OXFORD

Revalidation FOR ANAESTHETISTS RCA Revalidation matrix Matrix reference 1A01, 2A03, 3A03

BJA Education, 17 (9): 312–316 (2017)

doi: 10.1093/bjaed/mkx015
Advance Access Publication Date: 15 May 2017

Starvation, carbohydrate loading, and outcome after major surgery

William J Fawcett FRCA FFPMRCA[1,*] and Olle Ljungqvist MD PhD[2]

[1]Consultant Anaesthetist, Royal Surrey County Hospital, Egerton Road, Guildford, Surrey GU2 7XX, UK and [2]Professor of Surgery, Department of Surgery, Faculty of Medicine and Health, School of Health and Medical Sciences, Örebro University, SE-701 85 Örebro, Sweden

*To whom correspondence should be addressed. E-mail: wfawcett@nhs.net

Key points

- Major surgery induces a number of metabolic changes, with insulin resistance fundamental within these processes, often causing hyperglycaemia.
- Perioperative hyperglycaemia should be avoided in patients undergoing major surgery, whether they have previously diagnosed diabetes or not.
- Preoperative carbohydrate loading modifies insulin resistance, improves patient comfort and well-being, minimizes protein losses, and improves postoperative muscle function. It is a key aspect of 'enhanced recovery' protocols.
- Preoperative carbohydrate loading does not increase the risk of pulmonary aspiration, but its place in patients with diabetes is uncertain.
- Preoperative carbohydrate loading reduces length of stay and may reduce complications for some surgery.

The concept of a period of preoperative starvation prior to elective surgery to avoid regurgitation and aspiration of gastric contents is so deeply enshrined in anaesthetic practice that it has taken many years to revisit this area. However, in the last quarter of a century, patients have experienced and benefited from a number of significant changes in this area.

While the perceived benefit of preoperative fasting may be self-evident, what are the disadvantages? One area is dehydration, with a number of articles from the 1980s highlighting that withholding water for excessive periods was not only unnecessary[1] but also had no deleterious effect on both the volume and the pH of gastric contents when administered up to 2 h prior to surgery.

Stress response

The major issue surrounding a period of starvation needs to be viewed within the context of the pathophysiological changes that accompany major surgery. The stress response describes the process whereby pituitary and sympathetic nervous system activation leads to a number of predictable metabolic changes such as hyperglycaemia, nitrogen loss, and lipolysis. A secondary area is a systemic inflammatory response mediated by various cytokines (e.g. interleukins and tumour necrosis factor). A key area of interest has been surgical stress response modification, for while its evolutionary benefits are evident—substrate mobilization and water conservation when access to food and water is restricted—there is little benefit and indeed much potential harm due to this unmodified pathophysiological upset. Indeed, it has been this approach that has formed the basis for modern enhanced recovery (ER) pathways. In addition, it is now recognized that anaesthetic and surgical complications (such as hypovolaemia, infection, and hypothermia) can magnify these changes further.

There are many ways of assessing the magnitude of the stress response. These principally include the neuroendocrine sequelae, measuring the hormones themselves—plasma concentration of cortisol, growth hormone, catecholamines, insulin, and so on—or some of the other metabolic changes, in

Editorial decision: March 2, 2017; **Accepted:** March 8, 2017

particular hyperglycaemia and nitrogen loss. At the very heart of these changes lies a core physiological disruption: insulin resistance.

Insulin resistance

Insulin is the body's major anabolic hormone, but very soon after the onset of surgical stress the body enters a state of insulin resistance (IR) with a shift from the anabolic state to the catabolic state with the mobilization of carbohydrates, protein, and fats as fuels to support the process of tissue healing and synthesis of other substances such as acute phase proteins. This resultant IR has been extensively studied and its impact can be considered in two fundamental areas: in the periphery (particularly muscle) and in the liver. Peripheral IR will reduce glucose uptake leading to hyperglycaemia, whereas hepatic IR will result in an increase in gluconeogenesis. Both will contribute to elevated plasma glucose concentrations, the so-called 'diabetes of injury'. While it has been widely appreciated that previously known diabetic patients have had a poorer outcome than non-diabetic patients, more recently, there has been the recognition that hyperglycaemia in all patients has a significant impact on patient outcome, with an increased length of stay in both the hospital and the intensive care unit, increased rate of infection (septicaemia, urinary tract, and lung), myocardial infarction and renal failure,[2] and reoperation and death.[3] Moreover, the risks of death increased in proportion to the perioperative serum glucose concentration[2] and successful treatment of hyperglycaemia with insulin reversed these risks.[3] A secondary issue is the effect of IR on muscle metabolism, with reduced glucose uptake, glycogen storage, and increased protein catabolism. This will result in a reduced energy supply to the muscle after operation, with weakness and reduced mobilization.

