Preoperative oral carbohydrate therapy

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Purpose of review
Management of the postoperative response to surgical stress is an important issue in major surgery. Avoiding preoperative fasting using preoperative oral carbohydrates (POC) has been suggested as a measure to prevent and reduce the extent to which such derangements occur. This review summarizes the current evidence and rationale for this treatment.

Recent findings
A recent review from the Cochrane Collaboration reports enhanced gastrointestinal recovery and shorter hospital stay with the use of POC with no effect on postoperative complication rates. Multiple randomized controlled trials demonstrate improved postoperative metabolic response after POC administration, including reduced insulin resistance, protein sparing, improved muscle function and preserved immune response. Cohort studies in patients undergoing major abdominal surgery have shown that the use of POC as part of an enhanced recovery after surgery protocol is a significant predictor for improved clinical outcomes.

Summary
Avoiding preoperative fasting with POC is associated with attenuated postoperative insulin resistance, improved metabolic response, enhanced perioperative well-being, and better clinical outcomes. The impact is greatest for patients undergoing major surgeries.

Keywords
insulin resistance, preoperative fasting, preoperative oral carbohydrates

INTRODUCTION
Despite improvements in surgical and anesthetic techniques, postoperative changes in metabolism, increased catabolism and reduced functional capacity are significant problems in patients undergoing major surgery. Once developed, these changes not only increase the risk of early postoperative complications but also affect long-term survival after major surgery. Avoiding preoperative fasting by providing a carbohydrate drink before surgery has been shown to prevent these metabolic derangements from occurring. This review will cover the evidence in favor of the use of preoperative oral carbohydrates (POC), specifically the rationale for their role in reducing the response to surgical stress and in improving clinical outcomes.

METABOLIC RESPONSE TO TRAUMA AND INSULIN RESISTANCE
Trauma, including elective surgery, induces a well characterized neuroendocrine response mediated by the release of catabolic or ‘stress’ hormones, as well as proinflammatory cytokines [1]. The metabolic response includes depletion of glycogen stores in the liver and skeletal muscle, as well as release of free fatty acids and amino acids from adipose tissue and skeletal muscle, respectively. An increasing body of evidence has demonstrated that a key feature of this shift in metabolism is the development of insulin resistance with impairment of insulin’s anabolic effects [1]. Although the best recognized manifestation of stress-induced insulin resistance is hyperglycemia in the presence of a normal or supranormal insulin concentration, marked impairments in insulin’s effect on protein and fat metabolism are present as well. Moreover, by ‘compensating’ for insulin resistance by infusion of exogenous insulin,
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KEY POINTS

- POC attenuate the body’s response to surgical stress including insulin resistance.
- POC favorably affect clinical outcomes such as well-being, gastrointestinal recovery and hospital stay.
- The use of POC is a predictor for improved outcome in the ERAS setting after major surgery.

Normalization of key components of glucose, fat and protein metabolism is possible, as demonstrated in patients undergoing major abdominal surgery [2].

Insulin resistance invariably develops in otherwise healthy individuals and patients with diabetes following elective surgery. Its severity is proportional to the degree of surgical trauma [1,3]. Insulin resistance has been shown to be an independent predictor for length of hospital stay after elective surgery [1,3]. Perhaps, the most striking data illustrating the clinical impact of insulin resistance are the findings reported by van den Berghe et al. [4]. They showed that infusion of sufficient amounts of insulin to achieve normoglycemia in surgical ICU patients had tremendous effects on outcome parameters, including a 34% reduction in in-hospital mortality, 46% reduction in bloodstream infections and 41% reduction in acute renal failure.

By the use of multiple regression analysis, factors influencing the development of postoperative insulin resistance were shown to include type of surgery (degree of trauma) and perioperative blood loss, whereas age, sex, BMI, and length of the operation were not [3,5]. The contribution of other ‘interventions’ associated with surgical treatment, apart from the surgical operation per se, has been evaluated as well. Thus, hypocaloric nutrition [2-1 glucose 5% (400 kcal/24 h)] for 24 h and 48 h in healthy volunteers induced approximately a 30% and 50% reduction of preintervention insulin sensitivity, respectively, whereas immobilization for the same lengths of time had much less influence [6].

