Preoperative Oral Carbohydrate Treatment to Prevent Perioperative Complications in Adults: A Systematic Review of the Evidence

by
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Thesis presented in partial fulfilment of the requirements for the degree Master of Nutrition in the Faculty of Medicine and Health Sciences at Stellenbosch University

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March 2017

DECLARATION

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ABSTRACT

Background: Preoperative standard fasting is associated with deleterious effects with consequent negative clinical outcomes. Preoperative oral carbohydrate loading (POCL) is considered a safe alternative to fasting, and recommended by numerous anaesthesia societies worldwide. The evidence supporting this intervention is increasing and pooling of data is required to promote clinical relevance.

Objectives: To systematically review the effect of POCL on perioperative complications and well-being in adult patients undergoing elective surgery.

Search strategy: Electronic databases, article reference lists and personal files were searched from inception up to May 2015.

Selection criteria: Randomised controlled trials (RCTs) of POCL compared with other preoperative regimens in adult patients undergoing elective surgery. The experimental group had to receive at least 45 g of carbohydrates with an osmolality of less than 300 mOsm/kg within three hours before surgery.

Data collection and analysis: Details of the eligible studies were extracted by the principal investigator and independent reviewer. Authors were contacted to obtain missing information. Methodological quality was assessed according to methodology described by The Cochrane Collaboration.

Results: Twenty four RCTs involving 1 903 participants were identified for inclusion. The majority of the trials were conducted in developed and emerging countries and were based on otherwise healthy adult participants who were not considered to be at increased risk of regurgitation or aspiration. The quality of the evidence was moderate to low, hence the high risk of bias. Due to the heterogeneity of trials and the small number of included trials per comparison, limited data could be pooled for inclusion in a meta-analysis. Twenty-three trials including 1 841 participants reported on the primary outcomes. The immune status (in terms of C-reactive protein levels) of patients receiving POCL was better preserved compared to those in the standard fasting group ($p = 0.006$). No significant evidence of effect for POCL was demonstrated for any other clinical outcomes. Adverse events in terms of regurgitation, aspiration, morbidity and mortality were either not reported to occur or were not investigated in the included trials. As reported by 16 trials involving 1449 participants, the well-being of patients receiving POCL was improved or at least maintained in most of the trials.

Conclusion: POCL is a safe alternative to standard fasting with no associated adverse events. There is not enough evidence to draw conclusions with absolute certainty on the clinical outcomes. However, there is a trend that POCL improves the well-being of surgical patients. Therefore, the potential benefits of POCL need to be balanced against the cost as well as patient preference. Emphasis should be on the type of surgery performed as well as the effect of minor versus major surgery on outcomes. Keep in mind that POCL is time (up to two hours before surgery), dose (at least 45 g carbohydrates) and patient (otherwise healthy elective surgery patients) specific. POCL should be perceived as a single element of enhanced recovery and the combination of different elements might produce more beneficial results than a single element by itself.

OPSOMMING

Agtergrond: Standaard vasperiodes voor chirurgie word gekenmerk deur nadelige effekte wat ’n negatiewe kliniese uitkoms veroorsaak. Preoperatiewe orale koolhidraat inname (POCL) is ’n veilige alternatief vir vas, en dit word wêreldwyd aanbeveel deur verskeie narkoseverenigings. Die literatuur wat hierdie intervensie ondersteun, is besig om toe te neem en die groepering van data is nodig om kliniese toepaslikheid te bevorder.

Doelwitte: Om sistematies die effek van POCL op perioperatiewe komplikasies en welstand in volwasse pasiënte wat elektiewe chirurgie ondergaan, te ondersoek.

Soekstrategie: Elektroniese databasisse, artikels se verwysingslyste en persoonlike dokumente tot en met Mei 2015 is bestudeer.

Seleksiekriteria: Ewekansig gekontrolleerde proewe van POCL in vergelyking met ander preoperatiewe praktyke in volwasse pasiënte wat elektiewe chirurgie ondergaan. Die eksperimentele groep moes ’n koolhidraatlading van minstens 45 g koolhidrate ontvang met ’n osmolaliteit van minder as 300 mOsm/kg binne drie ure voor die aanvang van chirurgie.

Dataversameling en –analise: Inligting van relevante studies is deur die hoof navorser en onafhanklike hersiener onttrek. Outeurs van artikels is gekontak om alle relevante inligting te bekom. Die metodologiese kwaliteit van studies is geassesseer soos voorgestel deur *The Cochrane Collaboration*.

Resultate: Vier-en-twintig ewekansig-gekontrolleerde proewe waarby 1 903 deelnemers betrokke was, is ingesluit. Die meeste proewe is uitgevoer in ontwikkelde lande en lande wat besig is om te ontwikkel, en is gebaseer op andersins gesonde volwasse deelnemers wat nie ’n verhoogde risiko vir regurgitasie en aspirasie getoon het nie. Die kwaliteit van die inligting was middelmatig tot laag, daarom die hoë risiko vir sydigheid. Weens die heterogene inligting in die proewe en die klein getal proewe per vergelyking wat ingesluit kon word, is daar beperkte inligting wat gegroepeer kon word vir insluiting in ’n meta-analise. Drie-en-twintig proewe met 1 841 deelnemers het verslag gedoen oor die primêre uitkomstes van hierdie oorsig. Die immuunstatus (in terme van CRP-vlakke) in pasiënte wat POCL ontvang het, was beter in vergelyking met die standaard vasgroep ($p = 0.006$). Geen beduidenheid is gevind vir die effek van POCL op enige ander kliniese uitkomste nie. Nadelige effekte in terme van regurgitasie, aspirasie, morbiditeit en mortaliteit is of nie aangedui of nie ondersoek by enige van die proewe nie. Soos aangedui deur 16 proewe, waarby 1 449 deelnemers betrokke was, was die welstand van die pasiënte wat POCL ontvang het, verbeter of ten minste onderhou in meeste van die proewe.

Gevolgtrekking: POCL is ’n veilige alternatief vir standaard vasperiodes deurdat dit geen addisionele nadelige effekte inhou nie. Daar is egter nie genoeg bewyse in hierdie oorsig om gevolgtrekkings met sekerheid te maak oor die kliniese uitkomstes nie. Ongeag daarvan is daar ’n neiging dat POCL die welstand van chirurgie-pasiënte verbeter. Dus moet die potensiële voordele van POCL gemeet word teen die koste van die intervensie sowel as die pasiënt se voorkeur. Daar moet aandag geplaas word op die tipe chirurgie wat uitgevoer word sowel as die effek van klein teenoor groot chirurgie op die uitkomstes. Hou in gedagte dat die effek van POCL is tyd- (tot twee ure voor chirurgie), dosis- (tenminste 45 g CHO) en pasiënt- (andersins gesonde, elektiewe chirurgie-pasiënte) spesifiek. POCL is ’n enkele element van spoedige herstel, en die kombinasie van verskillende elemente mag meer voordelige resultate lewer as ’n enkele element.

ACKNOWLEDGEMENTS

I would like to thank the following people who assisted me in the completion of this journey:

- Janicke Visser (principal supervisor) for awakening my enthusiasm in the profession by being a role model through your dedication to nutrition, science and education.
- Renee Blaauw (co-supervisor) for being an exceptional leader whose knowledge is a great inspiration and forms a fundamental part of my development in the field of clinical nutrition.
- Alfred Musekiwa (statistician) for his immense contribution in analysing the data for this review in a short period of time.
- Wilhelmine Pool (healthcare librarian) for her excellent assistance with the electronic searches and quick response in providing full text articles.
- Lauren Pietersen (reviewer) for her willingness to assist with the data extraction, and her continuous motivation during the review process.
- Lize Vorster (language editor) for her assistance in making this document reader friendly.
- And on a personal note: my family, friends and colleagues for their continued support and motivation. My best friend, Mathee Schreuder for encouraging me to achieve my goals and supporting me to finish this journey. My parents, Albri and Comine Kriel, for providing me with the basis to initiate this journey and constantly reminding me of the value of learning. My brother, Ryno Dippenaar, for his humorous support and being a rock to lean on.

CONTRIBUTION OF AUTHORS

The principal author**,** Janine Kriel, conceived the idea and designed the protocol of this review. The principal author also conducted the searches (with the assistance of the healthcare librarian, Wilhelmine Pool), screened and evaluated data for eligibility (with the assistance of an independent reviewer, Lauren Pietersen), captured the data for analyses, interpreted the data and drafted the thesis. Alfred Musekiwa, statistician trained in systematic reviews, analysed the data under supervision of the principal author. Janicke Visser and Renèe Blaauw provided guidance at all stages of the review process, and revised the protocol and thesis. Language editing of the thesis was undertaken by Lize Vorster.

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Bias:[1] Bias is a systematic error, or deviation from the truth. Bias can lead to underestimation or overestimation of the true intervention effect. Bias can vary in magnitude – some are small and trivial compared to the observed effect, and some are substantial to the point where an apparent finding may be entirely due to blinding. Bias and imprecision are different entities. Bias is a systematic error which leads to the wrong answer on average when the same study is multiplied several times. Imprecision is a random error, meaning that multiple replications of the same study will produce different effect estimates due to sample variation, even if they would give the right answer on average.

