up to 2 hours before surgery may be permitted without an increase in gastric residual volumes or risk of aspiration of gastric contents. This prompted anaesthetic guidelines to allow free intake of clear fluids up to 2 hours prior to induction of anaesthesia. However, free fluids do not provide what is required to change the fasted state and reduce postop insulin resistance. Preoperative carbohydrate treatment aims to replicate normal

metabolic responses to eating breakfast. This treatment stimulates an endogenous insulin release, which switches off the overnight fasting metabolic state and is given to decrease the extent of peripheral insulin resistance while ameliorating the surgical stress response.

To test the hypothesis, a series of randomized studies were performed (Figure 1) where glucose was administered either as a preoperative infusion or as a carbohydrate-rich drink (400 mL, 50 g glucose) taken 2-3 hours before surgery. Scintigraphic studies showed that gastric emptying was complete within 2 hours after intake of this beverage. The amount of energy was enough to increase insulin to levels to that seen after a mixed meal, and insulin action enhanced by about 50% was shown 2-3 hours after intake. Randomized studies involving either preoperative glucose infusion or the carbohydrate-rich drinks all show that postoperative insulin resistance may be reduced by about 50% when preoperative fasting is avoided.

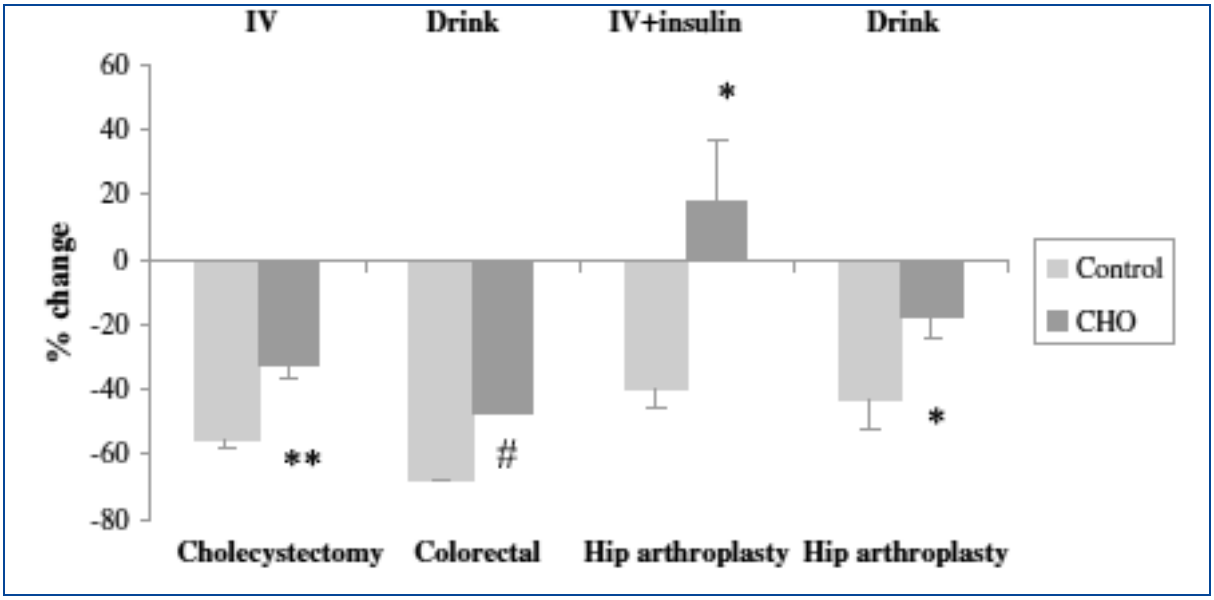

Figure 1. *The relative change in insulin sensitivity at postoperative measurement versus before surgery in patients fasted overnight before surgery (Control) and patients given carbohydrates (CHO) as an intravenous infusion (IV), an intravenous infusion together with insulin before and during surgery (IV + insulin), or as a carbohydrate-rich beverage 2 hr before surgery (Drink).*