PREOPERATIVE FASTING

One of the oldest routines in modern medicine is fasting from midnight the day before surgery, the main underlying reason being to avoid aspiration in association with induction of anesthesia. This routine came into question in the 1980s, when it was realized that it was unnecessary from a safety point of view and, on the contrary, only increased patient discomfort [7]. Since then, many countries have adopted new routines for patients undergoing elective surgery involving the allowance of clear fluids (water, coffee, tea with no milk and clear juices) until 2 h before induction of anesthesia [7]. Moreover, findings from studies in animal models of severe stress –mainly hemorrhagic– have demonstrated markedly impaired outcomes in fasted compared with nonfasted animals [8]. It was, therefore, reasonable to question whether fasting was the preferable way to prepare humans for the stress of surgery.

To address this question, the effect of reversing the fasted to a fed state was evaluated by the use of an intravenous glucose infusion. In a small study in patients undergoing open cholecystectomy, postoperative insulin resistance was reduced by 50% using a 20% (% weight/volume) glucose infusion compared with patients submitted to traditional preoperative fasting [9]. This was in accordance with an earlier finding of improved postoperative nitrogen economy with similar treatment after major abdominal surgery [10]. Markedly improved postoperative insulin resistance using preoperative glucose infusion was also confirmed in patients undergoing hip replacement [11]. In that study, the effect of glucose infusion in combination with insulin was also associated with reduced release of cortisol and improved substrate utilization, demonstrating an effect on the stress response itself and fat metabolism as well. It should also be acknowledged that glucose infusion, either alone or in combination with insulin and/or potassium prior to various types of cardiac surgery, has consistently been shown to markedly improve outcomes, mainly manifested as reduced episodes of arrhythmias and need for vasopressor support [8].

DEVELOPMENT AND TESTING OF PREOPERATIVE ORAL CARBOHYDRATES

A more convenient means by which carbohydrates might be provided to patients prior to surgery is by the oral route. The aim with such a treatment was to stimulate an insulin response corresponding to that of a regular meal to switch metabolism from a fasted to a nonfasted state. However, current recommendations regarding fasting do not include allowance for intake of energy-rich beverages. Any solution used in the preoperative clinical situation needs to be evaluated from a safety point of view to minimize the risk of aspiration. A carbohydrate-rich drink with high energy content was, therefore, developed. Because gastric emptying time after intake of liquids is proportional to osmolality, carbohydrates in the form of polymers were used to keep the osmolality as low as possible. The
beverage was first tested in healthy volunteers and found to induce a sufficient insulin response and to be completely emptied from the stomach within 90 min after intake. This was also later confirmed in patients undergoing elective surgery [12]. To date, this beverage has been used in over 4000 patients participating in studies and in more than 3 million patients in clinical practice without significant adverse events being reported to the manufacturer (Nutricia AS, The Netherlands, personal communication).

**METABOLIC EFFECTS OF PREOPERATIVE ORAL CARBOHYDRATE**

In clinical practice, POC treatment has usually been given as an evening dose of 800 ml and half that amount on the morning of the day of surgery. The effect of POC on postoperative insulin resistance was evaluated by the use of the hyperinsulinaemic euglycemic clamp technique in patients undergoing elective surgery. In two clinical trials, insulin resistance was found to be reduced after POC by 47% and 57% in patients undergoing colorectal [12] and hip replacement surgery [13], respectively. A recent clamp study in which the postoperative measurement was performed 2 days after hip replacement did not show an effect of POC on postoperative insulin resistance [14]. However, only whole body glucose disposal was measured, and on the basis of previous studies, it is known that insulin resistance and the metabolic effects from POC observed in the immediate postoperative period are likely not sustained in the days following hip replacement surgery, as opposed to abdominal surgery [3,13]. Indeed, also in a placebo-controlled randomized controlled trial (RCT) in patients undergoing hip replacement, in which insulin resistance was measured 3 days postoperatively, no difference was found in whole body glucose disposal after POC; however, patients with POC displayed an attenuation of the postoperative increase in endogenous glucose release and mean nitrogen losses [15], indicating a significant metabolic effect from treatment.