Blinding:[1] Blinding (or masking) is the process of preventing those involved in a trial from knowing to which comparison group a particular study participant belongs. Effective blinding can also ensure that the compared groups receive the same amount of attention, ancillary treatment and diagnostic interventions.

Chi-squared (Chi^2) test:[1] A statistical test based on comparison of a test statistic to a chi-squared distribution to test the statistical significance of the heterogeneity. It assesses whether observed differences in results are comparable with chance alone. A low p-value (or a large Chi-squared statistic relative to its degree of freedom) provides evidence of the heterogeneity of the intervention effects (variation in effect estimates beyond chance). Care must be taken in the interpretation of the Chi^2 test, since it has an insignificant effect on the situation of meta-analyses when studies have small sample size or are few in number. This means that while a statistical significant result may indicate a problem with heterogeneity, a non-significant result should not be taken as evidence of no heterogeneity. Therefore, the p-value of 0.10 rather than the conventional 0.05 is sometimes used to determine statistical significance.

Cluster-randomised trial:[1] A trial in which clusters of individuals (e.g. clinics, families, geographical areas), rather than individuals themselves, are randomised to different arms.

Co-intervention:[1] The application of additional diagnostic or therapeutic procedures to people receiving a particular programme of treatment.

Concealment of allocation:[1] Allocation concealment is the process used to ensure that the person deciding to enter a participant into a randomised controlled trial does not know the comparison group into which that individual will be allocated. This is distinct from blinding and is aimed at preventing selection bias.

Confidence interval (CI):[1] A measure of the uncertainty around the main finding of a statistical analysis. Study results are reported with a point estimate together with an associated CI. The CI describes the uncertainty inherent in the estimate and describes a range of values within which we can be reasonably sure that the true effect actually lies. If the CI range is relatively narrow, the effect size is known precisely. If the CI range is wider, the uncertainty is greater, although there may still be enough precision to make decisions about the utility of the intervention. If the CI range is very wide, it indicates that there is very little knowledge about the effect and that further information is needed. A 95% CI is often interpreted as indicating a range within which we can be 95% certain that the true effect lies. The stricter interpretation CI is based on the hypothetical notion of considering the results that would be obtained if the same study were to be repeated many times. If a study was repeated infinitely, and on each occasion a 95% CI calculated, then 95% of these intervals would contain the true effects.

Confounding:[1] A confounder is a factor that can significantly affect validity and leads to incorrect conclusions being drawn. Two characteristics are confounded if their influences on the intervention effect cannot be disentangled.

Continuous data:[1] Data with a potentially infinite numerical quantity that can take any value in a specified range (e.g. weight, height).

Cross-over trial:[1] A type of clinical trial comparing two or more interventions in which the participants, upon completion of the course of one treatment, are switched to another.

Dichotomous data:[1] Data of which the outcome is one of only two possible categorical responses (e.g. yes or no, present or absent).

Fixed-effect model:[1] A model that calculates a pooled effect estimate using the assumption that all observed variation between studies is caused by the play of chance. Studies are assumed to be measuring the same overall effect. An alternative model is the random-effects model.

Forest plot:[1] A graphical representation of the individual results of each study included in a meta-analysis together with the combined meta-analysis result. The plot also allows readers to see the heterogeneity among the results of the studies. The results of individual studies are shown as squares centred on each study's point estimate. The overall estimate from the meta-analysis and its confidence interval are shown at the bottom, represented as a diamond. The centre of the diamond represents the pooled point estimate, and its horizontal tips represent the confidence interval.

Funnel plot:[1] A funnel plot is a simple scatter plot of the intervention effect estimates from individual studies against some measure of each study's size of precision. The effect estimate is plotted on the horizontal line, and the measure of the study size on the vertical axis. The name

'funnel plot' plot arises from the fact that the precision of the estimated intervention effect increases as the size of the study increases. Effect estimates from small studies will scatter more widely at the bottom of the graph whereas the spread narrows among larger studies. In the absence of bias the plot should resemble a symmetrical (inverted) funnel.

Grey literature:[1] Material that is not published in easily accessible journals or databases.

Heterogeneity:[1] Used in a general sense to describe the variation in or diversity among studies included in a systematic review. Clinical heterogeneity refers to variability in the participants, interventions and/or outcomes. Methodological heterogeneity refers to variability in study design and risk of bias. Statistical heterogeneity is the variability in the intervention effects, and occurs when the observed intervention effects differ more from each other than expected from random error alone.

I^2:[1] A measure used to quantify heterogeneity. It describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance). A value greater than 50% may be considered to represent substantial heterogeneity.

Incomplete outcome data:[1] Any data that is missing from the study can lead to risk of bias. Missing outcome data can be due to attrition (participants lost to follow-up, treatment withdrawals or trial group changes) or exclusions from the analysis.

Intention-to-treat analysis (ITT):[1] A strategy for analysing data from a randomised controlled trial. All participants are included in the arm to which they were allocated, whether or not they received (or completed) the intervention given to that arm. Intention-to-treat analysis prevents bias caused by the loss of participants, which may disrupt the baseline equivalence established by randomisation and which may reflect non-adherence to the protocol. The term is often misused in trial publications when some participants were excluded.

Likert scale:[2] A psychometric scale commonly used in questionnaires that is widely used in survey research. Respondents specify their level of agreement or disagreement on a symmetric agree–disagree scale for a series of statements. The scale captures the intensity of feelings. For example, a five-point Likert scale could include "strongly disagree, disagree, neither disagree or agree, agree, and strongly agree".

Mean:[1] An average value, calculated by adding all the observations and dividing by the number of observations (also called arithmetic mean.)

Mean difference:[1] The mean difference is a standard statistic which measures the absolute difference between the mean value in two groups in a trial. It estimates the amount by which the experimental intervention changes the outcome on average compared with the control. It can be

used as a summary statistic in a meta-analysis when outcome measurements in all studies are made of the same scale.

Median:[1] The value of the observation that occurs half-way when the observations are ranked in order.

Meta-analysis:[1] The use of statistical techniques in a systematic review to integrate the results of included studies. It can be used to combine the numerical results of all or some of the studies included in a systematic review. This yields an overall statistic, together with its confidence interval, that summarises the effectiveness of the experimental intervention compared with the control intervention.

Methodological quality:[1] The extent to which the design and conduct of a study are likely to have prevented bias. Variation in quality can explain variation in the results of studies included in a systematic review. More rigorously designed (better quality) trials are more likely to yield results that are closer to the truth. (Also called methodological quality but better thought of as relating to bias prevention.)

Narrative review:[1] A review article in the medical literature that summarises a number of different studies and may draw conclusions about a particular intervention. Narrative review articles are not systematic. (Also called overviews.)

Odds ratio:[1] The ratio of the odds of an event in one group to the odds of an event in another group. In studies of treatment effect, the odds in the treatment group are usually divided by the odds in the control group. An odds ratio of one indicates no difference between comparison groups. For undesirable outcomes an odds ratio that is less than one indicates that the intervention was effective in reducing the risk of that outcome. When the risk is small, odds ratios are very similar to risk ratios.

PRISMA flow diagram:[1] Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA); is the evidence-based minimum set of items for reporting in systematic reviews and meta-analyses; it consists of a four-phase flow diagram that is useful for the critical appraisal of systematic reviews.

Quasi-random allocation:[1] Methods of allocating people to a trial that are not random, but were intended to produce similar groups when used to allocate participants. Quasi-random methods include: allocation by the person's date of birth, by the day of the week or month of the year, by a person's medical record number, or just allocating every alternate person. In practice, these methods of allocation are relatively easy to manipulate, introducing selection bias.

Random-effects Model:[1] A statistical model in which both within-study sampling error (variance) and between studies variation are included in the assessment of the uncertainty (confidence interval) of the results of a meta-analysis. See also fixed-effect model. When there is heterogeneity among the results of the included studies beyond chance, random-effects models will give wider confidence intervals than fixed-effect models.

Randomisation:[1] The process of randomly allocating participants into one of the arms of a controlled trial. There are two components to randomisation: the generation of a random sequence, and its implementation, ideally in a way so that those entering participants into a study are not aware of the sequence (concealment of allocation).

Randomised controlled trial:[1] An experiment in which two or more interventions, possibly including a control intervention or no intervention, are compared by being randomly allocated to participants.

RevMan (Review Manager):[1] Software developed for The Cochrane Collaboration to assist reviewers in preparing Cochrane Reviews and systematic reviews in general.

Risk ratio:[1] The ratio of risks in two groups. In intervention studies, it is the ratio of the risk in the intervention group to the risk in the control group. A risk ratio of one indicates no difference between comparison groups. For undesirable outcomes, a risk ratio that is less than one indicates that the intervention was effective in reducing the risk of that outcome. (Also called relative risk.)

Sensitivity analysis:[1] An analysis used to determine how sensitive the results of a study or systematic review are to changes in how it was done. Sensitivity analyses are used to assess how robust the results are to uncertain decisions or assumptions about the data and the methods that were used.