IR has attracted interest for many years outside of major surgery. It is viewed as a precursor to metabolic syndrome and type 2 diabetes mellitus (T2DM). Yet its assessment is complex, and there are many methods described to assess IR. These can broadly be divided into two categories: dynamic and simple tests. The gold standard is widely regarded as the hyperinsulinaemic–euglycaemic clamp (HEC) and is a dynamic test in which a high-dose insulin infusion (e.g. >80 milliunits m^{-2} min^{-1}) is administered, which will suppress hepatic glucose production. This is administered alongside an i.v. glucose infusion to maintain normoglycaemia. If serum glucose concentrations remain unchanged, at steady state, the glucose infusion must equal whole-body glucose disposal, sometimes referred to metabolizable glucose (M). The amount of glucose infused required for these conditions is typically expressed in milligrams glucose per body mass per minute, with a low value defining IR, whereas subjects without IR require much higher levels of glucose to maintain euglycaemia. Unsurprisingly, this test is very labour–intensive, requiring frequent blood tests with the ever-present risk of hypoglycaemia.

As a result, many simpler tests have been described, of which the most common is homeostatic model assessment (HOMA) in which in fasting plasma glucose and insulin concentrations are measured. As the product of these two measurements decreases, the subject is deemed to be more insulin sensitive (i.e. less IR). Unfortunately, HOMA is often used as a substitute for the clamp method and described as insulin resistance. This is erroneous as the two methods are not interchangeable, with HOMA measuring only basal fasting insulin levels, during which insulin will be inactive. The entire changes causing insulin resistance are thus missed and therefore HOMA gives no insight into the development and magnitude of insulin resistance, with the level of the error increasing with increasing insulin resistance. Other tests have also been described based on an oral glucose tolerance test and often represent better alternatives compared with the HOMA.

IR has been extensively studied perioperatively. It increases with the magnitude of surgery, with laparoscopic surgery causing less resistance than minor open surgery, and major open surgery producing the largest increase. IR increases occur early and are most marked on the first day after surgery, with large inter-individual variations. These increases in IR may average approximately 50% (and may be as much as 90%) following abdominal surgery, lasting at least 5 days and sometimes several weeks. It does not necessarily mirror other markers of the stress response such as raised cortisol, growth hormone, and epinephrine. Moreover, IR itself is associated with an increase in complications (including the rate of infections) and length of stay. A study by Sato *et al.*[4] on cardiac patients showed that for every 20% decrease in intraoperative insulin sensitivity, the risk of serious mortality (myocardial failure, stroke, the need for dialysis, and the presence of serious infection) more than doubled, irrespective of whether or not the patient was a previously known diabetic.

So, if we accept that IR is deleterious, what can we do to restore insulin sensitivity and reduce hyperglycaemia? One approach is to use insulin infusions to control the latter, but altering the pathophysiology upstream in the process is a logical alternative. The use of minimally invasive surgery, thoracic epidural anaesthesia (for open surgery), and early preoperative feeding to reduce the prolonged effects of starvation have a major effect on restoring insulin sensitivity. Another approach is to provide glucose preoperatively, as data from animal models demonstrated that starvation considerably magnified insulin resistance. Nearly 20 years ago, Ljungqvist *et al.*[5] showed that overnight infusions of glucose in patients improved insulin sensitivity (as measured with HEC), with the sensitivity in the glucose group falling by about 45%, whereas in the control (no glucose) the sensitivity fell by about 68%. A later paper also demonstrated that an overnight glucose infusion in patients at a rate of 5 mg kg^{-1} min^{-1} increased hepatic glycogen content by 65% compared with the controls.[6] These landmark papers set the scene for the development of carbohydrate loading.