J. Nygren. Metabolic effects of fasting and surgery. Best Practice & Research Clinical Anaesthesiology. Vol. 20, No. 3, pp. 429-438, 2006

The effects on postoperative glucose production by avoiding preoperative fasting indicate that there may also be effects on protein breakdown and gluconeogenesis. In support of this, other placebo-controlled, randomized studies have shown better maintained lean body mass (mid-arm circumference) and less reduced muscle strength (voluntary quadriceps strength) after gastrointestinal surgery when preoperative fasting was avoided. The avoidance of preoperative fasting has not been associated with differences in cytokine or stress hormone levels.

The metabolic effects of providing fluid and energy before surgery using a carbohydrate-rich drink versus placebo was also shown in randomized trials to affect patient well-being (thirst, hunger, anxiety) before surgery and to reduce postoperative nausea and vomiting (PONV) after laparoscopic cholecystectomy.

Indeed, there are also other important determinants of the surgical stress response. Both minimally invasive procedures as well as epidural anaesthesia have been shown to reduce postoperative insulin resistance. Mechanisms related to these effects may be a reduction in cytokine responses (laparoscopic surgery) and lower release of stress hormones (epidural anaesthesia). In studies where patients undergoing open colorectal surgery were treated with an enhanced recovery protocol, including avoidance of preoperative fasting and epidural anaesthesia, postoperative insulin sensitivity was well maintained.

Controversial patient groups

- Obesity

Harter et al in Anaesthesia & Analgesia (1998) compared 256 fasted patients (75 obese and 157 lean). They found that in the obese patients who were otherwise healthy, there was no increase incidence of increased gastric volumes and low stomach pH contents in the fasted state.

In addition, Maltby et al in the Canadian Journal of Anaesthesia (2004) studied 126 patients who were obese ASA 1 or 2 patients. They also could not demonstrate an increase in gastric volume or lower pH in these patients after being routinely fasted. They concluded that obesity per se should not be considered a risk factor for pulmonary aspiration and that healthy obese patients should be allowed to drink clear fluids up to 2 hours before elective surgery.

- Diabetes

Gustafsson et al in Acta Anaesth Scand (2008) studied gastric emptying time of 25 type 2 diabetics vs 10 healthy control subjects. They were given carbohydrate rich drink with paracetamol 1.5g. The diabetic patients demonstrated elevated glucose levels at the 2 hour mark but this had returned to normal at 3 hours. There was no difference in gastric-emptying half time. They concluded that the preoperative carbohydrate rich drinks could be used safely in diabetics but that these drinks should be given 3 hours preop instead of 2 hours.

Conclusion

ERAS protocols strongly recommend the use of carbohydrate-rich drinks in patients undergoing major elective surgery. Although this approach does not appear to cause any harm to patients (aspiration risk), its clinically relevant outcome benefit is supported by reasonably low quality evidence. There is however no doubt that unnecessarily prolonged starvation times causes patient discomfort and is potentially detrimental to postoperative patient outcomes.

Key Words

- **Glycogenolysis** - glycogen breakdown to glucose
- **Gluconeogenesis** - glucose synthesis from non-carbohydrate sources – lactate, pyruvate, amino acids & glycerol. Enhanced by glucocorticoids, catecholamines, glucagon and thyroid hormone, whereas insulin inhibits it.
- **Proteolysis** - the breakdown of proteins or peptides into amino acids by the action of enzymes
- **Glycolysis** - breaks down glucose and forms pyruvate with the production of two molecules of ATP. The pyruvate end product of glycolysis can be used in either anaerobic respiration (if no oxygen is available) or in aerobic respiration via the citric acid cycle which yields much more usable energy for the cell
- **Lipolysis** - the breakdown of lipids and involves hydrolysis of triglycerides into glycerol and free fatty acids.

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