Standardised mean difference:[1] The difference between two estimated means divided by an estimate of the standard deviation. It is used to combine results from studies using different ways of measuring the same concept. By expressing the effects as a standardised value, the results can be combined since they have no units. Standardised mean differences are sometimes referred to as a d-index.

Sub-group analysis:[1] An analysis in which the intervention effect is evaluated in a defined subset of the participants in a trial, or in complementary subsets, such as by sex or in age categories.

Systematic review:[1] A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review. Statistical methods (meta-analysis) may or may not be used to analyse and summarise the results of the included studies.

Visual analogue scale (VAS):[3] Measurement instrument that tries to measure a characteristic or attitude that is believed to range across a continuum of values and cannot easily be directly measured. Operationally a VAS is usually a horizontal line, 100 mm in length, anchored by word descriptors at each end. The VAS score is determined by measuring in millimetres from the left hand end of the line to the point that the patient marks. As such a VAS assessment is subjective of nature; these scales are of most value when looking at change within individuals, and are of less value for comparing across a group of individuals at one time point. It could be argued that a VAS is trying to produce interval/ratio data out of subjective values that are at best ordinal.

Verbal descripive scale (VDS):[4] Measurement instrument that tries to measure a characteristic or attitude using a scale of descriptive words. Also called a verbal descriptor scale.

LIST OF ABBREVIATIONS

ASA score	American Society of Anesthesiologists physical status classification system
ASPEN	American Society of Parenteral and Enteral Nutrition
B.C.	Before Christ
CHO	carbohydrate
CRP	C-reactive protein
DIGAMI	diabetes insulin-glucose in acute myocardial infarction
EBM	evidence-based medicine
EBN	evidence-based nutrition
EIAS	ERAS Interactive Audit System
EIP	ERAS Implementation Programme
ERAS	Enhanced Recovery After Surgery
ESPEN	European Society of Parenteral and Enteral Nutrition
GRADE	grade of recommendation, assessment, development and evaluation
HEC	hyperinsulinaemic euglycaemic clamp
HOMA-IR	homeostatic model assessment – insulin resistance
ICU	intensive care unit
IV	intravenous
ITT	insulin tolerance test
MD	mean difference
MMC	migrating motor complex
n	number of study participants or trials
NICE-SUGAR	normoglycemia in intensive care evaluation – survival using glucose algorithm regulation
NPO	nil per os/nulla per os/non per os/nothing by mouth
NR	not reported
NS	non significant
ONS	oral nutritional supplement
p-value	level of significance
PCOL	preoperative oral carbohydrate loading
pH	figure expressing acidity and alkalinity
postop	postoperative
preop	preoperative
PRISMA	preferred reporting items for systematic reviews and meta-analysis
QUICKI	quantitative insulin sensitivity check index
RCT	randomised controlled trial
SD	standard deviation
STAI	state-trait anxiety inventory
VAS	visual analogue scale
VDS	visual descriptive scale
VISEP	volume substitution and insulin therapy in severe sepsis
↓	decrease
↑	increase

CHAPTER 1: LITERATURE REVIEW

1.1 INTRODUCTION

In the twenty-first century, elective surgery is one of the foremost treatments in modern medicine to treat medical disorders with over 312 million major surgical treatments performed globally each year.[5-7] Traditionally, surgery is performed in the overnight fasted state; meaning that millions of the population are unnecessarily starved preoperatively. *Nil per os, nulla per os* or *non per os* (NPO) is Latin for *nothing by mouth*, meaning that no intake of fluids or solids is allowed from midnight to the time of surgery.[8] Even though preoperative fasting is mandatory before anaesthesia, patients are often fasted in excess of eight to 16 hours from their last intake in the evening until the induction of anaesthesia the following day.[9,10] Fasting from midnight is one of the most well-known medical routines during the past century. The routine is simple to write, easy for nursing staff to follow, basic for patients to understand, and if a cancellation occurs there is no problem with operating another patient earlier than scheduled.[6] The routine was established by tradition and traditions are difficult to break. The dogma resulted from the extrapolation of pulmonary aspiration risk in full stomach emergency cases to healthy elective cases. It appears that the practice of prolonged fasting before anaesthesia is a fixed tradition that depends more on clinical experience than scientific evidence.[11,12]

Prolonged fasting before surgery has a number of deleterious consequences due to the trigger of the metabolic response causing increased insulin resistance, loss of lean body mass and amplifying the acute-phase response.[13] Surgery, with its deliberate insult to the body, also causes a change in metabolism to catabolism, including a rapid neuroendocrine response, setting off stress hormones and activation of cytokines and immune reactions.[14] Changing the metabolic rate from a fasted to a fed state before surgery has clinical benefit. As realised many years ago, certain elements can be influenced during the perioperative care of a patient that will have a beneficial effect on the outcomes.

The clinical goal for any patient receiving elective surgery is to recover to the preoperative function; i.e. return of bowel function, pain control, mobilisation, and no complications associated with early discharge.[15] Optimal glycaemic control is essential to reduce morbidity and mortality; however, glucose homeostasis is affected by different mechanisms during the perioperative period.[15,16,17] Improved glycaemic control by insulin treatment has reduced mortality and morbidity in surgery patients; [18,19] however, intensive insulin therapy is associated with difficulties such as medical inaccuracies causing significant hypoglycaemia with consequent death.[20,21] Therefore, the need arose to change practice to optimise glucose control and prevent complications during the perioperative period.

1.2 STANDARD FASTING

1.2.1 History behind standard fasting

The history of standard fasting dates back to 1847 when the first book on anaesthesia was published, which did not even mention fasting before surgery.[22] During the following century, there were conflicting results and interpretations with regards to fasting before anaesthesia. Before the 1960s, the consensus was that an absolute fast before anaesthesia was not necessary. However, from the 1960s, the universal adoption of standard fasting for healthy patients with no risk factors undergoing elective surgery appears to have begun. A clear distinction between the gastric emptying of solids and fluids were already made in 1833.[23] Some authors mentioned a light meal while others gave detailed descriptions of particular items of food they recommended: milk could be part of a light meal while clear fluids included tea, China tea, beef-tea and fruit juice. The guidelines applied to healthy patients undergoing elective procedures, except for gastrointestinal surgery where no solid food and occasionally no fluid was permitted on the day of surgery.[6] See Table 1.1 for a detailed description on the history of fasting.[23 – 46]

Table 1.1: The history behind fasting before surgery

Year	Findings with regards to fasting before anaesthesia
1833	The first distinction between the gastric emptying of liquids and solids dates back to William Beaumont, American military surgeon, who treated a hunter for an abdominal gunshot wound.[23-26] The wound left a permanent gastric fistula through which the emptying of gastric contents could be observed. Digestion of water and most other fluids were not affected by gastric juices and had a quick emptying time whereas easily digested solids (i.e. meat, potoatoes, bread) emptied within 5 hours.[23]
1848	The first reported death under anaesthesia was reported when a 15 year old girl Hannah Greener died with a full stomach after receiving a chloroform anaesthetic for the removal of a toenail.[27,28] The exact cause of her death is unknown since it could have been aspiration of gastric content (since her stomach was full) or the fluid to revive her (cold water followed by brandy), either by obstructive action or by stimulating laryngospasm.[29]
1853	During surgery for a gunshot wound to the thigh a soldier vomited, and the autopsy confirmed that the vomited matter appeared in the trachea. Even though the case happened in 1853 it was only reported in 1862 as a new cause of death under chloroform at a medical meeting in Edinburg.[30]
1883	Sir Joseph Lister, British surgeon, also emphasised the distinction of gastric emptying between liquids and solids. He published the following broad fasting guidelines: '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.[31]
1901	Hewitt stated that a meal can be consumed up to 4 hours before surgery but warned that milk must be avoided since it becomes a solid in the stomach.[32]
1914	Gwathmey emphasised that there is no reason to fast for extensive periods, and recommended a fast of 2 to 3 hours after the intake of thin porridge.[33]
1920	Buxton recommended that patients scheduled for morning surgery should be allowed to have a small cup of China tea up to 3 hours before induction while those scheduled for afternoon surgery should have a light breakfast consisting of tea, bread in milk and fish but no meat followed by tea up to 3 hours before induction.[34]
1946	Mendelson, New York obstetrician, reported 66 cases (out of 44016 pregnancies) of aspiration during general anaesthesia from over a decade.[35] He recommended that since gastric emptying is delayed during labour, pulmonary aspiration could be reduced by implementing fasting guidelines to ensure emptying of gastric contents before anaesthesia.
1947	In the first edition of *A Synopsis of Anaesthesia* clear fluids was not even mentioned. Lee recommended that apart from candies no food should be taken up to 6 hours before surgery.[36]
1951	Morton and Wylie, Association of Anaesthetists of Great Britain and Ireland, reported 43 fatalities due to