Oral carbohydrate loading: practicalities

With the realization that i.v. glucose administration conferred significant physiological advantages, it was natural that the oral route would be explored to administer preoperative carbohydrates, with the first study published in 1995.[7] Interestingly, the concept is not new: the surgeon Sir Joseph Lister (1827–1912) declared: 'While it is desirable that there should be no solid matter in the stomach when chloroform is administered, it will be found very salutary to give a cup of tea or beef tea about two hours previously.' The key composition of oral carbohydrate loading is mainly maltodextrin (a polysaccharide), which is reliably emptied from the stomach after 2 h. The most commonly used formulation is a 50 g sachet, diluted to 400 ml to make 12.5% high-energy drink with an osmolality of 135 mOsm/ kg^{-1} (promoting rapid gastric emptying) and containing 200 calories. Two sachets (800 ml) are taken the evening prior to surgery and one sachet (400 ml) 2–4 h prior to surgery. Common brands in the UK include Preload™ (Vitaflo® International Ltd,

Liverpool, UK) and preOp® (Nutricia Ltd, Trowbridge, Wiltshire, UK).

Carbohydrate loading is not restricted to surgical patients. There is a parallel between athletes undertaking a major sporting challenge and elective patient undergoing surgery, as both groups benefit from carbohydrate loading. Physiologically, both groups require an increase in oxygen delivery (DO_2), as oxygen consumption (VO_2) rises and if the required increase in DO_2 fails, there is a progressive switch to anaerobic metabolism resulting in a rise in serum lactate concentrations. In athletes, this results in impaired performance and early fatigue, and in surgical patients there is poorer outcome with increased morbidity and mortality.[8]

There are several practical issues surrounding introduction of carbohydrate preloading. The volume of the first preload (800 ml) is difficult for some patients to tolerate and may cause the patient to wake to urinate in the night. Of note, the evening dose secures glycogen loading (with very little, if any, impact on insulin sensitivity prior to surgery). It is the morning dose that causes changes from the fasted to the fed state, so if patients eat dinner the evening dose may be unnecessary.[9] Other areas encountered include reluctance by both patients and staff (concerned about breaching nil by mouth orders) and also, in some institutions, whether or not it is viewed as a drug (funded by the pharmacy) or to be funded by the surgical ward or operating theatre budget.

Oral carbohydrate loading: clinical evidence

Preoperative oral carbohydrate loading has brought many benefits to patients undergoing major elective surgery (Table 1). A major—if seemingly somewhat obvious—benefit is generally to improve patient comfort or well-being,[10] with the incidence of various parameters tested such as thirst, hunger, tiredness, malaise, anxiety, and mouth dryness reduced in the oral carbohydrate group. Interestingly, i.v. carbohydrates were effective at reducing weakness and tiredness but not thirst and hunger.[11] Some patient groups also had less nausea and vomiting. In addition, the patient is 'fed' and is metabolically prepared to withstand the ensuing physiological changes of surgery. These include a reduction in IR by up to 50% for a range of major surgeries.

A key feature is that carbohydrate loading prevents protein loss as measured by urea and 3-methylhistidine excretion (with the original data from i.v. glucose infusions[12]), as well as the preservation of muscle mass (as measured by upper arm circumference[13]), and quadriceps strength at 1 month,[14] both of which suggest that overall muscle function (and thus rehabilitation) may be improved. At a cellular level, it is recognized that IR can be assessed by studying the expression of insulin-induced activation of phosphatidylinositol 3-kinase (PI3K)/protein kinase B (PKB) signalling pathway as well as protein tyrosine kinase (PTK) activity. Carbohydrate loading attenuated IR by stimulating the P13K/PKB pathway, as well as increasing PTK activity in the rectus abdominus muscle.[15] The effects of carbohydrate loading may also potentially have an effect on improving cardiac muscle function after cardiopulmonary bypass.

Table 1 Benefits of oral carbohydrate loading

Reduction in postoperative insulin resistance
Improvement in preoperative patient well-being (thirst, hunger, dehydration, headache, nausea, and vomiting)
Reduction in protein loss
Improved postoperative muscle function
Reduced length of hospital stay

The findings of preserved muscle function, as measured clinically, are not universal and require more study. However, given the current enthusiasm worldwide for implementation of ER programmes (*vide infra*) in which rapid return to preoperative physiological function is a key concept, the prevention of further muscle wasting, particularly in those patients with pre-existing frailty and sarcopaenia, is viewed as fundamental. Weakness causes immobility and *vice versa* and inevitably leads to poor outcomes. In addition, carbohydrate loading complements the concept of prehabilitation programmes, in which preoperative exercise training improves postoperative muscle function and exercise capacity.