In a study using stable protein and glucose isotopes in combination with the hyperinsulinaemic clamp, POC were also found to improve whole body protein balance in patients undergoing colorectal resections [16]. The authors reported that the improvement of whole body glucose disposal was mainly accounted for by better preserved effect of insulin to suppress endogenous glucose production [16]. Several RCTs support an effect of POC on other aspects of the postoperative metabolic response such as protein sparing, lean body mass, muscle strength and immunity [1,17].

To investigate the relative role of the evening and morning doses of POC, respectively, for improved insulin sensitivity postsurgery, a study in healthy volunteers was performed. This study found that POC improves insulin sensitivity by 50%, 3 h after intake (corresponding to the effect of the morning dose). The evening dose prior to the clamp did not improve insulin sensitivity the following day [18]. The effect of solely a single-dose carbohydrate on the morning of surgery was also later confirmed in an experimental pig model [19**]. These findings, therefore, suggest that a morning dose of POC is sufficient to achieve the effects on postoperative insulin resistance and that this effect is explained by an increase in insulin sensitivity after POC administration.

**MECHANISMS BEHIND EFFECTS OF PREOPERATIVE ORAL CARBOHYDRATES**

The precise mechanisms by which POC attenuates postoperative insulin resistance are not fully understood. Surgical stress activates inflammatory pathways in skeletal muscle [20] and adipose tissue [21], and a relation between circulating concentrations of IL-6 and postoperative insulin resistance has been reported [22]. On a cellular level, surgery has been shown to attenuate insulin-stimulated glycogen synthase activity and GLUT4 translocation [23]. It is, therefore, possible that POC might, to some extent, reduce the inflammatory response to surgical stress. Moreover, because insulin is known to have anti-inflammatory properties, it is likely that at least some of the effects on postoperative insulin resistance exerted by POC might result from the physiological hyperinsulinaemia and not from the glucose load itself. Indeed, reduced inflammation as reflected by lower postoperative concentrations of IL-6 [24], C-reactive protein levels [25,26] and postoperative immune response [17] have been reported after POC administration compared with after preoperative fasting or placebo administration.

In an animal model of surgical stress, Gjessing et al. [19**] reported that POC reduced free fatty acid concentrations intra and postoperatively and increased postoperative oxidative glucose disposal, whereas neither hepatic insulin sensitivity nor non-oxidative glucose disposal was improved. To further elucidate this improved glucose oxidation, the same authors [27**] performed a follow-up study in a similar model with quantitative reverse transcription polymerase chain reaction and infrared Western Blotting in specimens from skeletal muscle. They reported improved insulin inhibition of FOX01-mediated PKD4 mRNA and protein expression in muscle after surgery in POC pigs, suggesting that one mechanism by which POC improves
insulin sensitivity is by increasing carbohydrate-derived pyruvate flux into the mitochondria.

A similar finding was also reported by Awad et al. [28] in patients undergoing laparoscopic cholecystectomy, although the preoperative beverage used in their study contained glutamine and antioxidants as well, making the interpretation of their data more uncertain. In addition, an RCT from China after radical gastrectomy [29] reported that improved postoperative metabolism from POC was associated with improved mitochondrial function and less marked structural changes in the mitochondria, as shown by transmission electron microscopy.

**PREOPERATIVE ORAL CARBOHYDRATES AND EFFECTS ON CLINICAL OUTCOME**

In a recent Cochrane review [30**, clinical effects from preoperative carbohydrate treatment were reviewed. On the basis of 27 trials involving 1976 patients, it was concluded that this treatment not only reduced postoperative insulin resistance, but also significantly reduced hospital length of stay [mean difference = −0.30, 95% confidence interval (CI) −0.56 to −0.04]. Furthermore, this effect was larger and more clinically relevant when procedures such as major abdominal surgeries with an estimated hospital stay more than 2 days were analyzed separately (mean difference = −1.66, 95% CI −2.97 to −0.34). No effects were found on postoperative complications. Importantly, no events involving aspiration pneumonitis have been registered in any of the clinical trials of POC thus far.