Year	Findings with regards to fasting before anaesthesia
	regurgitation or vomiting of gastric contents for the period 1950 to 1951.[37] Interesting to note is that the deaths occurred in high risk patients and patients with full stomachs, the anaesthetists were inexperienced and the total number of anaesthetics administered is not known.
1964	In the fifth edition of *A Synopsis of Anaesthesia* it is recommended that fluids and solids should be withheld for up to 6 hours before surgery. Lee contradicts himself by stating that it is a good idea to order nothing on the day of surgery, but stresses that unnecessary starvation and dehydration should be eluded.[38]
1970	Cohen and Dillon recommended that preoperative patients should receive a list of guidelines stating that they should not eat or drink anything from midnight of the day before surgery, and emphasising the extreme danger of receiving anaesthesia on a full stomach.[39] However, on the same list of preoperative instructions they recommend that children can receive sweetened fluids per os until 2 hours before anaesthesia.
1972	Wylie and Churchill-Davidson made a clear distinction between the rapid gastric emptying of clear liquids and the slower emptying of solids but went on and still recommended a 5 hour fast for both clear fluids and solids.[40]
1974	Roberts and Shirley made a statement that made the medical profession belief that otherwise healthy patients with no aspiration risk are also at high risk of aspiration before induction of anaesthesia. Preliminary work on Rhesus monkey indicated that individuals with 25 ml gastric content of pH < 2.5 is at high risk of aspiration.[41] The preliminary data on animals had extensive implications, and it was not until 1980 that they revealed that the monkeys did not regurgitate or vomited but acid was instilled directly into the bronchus with a syringe. From this it is evident that the investigators used the volume in the fasting stomach as a surrogate marker for the risk of aspiration, and did not take into account that the total volume in the stomach will not reach the lungs during aspiration. Now it is known that 0.8ml/kg gastric contents at pH 1.0 injected directly into the trachea of anaesthetized monkeys produced severe pneumonitis (equivalent to 50 ml in adult humans).[42] Interestingly, clinical data demonstrated that 40 – 80% of patients who fasted for at least 8 hours before surgery had more than 25 ml gastric contents in their stomach with a pH < 2.5. [43,44]
1977	Hester and Heath made the incidental finding that fasting for more than 4 hours did not have a clinical advantage on the gastric volume or pH of a patient before surgery.[45]
1983	Miller et al concluded that a light breakfast within the recommended 4 hours before surgery made no significant difference to volume or pH of gastric contents compared with a standard fast of no intake.[46] Therefore, if a 4 hour fast was safe for solids, it was likely that a shorter interval would be safe for fluids.

1.2.2 Physiology of Gastric Emptying

The gastric capacity of the adult stomach is approximately 1500 ml and can accommodate up to 1000 ml before intra-gastric pressure increases.[47] The stomach can be divided into two functional parts, i.e. the proximal and the distal part.[48] The proximal part consists of the fundus, cardia and the upper part of the corpus and acts as a reservoir for ingested food regulating the intra-gastric pressure and the speed of gastric emptying. The distal part of the stomach includes the lower part of the corpus, antrum and pylorus; the contractions of the distal part of the stomach mix the larger solid food particles with gastric fluid. One important factor that determines gastric emptying is the blood glucose level, which at physiological levels of ≥ 8 mmol/l slows gastric emptying.[49,50] Therefore, the blood glucose levels should always be maintained at physiological levels (fasting plasma glucose of 4.0 – 5.6 mmol/l and/or 2 hours post prandial value < 7.8 mmol/l) before other influences on gastric emptying are considered.[51,52,53]

There is a striking difference between the gastric emptying of solids and fluids from the stomach. Modern physiological gastric emptying studies use a dual isotope labelling technique in which solids and fluids are tagged with different radioactive isotopes.[54] Fluids empty in a mono-exponential phase whereas solids empty biphasically in a lag-phase as well as a linear emptying phase (Figure 1.1).[55] Ingested fluids are rapidly distributed throughout the entire stomach, and empty at an exponential rate that is primarily a function of the pressure gradient between the

stomach and duodenum, and the volume, caloric density, pH and osmolality of the gastric fluid. In otherwise healthy patients, gastric fluid content is not increased in the immediate preoperative period despite the theoretical negative impact of anxiety on gastric emptying.[56,57] Gastric emptying of water and non-caloric fluids follow an extremely fast exponential curve with a mean half-emptying time of 20 minutes.[58] Initially, caloric-containing fluids empty at a slower rate, but after 90 minutes this difference is negligible.[48,59] In contrast, the gastric emptying of solids shows a biphasic pattern. The lag phase starts after ingestion of a solid meal, a midgastric transverse band separates the proximal and distal parts of the stomach; this is suggested to represent a physiological division important for the intra-gastric distribution of solid contents. During this phase, solids are redistributed from the fundus and broken down to smaller particles (1–2 mm), which then can pass through the pylorus during the linear emptying phase.[60]

Gastric emptying of solid food starts approximately 60 minutes after a meal, and within 120 minutes approximately 50% of the solid food ingested is passed to the duodenum.[55] Gastric emptying for solids depends on the type and quantity of food and the size of the food particles. The pylorus prevents passage of particles > 2 mm in size, so digestible solids are first broken down to chyme, a particulate fluid. Indigestible solids, such as cellulose-containing vegetables, may not break down to < 2 mm particles and these larger particles empty by a different mechanism after the stomach has emptied liquids and digestible food (interdigestive myoelectric complex).[61,62] Caloric particles are delivered more slowly to the duodenum than non-caloric particles due to a negative feedback mechanism mediated by duodenal receptors – this ensures that a constant rate of nutrient delivery to the small intestine is maintained through the action of the small intestine peptide hormone cholecystokinin.[63] Another negative feedback system on upper intestinal motility has also been seen where the intestine-derived peptide hormones, glucagon-like peptide-I and peptide YY, exert this ‘ileal brake’ mechanism.[64] After the intake of food, the fed state reaches a maximum at approximately 30 minutes, and takes place all over the gastrointestinal tract and occurs for about four hours after a standard 600 kcal meal.[65]

After cessation of the fed state, a cyclic pattern of motor activity, secretion and blood flow migrates from the distal stomach towards the ileum.[66] This pattern is named the migrating motor complex (MMC). During the fasting state the MMC in the stomach mainly features periods of pressure waves that repeat at highly variable intervals but are usually recurrent every 80 to 120 minutes and are characterised by a frequency of three contractions per minute.[66] The MMC cycle is divided into three separate phases where phase I is characterised by inactivity, phase II by random irregular contractions, and phase III by continuous phasic contractions lasting for up to 5 minutes.

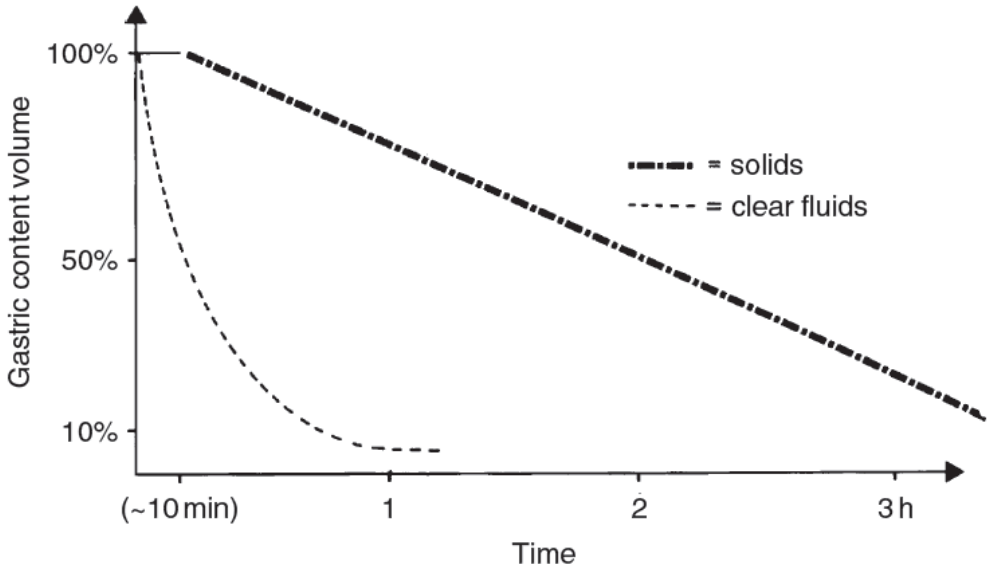


Figure 1.1: Gastric emptying of clear fluids and solids[55]