Enhanced recovery

The advent of ER pathways led initially to a focus on length of hospital stay (LOS). Carbohydrate loading is a component contributing to ER, and there are many studies looking at its impact within ER programmes. The benefits of oral carbohydrate loading, along with restriction of i.v. fluids were the two major independent predictors for reducing both adverse symptoms and complications in one report.[16] In this article, in which over 900 patients were studied, the authors examined the impact of an improved adherence to ER protocols which increased from 43.3% to 70.6% between the two study periods, with postoperative complications reduced by 25% and postoperative symptoms delaying discharge by nearly 50%. On multivariate analysis, adjusted for confounding, for the patients treated with carbohydrates, the risk of adverse postoperative symptoms (such as nausea, vomiting, pain, diarrhoea, and dizziness) was reduced by 44%, as well as the risk of wound dehiscence, possibly an effect of the protein sparing effect of improved insulin sensitivity.

Two meta-analyses on carbohydrate loading have provided further data for the adoption of carbohydrate loading. Awad *et al.*,[17] while showing no benefit for surgeries with an expected LOS of less than 2 days, nor in patients undergoing orthopaedic surgery, did show a small but significant reduction in LOS for abdominal surgery 1.08 days [95% confidence interval (CI) 1.87 to 0.29 days]. They also confirmed the reduction of postoperative IR but no changes in hospital complications. A later systematic review published on the Cochrane Database Smith *et al.*[18] Patients principally undergoing elective abdominal, orthopaedic, and cardiac surgery, and showed similar results to Awad's *et al.* study, unsurprising given that many of the studies were included in both. Smith *et al.* demonstrated a smaller reduction in overall LOS (0.3 days, 95% CI 0.56–0.04 days) with a highly significant reduction in LOS of 1.6 days for patients undergoing abdominal surgery together with a shorter time for passage of flatus (0.39 days, 95% CI 0.70–0.07 days) and again a reduction in IR but no effect on complications. There was a lesser impact for patients undergoing orthopaedic and cardiac surgery (Fig. 1). It should be borne in mind that both these meta-analyses included studies of varying quality and open to potential bias.

Safety

A major area of concern for anaesthetists will centre on the safety of carbohydrate loading. Intuitively, significant volumes of ingested fluid may cause concern as, if they are still present in the stomach at the induction of anaesthesia, these may