In addition, in two studies including 86 patients, return of gastrointestinal function was measured, and, in agreement with previous experimental studies [31], a shorter time for return of flatus was demonstrated after POC (mean difference 0.39 days, 95% CI −0.70 to −0.07) [30**]. Although reported in some studies [32], no overall effect from POC was found on postoperative nausea or well-being in the Cochrane review. However, in two RCTs published more recently, favorable effects from POC on postoperative nausea and vomiting, pain and well-being were found after laparoscopic cholecystectomy [33**,34*].

**ROLE OF PREOPERATIVE ORAL CARBOHYDRATES IN ENHANCED RECOVERY AFTER SURGERY**

Enhanced recovery after surgery (ERAS) programs are evidence-based perioperative care protocols aimed at ameliorating the metabolic stress response and improving clinical outcomes. The first ERAS protocol was published in 2005 [35] based on the multimodal preoperative care protocol originally described by Professor Kehlet [36] in Copenhagen. The early work of ERAS was with patients undergoing colorectal surgeries, in which a key finding was that both preoperative fasting and prolonged postoperative nil per os status were detrimental to patient recovery. By minimizing insulin resistance immediately postoperatively, POC allow nutrients consumed early after surgery to be managed in an almost normal fashion [37]. In addition, POC have a favorable effect on perioperative fluid balance. Gustafsson et al. [38] reported in a single center series of 953 consecutive colorectal resections that POC reduced the need for intravenous infusions preoperatively that was associated with improved outcomes. POC and fluid overload were the only items in the ERAS protocol that significantly predicted clinical outcomes in a multivariate analysis.

A similar finding of improved outcomes from POC was shown in a multicenter study of more than 2300 patients from 13 centers in six countries [39**]. In this study using the ERAS Society database [40], POC was a significant predictor of shorter length of stay in an ERAS setting. In contrast, individual studies with a much lower number of analyzed patients, such as the laparoscopy in combination with fast track multimodal management trial, have not identified POC as a predictive variable in a multivariate analysis [41].

Thus, although there still may be some inconsistencies regarding the specific clinical effectiveness of POC, most data from a large series suggest that POC have an important role in reducing the stress response and improving patient outcomes after major surgery. As such, POC are recommended in both the ERAS Society guidelines [42–44] and major international anesthesia societies [45].

**CONCLUSION**

Recent evidence shows that avoiding preoperative fasting not only improves postoperative metabolism such as insulin resistance, but also affects clinical outcomes such as return of gastrointestinal function and hospital stay. Cohort studies indicate significant effects from POC within an ERAS environment after major surgery. Large multicenter RCTs are needed to further strengthen the evidence on the influence of POC on outcomes after various surgical procedures. Mechanistic studies, experimental and clinical, are also important to further increase our understanding of how best to ameliorate perioperative stress and improve outcomes.

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Conflicts of interest

O.L. holds the patent rights to Nutricia pre-op (the patent expired in 2011). O.L. serves on an advisory committee for Nutricia AS, The Netherlands, a company that sells clinical nutritional products. He also owns stock in Encare AB, Sweden, an information technology company that manages the ERAS Interactive Audit System. The other authors have no disclosures.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as follows:

* of special interest
** of outstanding interest


19. Gjessing PF, Hauge M, Fuskevåg OM, et al. Single-dose carbohydrate intervention in the immediate preoperative phase diminishes development of postoperative peripheral insulin resistance. Clin Nutr 2015; 34:156–164. This important experimental study in pigs obtained similar to what has been achieved in previous clinical studies in surgical patients. This experimental setting will provide an opportunity to further elucidate mechanisms behind the benefits of POC on postoperative metabolism.


This is one of several studies from the Tromsø group reporting that POC reduces inflammatory responses to surgery.


This is an important recent Cochrane review regarding the effects of POC on clinical outcomes.


This placebo-controlled RCT demonstrated the impact of POC on PONV and pain after laparoscopic cholecystectomy.


This placebo-controlled RCT demonstrated improved well-being, including reduced nausea, early after laparoscopic cholecystectomy.


39. ERAS Compliance Group. The impact of enhanced recovery protocol compliance on elective colorectal cancer resection: results from an international registry. Ann Surg 2015. [Epub ahead of print]. This is a large study of 2300 patients in 13 units from six countries from the ERAS Society database, showing that improved compliance with the ERAS protocol improved outcomes. POC was one independent predictor for improvement.