1.2.3 Risk for Aspiration

Pulmonary aspiration is defined as the entry of particles or liquid into the trachea-bronchial tree, as a consequence of passive regurgitation or active vomiting of gastric contents from patients without or attenuated laryngeal protection reflexes.[67] Aspiration is one of the most feared complications for anaesthesiologists – even though it is ranked at only the fifth-most common adverse events that can occur during anaesthesia.[68] The first death attributed to aspiration allegedly occurred in 475 BC, when the Greek poet Anacreon died from the inhalation of a grape seed.[69] Hippocrates realised the dangers of aspiration and in 400 BC, warned that "for drinking to provoke a silent cough, or for swallowing to be forced, is bad".[70] The investigation of aspiration dates from the 1700s when it was stated in a court of law that "it is in the mouth of everybody that a little brandy will kill a cat. I have made the experiment; in all those cases where it kills the cat, it kills the cat by getting into her lungs, not her stomach".[71] Mendelson was the first to adequately describe the aetiology of aspiration in 1946, and because of his pioneering report, aspiration has been referred to as Mendelson's syndrome.[35] A review published in 1966 highlighted that the aspiration of gastric content during anaesthesia is not a frequent event, but when it occurs it is catastrophic with a high mortality risk.[72] Fasting before anaesthesia is considered essential to patient safety in order to reduce the risk of regurgitation of gastric contents. During anaesthesia there is a reduction in the reflexes that function to protect the lungs. If regurgitation occurs with reflexes absent, then aspiration is likely to occur with the risk of the subsequent development of pulmonary complications.[73,74] The extent to which the reflexes are supressed depends on the level of anaesthesia.[74] This all is physiologically true, but according to evidence-based medicine, the occurrence of aspiration due to regurgitation under anaesthetics is infrequent.[6,8] The incidence of aspiration in elective surgery is one per 2000 to 3000 patients with a negligible morbidity and

mortality.[74-78] A 10-year review of morbidity attributable to anaesthesia in the general surgery population in South Africa found two deaths after regurgitation, vomiting and inhalation in 240 483 patients; one following a Caesarean section and one patient had an intestinal obstruction.[79]

The nature and amount of gastric aspirate will determine the type of injury and consequently, the clinical outcomes.[67] Large particles can obstruct the trachea and major or minor bronchi whereas smaller particles lodge in the segmental bronchi or bronchioles and may produce a foreign body reaction. Aspiration of solid particles is associated with a higher incidence of mortality compared with aspiration of liquids.[80] However, the aspiration of liquids during anaesthesia is more frequent than the aspiration of solids.[67] The severity of the aspiration depends on the chemical composition of the gastric aspirate. The volume and acidity of gastric content are a result of gastric secretions (approximately 0.6 ml/kg/h), swallowing of saliva (1 ml/kg/h), ingestion of solids and/or liquids, and the rate of gastric emptying.[81] The values of gastric volume and pH at which patients become at increased risk of aspiration are unclear. Arbitrarily critical values were set at a pH value of < 2.5 and a volume of > 0.4 ml/kg body weight or approximately 25 ml.[41] The accuracy of these values in humans has been questioned since this was based on unpublished data on animals.[42,82] Ethically, it is not possible to establish the precise values of gastric volume and pH that increase the risk of aspiration. Therefore, intraoperative gastric content parameters are used as surrogate outcome measures to evaluate the effect of different preoperative fasting regimes. For passive regurgitation and pulmonary aspiration to occur during anaesthesia, a certain gastric volume needs to be present. Studies indicated that more than 200 ml gastric fluid is needed for an adult patient to be at risk.[83] However, lower gastric aspirate volumes, in the range of 10 to 30 ml, are found in elective surgery patients not at risk of aspiration.[84-87] The extent of pulmonary damage increases proportionally as the acidity and volume increases with bile damaging the lungs more severely than gastric acid.[88,89]

There are three different complications as a result of pulmonary aspiration: acid-associated aspiration pneumonitis, bacterial infection associated aspiration pneumonia, or particle-associated aspiration (Table 1.2).[67] Damage to the lung parenchyma after aspiration has a biphasic pathogenesis: phase one is marked by a physiochemical process that is characterised by direct toxic damage to the respiratory epithelium from the acid, and as a consequence the lung compliance decreases and a discrepancy of ventilation and perfusion occurs; phase 2 (about two to three hours later) manifests as immigration and activation of neutrophil granulocytes, and presents as an acute inflammatory reaction.[90,91] Although there are similarities between aspiration pneumonitis and aspiration pneumonia, they are different clinical entities. Aspiration pneumonitis is the inhalation of sterile gastric contents while aspiration pneumonia is the inhalation of bacteria contaminated contents.[67] However, an acid-associated aspiration pneumonitis favours the secondary development of aspiration pneumonia by infection with bacteria due to the damaged respiratory epithelium.[92,93] Particle-associated aspiration is the consequence of the inhalation of

particulate matter, resulting in an acute obstruction causing sudden arterial hypoxemia and the development of atelectasis distal to the foreign content.[67]

Table 1.2: Pulmonary complications of aspiration[67]

Complications	Acid-associated aspiration (aspiration pneumonitis)	Bacterial infection associated aspiration (aspiration pneumonia)	Particle-associated Aspiration
Material Ingested	Aspiration of sterile acidic gastric contents	Aspiration of pathogenic bacterial contents	Aspiration of particulate matter
Pathophysiology	Acute lung injury	Acute pulmonary inflammatory response	Acute obstruction of smaller or larger airways with arterial hypoxemia and the development of atelectases
Clinical Presentation	Asymptomatically or symptoms ranging from a non-productive cough to tachypnoea, bronchospasm, productive cough, and respiratory distress a few hours after aspiration.	Tachypnoea, cough and signs of pneumonia.	Aspiration usually witnessed as acute choking and coughing that can be fatal.

There are several factors that have been identified to increase the risk for aspiration (Table 1.3).[67,76,80] Delayed gastric emptying is found in numerous situations and is the most profound reason for aspiration. Diabetes mellitus and increased blood glucose levels decrease gastric emptying – much more for solids than for fluids.[48] Several other diseases and symptoms, i.e. increased intracranial pressure, hiatus hernia, abdominal obstruction, recurrent regurgitation, and dyspepsia, are also known to decrease gastric emptying.[94] Pain, opioids and sedatives are well-known reasons for delayed gastric emptying.[77] Gastric emptying may also be delayed in patients who have previously undergone upper abdominal surgery.[80] There is a theoretical negative impact of anxiety on gastric emptying.[56,57] Gastric emptying is slower in males than in females.[81] Pregnant females seem to have a normal gastric emptying rate, except for the first trimester, where hormonal changes results in delayed gastric emptying.[95] However, when in labour gastric emptying will decrease and stay slow for almost 120 minutes after labour.[96] To what extent smoking affects gastric emptying is still controversial, but there seems to be good reason for avoiding smoking immediately before anaesthesia.[97,98] High doses of alcohol and recreational abuse of cannabinoids also inhibits gastric emptying.[99,100] Gastrointestinal stasis (tumour or obstruction) will definitely delay gastric emptying and increase the risk for aspiration. Even if the stomach is empty, vomitus may come from the small intestine.[80] Obesity does not delay gastric emptying (although intra-abdominal pressure is expected to be higher) but it is associated with other pathologies (i.e. hiatus hernia, diabetes mellitus) that increase the risk for aspiration.[77] Patients over 80 years have a tenfold increased risk in aspiration than the patients under 30 years.[75] Any factor decreasing the lower oesophageal sphincter pressure (i.e. peristalsis, vomiting, pregnancy and achalasia) will

increase the risk for aspiration. Surgery may be a risk for aspiration even if there is no other predisposing factor. Upper abdominal surgery can be considered a risk for aspiration since surgical manipulation may push gastric contents up into the mouth.[80] Patients receiving laparoscopic surgery may be at risk due to the head-down position.[80] Theoretically, a cholecystectomy may be a risk for aspiration since gastric secretion is increased and these patients may vomit bile.[88] However, the surgical group with the highest risk for aspiration are the patients receiving tracheostomies – probably because the airway is not protected during the change of cannule.[75] The lithotomy or head-down position may encourage regurgitation. Patients with difficult airways are prone to pulmonary aspiration, independent of their gastric content.[77] Anaesthetic gas that is insufflated into the stomach may increase the risk for regurgitation especially when high pulmonary inflation pressures are required.[80] The incidence of regurgitation increases as the duration of the surgery increases.[101] Removing an airway before a patient regains consciousness may evoke regurgitation and aspiration since both gastrointestinal motor responses (such as gagging or recurrent swallowing) and airway reflexes (such as gagging, hiccoughs or laryngospasm) return.[78] Inadequate anaesthesia may also evoke gastrointestinal motor responses and airway reflexes resulting in distension of the stomach, regurgitation and vomiting with increased risk for aspiration.[78] Any airway inserted in the oesophagus inlet will decrease the lower oesophageal sphincter tone and may increase the risk for regurgitation and aspiration.[102] Incorrect placement of an airway in the laryngeal inlet will trigger airway reflexes and increase risk for aspiration.[80] The choice of anaesthetic technique and airway management seems to be as important when it comes to reducing the change of pulmonary aspiration.[55] The ultimate aim of preoperative fasting is to reduce an event sequence, which begins with regurgitation and aspiration and may result in pulmonary damage causing pneumonia and even death.[74]

Table 1.3: Factors indicating an increased risk for aspiration[67,76,80]

Patient Factors	
Increased gastric content	• Delayed gastric emptying • Gastric hypersecretion • Drugs • Overfeeding • Lack of fasting • Males
Increased tendency to regurgitate	• Gastro-oesophageal reflux • Oesophageal obstruction • Hiatus hernia • Obesity • Pregnancy • Extreme age • Achalasia • Zenker's diverticulum • Diabetic autonomic neuropathy
Laryngeal incompetence	• Head injury • Cerebral infarction/haemorrhage • Neuromuscular disorders • Muscular dystrophies
Surgery Factors	
Procedure	• Upper abdominal surgery • Emergency surgery • Laparoscopic surgery • Night time surgery
Position	• Lithotomy
Anaesthesia Factors	
Airway	• Difficult intubation • Gas insufflation • Prehospital intubation
Maintenance	• Inadequate anaesthesia
Device	• Supraglottic airway