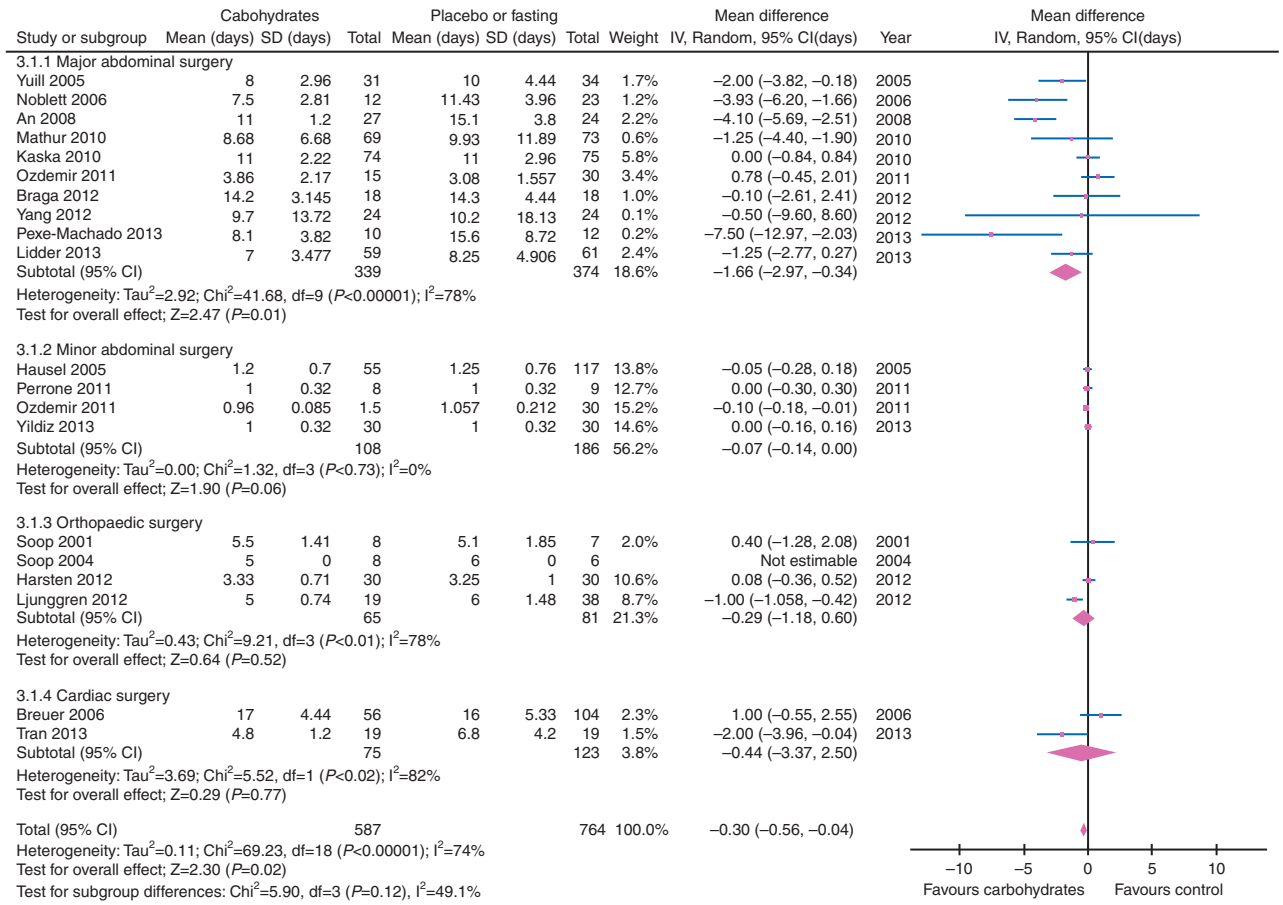

Fig 1 Forest plot for carbohydrate loading *vs* placebo or fasting. Outcome: length of hospital stay. From Smith *et al.*[18]

predispose to regurgitation and pulmonary aspiration. The maltodextrin (complex carbohydrate) constituent of the carbohydrate drink empties less quickly than water, but reliably from the stomach (in spite of the anxiety of impending surgery) within 90 min, as assessed by gamma camera.[7] More recent clinical studies on gastric emptying use either ultrasound assessment or the co-administration of paracetamol (with subsequent measurement of serum paracetamol concentrations). Whatever method is used, overall the administration of oral carbohydrate loading appears safe with no reports of pulmonary aspiration in either large meta-analyses or the estimated five million patients worldwide who have received carbohydrate loading as part of ER programmes. However, it should be borne in mind that pulmonary aspiration is rare (and serious complications and death extremely rare), so very large studies indeed would be required to confirm this.

Diabetes

Probably the most controversial area within oral carbohydrate loading is with patients who have diabetes, whether type 1 diabetes mellitus (T1DM) with lack of endogenous insulin or T2DM, which is characterized by insulin resistance. Diabetic patients may tolerate the carbohydrate load poorly, a situation that may then precipitate hyperglycaemia. In addition, if patients have autonomic neuropathy and gastroparesis, they may be at increased risk of having a large residual gastric volume, predisposing to pulmonary aspiration. These potential disadvantages therefore have to be balanced against the benefits of carbohydrate loading outlined above.

There is little evidence to provide definitive guidance. A small study by Gustafsson *et al.*[19] is often used to support the safety of carbohydrate loading in T2DM patients. Although there was a significant rise in serum glucose in the diabetic group (13.4 ± 0.5 *vs* 7.6 ± 0.5 mmol l^{-1}; $P < 0.01$), this had returned to normal by 3 h compared with 2 h in the control group. There was no evidence of autonomic neuropathy in the diabetic patients, assessed by the co-administration of paracetamol. One might reasonably expect the impact of carbohydrate loading in T1DM patients to have a greater physiological preoperative upset, but the expected reduction in IR postoperatively may confer considerable benefits to patients. This is a key area in carbohydrate loading, and there is a need for good quality data to address this.

Two areas are worthy of consideration. Firstly, it is possible to control the glycaemic load with insulin and perhaps that is a logical alternative to explore to provide the benefits and limit the hazards of carbohydrate loading. A second area is whether or not it is possible to reformulate conventional carbohydrate loading into a product that provides the metabolic advantages, but without the same concomitant changes in blood glucose. Attempts are already underway to explore this latter possibility with the introduction of a glycaemic endothelial drink. It has a lower maltodextrin content and also contains citruline (a precursor of arginine), which in turn leads to reduced gluconeogenesis, which may be of value both before and after surgery.