1.2.4 Modern Fasting Guidelines

The evidence for rigid fasting practices in elective surgery patients has been challenged and shown to be redundant for most study populations. The first randomised controlled trial evaluating drinking water versus standard fasting started in 1985, and concluded that the patients drinking water had significantly decreased gastric volumes and the pH was no different from the fasting group.[84] Between 1985 and 1993, several trials were conducted in different countries comparing the intake of water or clear fluids to standard fasting before induction of anaesthesia.[84,85,87,103-110] The trials had shortfalls and the ingested volumes varied between trials with some investigators allowing patients to decide how much fluid they want to drink preoperatively. However, a statistical significant reduction in gastric volume was found in the oral intake group [84,103,106] and there was no correlation between ingested volume or ingestion interval with gastric volume at induction of anaesthesia. The first review on the topic was published in 1995 and concluded that the intake of oral fluids until two hours before general anaesthesia is safe.[86] A Cochrane Review on the same topic concluded that allowing patients to drink water preoperatively results in significantly lower gastric volumes, and there is no evidence to suggest that a shortened fluid fast results in an

increased risk for regurgitation, aspiration or related morbidity when compared with standard fasting.[74] An editorial in The British Journal of Anaesthesia in 1993 recommended that the NPO after midnight should be abandoned and that clear fluids should be allowed until three hours before surgery.[112] In 1994, the Norwegian Society of Anaesthesiologists implemented evidence-based fasting guidelines recommending clear fluids until two hours before induction of anaesthesia.[113] The American Society of Anesthesiologists published their guidelines in 1999, also recommending the intake of clear fluids.[114] The liberal fasting guidelines are based on the following:[8]

- aspiration is not common in modern medicine (since regurgitation is not always associated with aspiration),
- prolonged fasting can be associated with adverse events,
- there is no significant relationship between fasting duration and gastric content,
- fluids and solids pass differently through the stomach.

Many anaesthesia societies followed suite and changed their guidelines to the intake of clear fluids such as water, tea, coffee and light apple juice up until 2 to 3 hours before anaesthesia.[55,115-118] However, such fluids contain only limited amounts of energy and cannot be expected to cause any major changes in the metabolism.[5,73] Therefore, the patient will undergo surgery in a metabolic fasted state. Literature shows that this may not be the ideal metabolic state before surgical stress, and that carbohydrate (CHO) feeding shortly before the surgery may be a better way to prepare for the stress of elective surgery.[5] A review published in 2011 on the role of CHO beverages in preoperative nutrition for elective colorectal surgery, concluded that the use of these beverages is both safe and effective, and that there is no increased risk for regurgitation and aspiration.[119] Another review published in 2012 that focused on POCL for elective surgery confirmed no aspiration was observed in any of the included trials.[120] A meta-analysis of 21 trials on POCL in elective surgery published in 2013 reported that there were no reported pulmonary complications in the group consuming oral CHO beverages.[121] Furthermore, a review on the role of POCL published in 2014 confirmed that the administration of an oral CHO beverage before surgery is safe since the volume and pH of gastric contents were nearly identical between a standard fast and a two-hour fast, the clear fluids emptied within 90 minutes; and therefore concluded that there is no increased risk for aspiration in patients who received a CHO beverage before surgery.[16] This is in line with a Cochrane Review published in 2014 showing that POCL does not increase postoperative complications.[122] The modern fasting guidelines from various international societies are presented in Table 1.4.[55,123-126]

Table 1.4: International recommendation for intake of clear fluids

Society	Duration for fluid fast	Type of fluid	CHO fluid	Volume of fluid
American Society of Anaesthesiology (2011)[123]	2 hours	Clear fluids (including, but not limited to water fruit juices without pulp, carbonated beverages, clear tea, black coffee)	No comment	Volume is less important than the type of liquid
Canadian Anaesthetists' Society (2015)[124]	2 hours	Clear fluids	No comment	No comment
European Society of Anaesthesiology (2011)[125]	2 hours	Clear fluids (including water, pulp-free juice, tea or coffee without milk)	Consider the use of oral carbohydrate drinks	No comment
Scandinavian Society of Anaesthesiology and Intensive Care Medicine (2005)[55]	2 hours	Clear fluids (non-particulate fluids without fat, for example, water, clear fruit juice, tea or coffee)	Include the pre-operative carbohydrate drink intended for pre-operative nutrition (Preop® Nutricia)	No comment
South African Society of Anaesthesiologist (2010)[126]	2 hours	Clear fluids (fluid which is non-particulate and through which newsprint is visible)	No comment	No comment

**CHO = carbohydrate*

Milk and milk-containing drinks should be treated as solids since it is believed that milk in large volumes acts like a solid due to curdling in the stomach – unfortunately this belief is mostly based on animal studies and there is uncertainty around the safe amount that can be consumed without delaying gastric emptying.[123,125] All the above-mentioned societies recommend a minimum fast of six hours for a light meal (typically consisting of toast and clear fluids).[55,123-126] Meals that include fatty food and meat may prolong gastric emptying time and additional fasting time of more than eight hours may be needed.[123] Chewing gum, sucking a boiled sweet or smoking immediately before anaesthesia should be discouraged due to the effect on gastric emptying, but should not be a reason to cancel or delay surgery.[125]

Studies of preoperative fasting have not evaluated high risk anaesthetic patients adequately to provide definite evidence on whether or not they can adhere to the two-hour cutoff for clear fluids. There is controversy in patients with obesity, gastro-oesophageal reflux, diabetes mellitus and pregnant women not in labour due to the unknown effect of POCL on the effect of glycaemia and gastric emptying.[125] The timing of emergency surgery should balance the risk of delaying surgery versus risk of aspiration of gastric contents.[6] Fasting in non-elective obstetric patients is a bit more complex since surgery during labour is usually an emergency and can range from minimal to life saving surgery. Logic dictates that women in labour should be fasted – however, literature shows that maternal death due to aspiration is extremely rare and women in labour should be allowed to drink clear fluids as desired.[125] Solid food should be discouraged during labour since it confers no benefit to obstetric outcomes. Preoperative fasting in elective obstetric patients is the same as for healthy patients: clear fluids can be consumed until two hours before surgery.[125]

There is consensus that the prophylactic use of prokinetic agents (e.g. metoclopramide, cisapride), H2-receptor antagonists (cimetidine, ranitidine, famotidine), proton pump inhibitors (omeprazole, lansoprazole), antacids (sodium citrate, sodium bicarbonate, magnesium trisilicate), antiemetics (droperidol, ondansetron) and anticholinergics (atropine, scopolamine, glycopyrolyte) in patients who are not at risk of aspiration is not recommended since there is insufficient evidence of clinical benefit.[123,125] Therefore, the routine use of preoperative multiple agents in patients who have no increased risk for aspiration is also not recommended.[123]

1.3 CARBOHYDRATE METABOLISM

1.3.1 Physiology of carbohydrate metabolism

Dietary CHO provide 50 to 55% of our total energy on a daily basis.[127] CHO are digested to glucose by the action of amylases and isoamylases in the gut and disaccharides in the enterocytes, and absorbed in the portal circulation. The glucose pool is located primarily in the plasma which contains glucose for freely available energy.[127,128] Plasma glucose concentration is the most closely regulated nutrient pool since glucose is the only fuel that the brain can metabolise (except in starvation).[128] Metabolism gives priority to the brain that if the glucose pool decreases below a certain concentration only the brain has access to glucose to ensure sufficient energy

supply.[128] If the plasma glucose concentration is within the normal range, most tissue uses glucose as their primary source of energy. Additional glucose is synthesised to glycogen (glycogenesis); however, glycogen stores are limited and additional excess glucose will be converted to fat (lipogenesis). If the plasma glucose concentration decreases, the body will metabolise glycogen back to glucose (glycogenolysis) or glucose can also be synthesised from an amino acid precursor (gluconeogenesis). If plasma glucose concentration increases and the renal threshold for glucose reabsorption is exceeded, excess glucose will be excreted into the urine (glucosuria). Figure 1.2 provides an overview of carbohydrate metabolism.[128]

Figure 1.2: Physiology of glucose metabolism[128]

The glucose metabolism is primarily regulated by the endocrine system with the ratio of insulin to glucagon regulating the hour-to-hour metabolism.[127,128] Insulin and glucagon act as antagonists to keep plasma glucose concentrations within the normal range. Both insulin and glucagon have short half-lives, and must therefore be continuously secreted to have a constant effect. Insulin promotes anabolism with the target cell response being increased glucose metabolism.

Tissues can be classified as insulin-sensitive or insulin-insensitive.[127] Insulin-sensitive tissues, like adipose tissue and skeletal muscle, use insulin to promote glucose uptake by stimulating the translocation of GLUT-4 transporters to the plasma membrane; these tissue use glucose during meals, and fat between meals for energy. Insulin-insensitive tissues, like the brain and epithelia of the kidney and gastrointestinal tract, are not dependent on insulin for glucose uptake; glucose transport and oxidation remains constant during the day due to specific GLUT-1 and GLUT-3 transporters as well as a specific enzyme named hexokinase. Interestingly, the brain uses about 1 mg/kg/min glucose throughout the day (about 1.5 g/kg/day).[127]

Glucagon is antagonistic to insulin with the goal to prevent hypoglycaemia.[128] The primary stimulus for glucagon release is plasma glucose concentration - when plasma glucose concentrations drop after a meal and fall below 5.6 mmol/l, glucagon secretion increases dramatically; when plasma glucose concentration increases above 5.6 mmol/l, insulin secretion increases and glucagon secretion is inhibited and stays at a constant low level.[128] The ratio of insulin to glucagon determines the direction of metabolism rather than the absolute amount of hormones.[128] During a fasted state, 75% of glucose comes from glycogenolysis and 25% from gluconeogenesis. Plasma glucose concentration is maintained during fasting at 4.4 – 6.7 mmol/l.[127] See Table 1.5 for a comparison of insulin and glucagon as potent regulators of a glucose metabolism.[128]

Table 1.5: Insulin and glucagon as regulators of glucose metabolism[128]

Hormone	Insulin	Glucagon
Classification	Anabolic hormone	Catabolic hormone
Secreted by pancreatic islets	Beta-cells	Alpha-cells
Primary goal	↓ plasma glucose concentration	↑ plasma glucose concentration
Primary stimulus	hyperglycaemia	hypoglycaemia
Metabolic state dominant	Fed state	Fasted state
Target tissue	Liver Adipose tissue Skeletal muscle	Liver
Metabolic action	↑ glucose synthesis ↑ protein synthesis ↑ fat synthesis	↑ glycogenolysis ↑ gluconeogenesis ↑ ketogenesis

Anabolic hormones (i.e. insulin) remain relatively low between meals to regulate hepatic glucose production while catabolic hormones (i.e. glucagon, adrenaline, cortisol and growth hormone)

increase between meals or during stress to decrease glucose uptake in insulin-sensitive tissues and hepatic glucose production is stimulated. Therefore, glucose production is regulated by the balance between anabolic and catabolic hormones. See table 1.6 for the effect of different hormones on glucose metabolism.[127]

Table 1.6: Effect of hormones on glucose metabolism[127]

Glucose Metabolism	Insulin (anabolic)	Glucagon (catabolic)	Adrenaline (catabolic)	Cortisol (catabolic)	Growth Hormone (catabolic)
Glucose uptake (in insulin sensitive tissues)	↑↑	↓↓	↓	↓	↓
Glycogenesis	↑	↓	↓	↑	↓
Glucose Oxidation	↑	↓	↓	↓	↓
Glycogenolysis	↓↓	↑↑	↑↑		
Gluconeogenesis	↓	↑	↑	↑↑	↑

1.3.2 Effect of fasting on carbohydrate metabolism

Food intake is an intermittent process while energy expenditure is a continuous process. Glucose stores in the body are limited to approximately 500 to 800 g and are rapidly exhausted.[127,129] The energy value of one gram of glucose is approximately 4 kcal, one gram of protein also yields about 4 kcal while one gram of muscle has an energy value of 1 kcal (due to being 75% water), and one gram of pure triglycerides yields 9 kcal.[129] Reaction to fasting is dependent on energy reserves, duration of fasting and any additional stressful influences. The metabolism can be divided into the fed and fasted states, and the fasted state can be divided into short-term (less than 72 hours) and long-term (more than 72 hours) fasting.[129]

The fed state (absorptive state or anabolic state) is the period after a meal when the products of digestion are being absorbed, utilised and stored; the fasted state (postabsorptive state or catabolic state) is the period where the nutrients of the meal are no longer in the bloodstream and as time passes, reserves will be utilised.[128] The fed state is recognised by increased insulin and decreased glucagon while the fasted state is recognised by decreased insulin and increased glucagon.[129] The change in plasma glucose concentration is the signal for the body to change from the fed to the fasted state. The challenge of the fasted state is to keep the plasma glucose concentration within the physiological range so that the brain and the rest of the body have adequate energy.[128] During the fasted state, the liver glycogen is the primary source of glucose production, and can provide enough glucose through glycogenolysis to meet 12 to 24 hours' energy needs. Skeletal muscle glycogen cannot be metabolised to glucose through direct conversion since muscle cells lack the enzyme that makes glucose from glucose-6-phosphate.

Therefore, glucose-6-phospate is metabolised to pyruvate (aerobic conditions) or lactate (anaerobic conditions), and transported to the liver to make glucose.[128]

During the fasted state, glucose needs are initially met by glycogenolysis but later from gluconeogenesis. Additional glucose can be made from amino acids, particularly those in muscles. Enzymes remove the amino groups from the amino acids by deamination, and convert the amino group to urea, which is excreted, leading to a loss of up to 75 g protein per day (300 g of muscle).[128,129] Some deaminated amino acids act as an intermediate to produce energy while other amino acids are converted to pyruvate, which is transported to the liver and made into glucose.[128] During the fasted state, adipose tissue breaks down its stores of triglycerides into glycerol and fatty acids by lipolysis.[129] Glycerol goes to the liver where it is converted to glucose while fatty acids are released into the plasma where they are used as a source of energy for many tissues. If there is excess fatty acid breakdown, β-oxidation creates ketones, which are transported from the liver to the nervous system and muscle for energy. Besides glucose, ketones are the only source of energy that the brain can use. Therefore, ketones become a significant source of energy during prolonged starvation. The adaption of the brain to use ketones instead of glucose leads to a two-third reduction in gluconeogenesis (saving 25 g of protein equivalent to 100 g of muscle per day).[129] Unfortunately, ketones are moderately strong acids and excessive production leads to an acidosis state (known as ketoacidosis).[128] During short term fasting, the metabolic rate increases initially but begins to decrease after two days.[129] Table 1.7 gives a summary of the effect of the fed versus the fasted states on the metabolism.[129]

Table 1.7: Effect of the fed versus fasted state on metabolism[129]

	Fed State	Fasted State	
		Short Term Fasting	Long Term Fasting
Metabolism	↑ Glycogenesis	↑↑ Glycogenolysis	Depleted glycogen stores
	↑ Glucose oxidation	Glucose oxidation	↓↓ Glucose oxidation
	↓ Lipolysis	↑ Lipolysis	↑↑↑ Lipolysis
	↓ Lipid oxidation	Ketogenesis in liver	↑↑↑ Ketogenesis in liver
	↑ Protein synthesis	↑↑↑ Protein catabolism	↑ Protein catabolism
	↑↑ Energy expenditure	↑ Energy expenditure	↓ Energy expenditure

1.3.3 Effect of surgery on carbohydrate metabolism

The stress response is the name given to the hormonal and metabolic changes that follow injury or trauma.[130] Elective surgery is a treatment that deliberately causes an injury to the body to repair organs or remove disease.[15] The metabolic effect from surgery is characterised by a state of hypermetabolism.[17] Surgical trauma induces a catabolic response by the release of stress hormones and inflammatory mediators with a compensatory increase in insulin release and a

reduction in the effects of insulin resulting in insulin resistance with hyperglycaemia.[12,17] A state of metabolism resembling non-insulin dependent diabetes mellitus develops when glucose production is increased and there is a reduction in glucose uptake in the periphery (see Table 1.8 for the metabolic similarities between postoperative patients and patients with diabetes mellitus type 2).[15]

Insulin resistance occurs within hours after the initiation of surgery, with a definite insulin resistance after surgery.[17] Postoperative insulin resistance, which peaks on the first postoperative day, progresses after surgery in a dose-dependent mode directly related to the extent of the surgical procedure and may persist for up to three weeks after major abdominal surgery.[131-133] Several factors have an effect on insulin resistance after surgery: surgical technique, pain control, postoperative muscle activity, and the duration of preoperative fasting.[134-138] The surgical technique used makes a difference since laparoscopic techniques cause minimal insulin resistance, while the same procedure done using open techniques results in a rise in insulin resistance.[132] Interestingly, insulin resistance may start before surgery due to prolonged fasting and exacerbate the metabolic response to stress.[13] Postoperative insulin resistance occurs mainly in the periphery while the splanchnic tissue play an insignificant role.[117] Fasting-induced insulin resistance is caused by impaired GLUT-4 translocation from the microsomal membrane to the plasma membrane in skeletal muscle, blocking glucose uptake into the muscle and thereby not encouraging insulin release.[118] Insulin resistance causes less effective glucose transport into muscle cells as well as less glycogen storing, and loss of protein from muscle causing loss of lean body mass. Therefore, there will be less energy and less structural protein, resulting in lower muscle function and less mobilising capacity. Insulin resistance is a significant element for outcomes in surgical trauma due to the development of complications.[139] Insulin resistance following surgery is an independent element forecasting the length of stay in the hospital.[132]

Table 1.8: Metabolism in postoperative patients versus patients with diabetes mellitus[15]

Metabolism	Postoperative	Diabetes Mellitus Type 2
Hyperglycaemia	↑↑	↑↑
Insulin sensitivity	↓	↓↓
Glucose production	↑	↑↑
Peripheral glucose uptake	↓↓	↓↓
GLUT-4 translocation	↓	↓
Glycogen formation	↓	↓