The future

Carbohydrate loading has almost exclusively been studied in elective patients undergoing major surgery, where it has provided tangible benefits. Areas for further research include extrapolating the benefits to other areas of surgery—there is currently a trial under way to evaluate the impact of emergency surgery for fragility hip fracture patients (POINT study). Furthermore, we do not know whether we have the optimal approach in terms of dose and duration of carbohydrate loading and whether or not combining it with other substances such as immunonutrients (such as omega-3 fatty acids, glutamine, and arginine), oral nutritional supplements, ketone drinks (to conserve carbohydrate and protein stores), or beetroot (and other compounds rich in nitrates that supplement production of nitric oxide) may provide added clinical improvements. There is much interest in many of these agents, particularly those rich in nitrates, which have a number of potential benefits to muscle function, such as improved blood flow, mitochondrial efficiency, glucose uptake, and the sarcoplasmic calcium handling, all of which maximize resistance to fatigue, exercise performance, and muscle efficiency.[8]

While anaesthesia has come a long way since the reliance on total overnight fasting, the optimal preoperative drinks are yet to be elucidated.

Declaration of interest

Both authors are Executive Committee Members of The Enhanced Recovery after Surgery (ERAS®) Society. Professor Ljungvist has advisory board appointment with Nutricia and has received speaking honoraria from Nutricia.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at http://www.oxforde-learning.com/journals/ by subscribers to *BJA Education*.

References

1. Maltby JR, Sutherland AD, Sale JP, Shaffer EA. Preoperative oral fluids: is a five-hour fast justified prior to elective surgery? *Anesth Analg* 1986; **65**: 1112–6
2. Frisch A, Chandra P, Smiley D *et al*. Prevalence and clinical outcome of hyperglycemia in the perioperative period in noncardiac surgery. *Diabetes Care* 2010; **33**: 1783–8
3. Kwon S, Thompson R, Dellinger P, Yanez D, Farrohki E, Flum D. Importance of perioperative glycemic control in general surgery: a report from the Surgical Care and Outcomes Assessment Program. *Ann Surg* 2013; **257**: 8
4. 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**: 4338–44
5. 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**: 329–36
6. Thorell A, Alston-Smith J, Ljungqvist O. The effect of preoperative carbohydrate loading on hormonal changes, hepatic glycogen, and glucoregulatory enzymes during abdominal surgery. *Nutrition* 1996; **12**: 690–5
7. Nygren J, Thorell A, Jacobsson H *et al*. Preoperative gastric emptying. Effects of anxiety and oral carbohydrate administration. *Ann Surg* 1995; **222**: 728–34
8. Scott MJ, Fawcett WJ. Oral carbohydrate preload drink for major surgery—the first steps from famine to feast. *Anaesthesia* 2014; **69**: 308–13
9. Svanfeldt M, Thorell A, Hausel J, Soop M, Nygren J, Ljungqvist O. Effect of 'preoperative' oral cardohydrate treatment on insulin action—a randomized cross-over unblinded study in healthy subjects. *Clin Nutr* 2005; **24**: 815–21
10. Hausel J, Nygren J, Lagerkranser M *et al*. A carbohydrate-rich drink reduces preoperative discomfort in elective surgery patients. *Anesth Analg* 2001; **93**: 1344–50
11. Helminen H, Viitanen H, Sajanti J. Effect of preoperative intravenous carbohydrate loading on preoperative discomfort in elective surgery patients. *Eur J Anaesthesiol* 2009; **26**: 123–7
12. Crowe PJ, Dennison A, Royle GT. The effect of pre-operative glucose loading on postoperative nitrogen metabolism. *Br J Surg* 1984; **71**: 635–7
13. 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**: 32–7
14. Henriksen MG, Hessov I, Dela F, Vind Hansen H, 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**: 191–9
15. 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**: 317–27
16. Gustafsson UO, Hausel J, Thorell A, Ljungqvist O, Soop M, Nygren J. Adherence to the enhanced recovery after surgery protocol and outcomes after colorectal cancer surgery. *Arch Surg* **146**: 571–7
17. Awad S, Varadhan KK, Ljungqvist O, Lobo DN. A meta-analysis of randomised controlled trials on preoperative oral carbohydrate treatment in elective surgery. *Clin Nutr* 2013; **32**: 34–44
18. Smith MD, McCall J, Plank L, Herbison GP, Soop M, Nygren J. Preoperative carbohydrate treatment for enhancing recovery after elective surgery. *Cochrane Database Syst Rev* 2014; **8**:CD009161
19. Gustafsson UO, Nygren J, Thorell A *et al*. Pre-operative carbohydrate loading may be used in type 2 diabetes patients. *Acta Anaesthesiol Scand* 2008; **52**: 946–51