Stress starvation occurs when an individual is not only starved but subjected to the metabolic response of stress.[129] During this situation, normal adaptive responses of simple starvation to conserve body protein are overruled by the effects of injury. The metabolic rate increases, ketosis is minimal, and protein metabolism increases to meet the demands of tissue repair and gluconeogenesis – therefore, this state is recognised by hyperglycaemia and glucose

intolerance.[129] The metabolic goal during a stress response is to supply suitable substrates for tissues to meet energy requirements.[140] Stress initiates a strong increase in endogenous glucose production and turnover – up to 150% above normal levels. Glucose is a vital substrate since glycolysis does not require oxygen to produce energy. Therefore, it can be utilised in hypoxic and inflammatory tissues and in healing wounds where mitochondria are not developed or where capillaries are absent and fat cannot reach the cells. Glycogen can only supply glucose for 12 to 24 hours during the normal fasting state, and stores are exhausted in less time during a stress response. Therefore, new glucose is formed from amino acids and lactate during gluconeogenesis. This production cannot be fully suppressed by exogenous glucose or by insulin like during the fasted state – suggesting that gluconeogenesis is an obligatory process initiated by catabolic hormones and cytokines. Glucose is also formed from glycerol, released from adipose tissue during lipolysis. Amino acids are predominantly derived from muscle and are, together with glycerol, the main substrates for glucose production in the liver. The degree of protein catabolism during a stress response is large – reaching 260 g per day (corresponding to more than 1 kg of muscle). Amino acids released from muscles are also used for the synthesis of acute phase proteins. Net muscle protein gain can only be established during the anabolic phase of disease, provided adequate nutrition is administered, and protein turnover decreases. The oxidation of fat supplies almost 90% of the energy necessary for increased gluconeogenesis. Although an increased rate of lipolysis is part of the metabolic response to stress, the fatty acid release can exceed energy requirements. The excess fatty acids are re-esterified to triglycerides causing fatty infiltration of the liver and muscle tissues (especially when the high doses of glucose are administered continuously exceeding the glucose oxidation rate of 4 to 5 mg/kg/min). High insulin levels during the stress response cause ketogenesis to be stimulated to a lesser degree than during the fasting state alone. The stress response is essential for survival in the short term but it can be destructive when extreme or sustained (see Table 1.9 for the fed versus fasted state versus stress response on metabolism).[140]

Table 1.9: Fed versus fasted state versus stress response on metabolism[140]

Metabolism	Fed State	Fasted State	Stress Response
Gluconeogenesis	↓	↑	↑↑↑
Glycolysis	↑	↓	↑↑↑
Glucose oxidation	↑↑↑	↓	↓
Glucose cycling	↑	↓	↑↑↑
Proteolysis	↓	↓	↑↑↑
Protein synthesis	↑	↓	↑↑
Amino acid oxidation	↑	↓	↑↑↑
Lipolysis	↓↓	↑↑↑	↑↑
Lipid oxidation	↓	↑↑↑	↑
Ketogenesis	↓↓	↑↑↑	↑
Fatty acids	-	↓	↑↑

Insulin resistance is a state in which there is decreased responsiveness of skeletal muscle, adipose tissue and the liver to biological actions of insulin. The development of postoperative insulin resistance is associated with prolonged hospital stay, greater postoperative morbidity and mortality.[141] Most of the common complications developing during surgery are similar to those observed in diabetes mellitus type 2.[15] However, the complications develop within days of surgery whereas in diabetes mellitus they develop after a longer period. Interestingly, some of the cells involved in these complications are not dependent directly on insulin for their glucose uptake. Examples include immune cells involved in infection, neural cells for neuropathies, and endothelial cells for cardiovascular complications. These cells have no glucose storage capacity, so glycolysis is the only pathway for glucose once inside the cell. When there is an excess inflow of glucose into these cells they eventually start producing oxygen free radicals, consequently changing the gene expression in numerous cells causing further enhancement of inflammation, which results in further insulin resistance in an already vicious cycle.[142]

1.3.4 Glucose control

Depending on the definition of hyperglycaemia, the prevalence of hyperglycaemia can be as high as 97.5% when hyperglycaemia is defined as a blood glucose level above 6.1 mmol/l in tight glucose control settings.[19] Hyperglycaemia is common in critically ill patients – almost 60% of critically ill patients have increased glucose levels with just more than 20% of this population diagnosed with diabetes mellitus.[143] Although a number of metabolic interactions result in stress hyperglycaemia, such as neurohormonal alterations with cytokine release, the primary mechanisms behind stress hyperglycaemia are insulin resistance and gluconeogenesis.[144] Glucose control should be maintained at normal levels while feeding the severely stressed surgical patient since it is essential to reduce morbidity and mortality.[16,17,145] Metabolic changes during surgery can be reversed by the use of exogenous insulin.[146]

The first study on glucose control in critically ill patients was only published in 1995 since medical personnel did not feel that glucose control was important in the management of this population.[147] Hyperglycaemia was considered an adaptive response to critical illness and not treated until glucose levels exceeded the renal threshold of 12 mmol/l.[148] The Diabetes Insulin-Glucose in Acute Myocardial Infarction (DIGAMI) study was one of the first studies on tight glucose control, and mortality was reduced by 26% in one year.[149] However, the outcome was questioned since it was unclear whether tight glucose control or improved diabetes management after discharge lead to the decreased mortality. The DIGAMI 2 study found no effect on morbidity or mortality after two years of follow up, probably due to an inability to achieve tight glucose control.[150] The landmark Leuvin 1 study showed that patients in a surgical intensive care unit (ICU) benefited from intensive insulin treatment to normalise glucose levels at 4.5–6.0 mmol/dL.[18] In this study, patients were fed and showed that insulin action seems not only to be a key to successful immediate postoperative feeding but also to avoid further catabolic complications. A range of complications were lowered including infections, renal failure, polyneuropathy, and the need for ventilation. However, when the same authors applied the same protocol to medical ICU patients in the Leuvin 2 study, the results were different with mortality in the medical ICU population much smaller (6%) than in the surgical ICU population (42%).[151] From these two studies it seems that the beneficial effect of tight glucose control is more pronounced in severely ill surgical patients requiring prolonged ICU care. The Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) study applied the same protocol to septic patients and achieved lower blood glucose levels with no decrease in mortality.[152] Unfortunately, the VISEP study was stopped due to high rates of hypoglycaemia. The Normoglycemia in Intesive Care Evaluation – Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study showed that morbidity and mortality were increased when using an intensive insulin protocol maintaining glucose levels at 4.5 – 5.6 mmol/l versus physiologic levels below 10 mmol/l in a medical ICU with a heterogeneous group of patients that are severely stressed.[20] Despite the numerous methodological differences, the difference between results in various trials of glucose control can be attributed to the fact that in surgical patients, controlling plasma glucose concentrations by treating insulin resistance is beneficial in the sense that it avoids the development of complications, whereas in severely stressed septic medical patient, insulin is used to treat insulin resistance with the complications already present.[15] There is no definite blood glucose control target: although hyperglycaemia is associated with adverse events; the greatest risk of tight glucose control is hypoglycaemia. Table 1.10 indicates different blood glucose targets as proposed by various authors.[151,153-157]

Table 1.10: Target blood glucose recommendations

Study	Recommendation	Study Population
Van den Berge et al, 2001[18]	4.5 – 6.0 mmol/l	Surgical critically ill patients
Preiser et al, 2007[153]	7.7 – 9.9 mmol/l	Medical and surgical critically ill patients
Merz and Finfer, 2008[154]	7.7 – 9.9 mmol/l	Medical and surgical critically ill patients
Reider et al, 2009[155]	7.7 – 9.9 mmol/l	Heterogeneous group of critically ill patients
	6.1 – 7.7 mmol/l	Surgical critically ill patients
ASPEN, 2016[156]	7.77 – 9.99 mmol/l	General critically ill patients
NICE-SUGAR, 2009[20]	< 10 mmol/l	Medical and surgical critically ill patients
ADA, 2010[157]	7.7 – 9.9 mmol/l	Heterogeneous group of patient

**ASPEN = American Society of Parenteral and Enteral Nutrition; NICE-SUGAR = Normoglycemia in Intesive Care Evaluation – Survival Using Glucose Algorithm Regulation; ADA = American Dietetic Association*

Hyperglycaemia results in a number of undesirable physiological consequences that lead to poor clinical outcomes in the critically ill population (Figure 1.3).[144] These complications are the results of the vicious inflammation cycle, increased oxidative stress and altered nutrient utilisation. Hyperglycaemia increases the inflammatory state by increasing transcription of proinflammatory cytokines.[158,159] Increased oxidation stress is due to increased reactive oxygen species and depleted glutathione.[158,160] Hyperglycaemia and the consequent increase in inflammatory markers and oxidative species results in increased infectious complications due to decreased phagocytosis and glycosylation of immune globulins. Altered nutrient utilisation during hyperglycaemia causes a state of hypermetabolism, which can negate the efforts to improve or maintain nutritional status during the perioperative period.[144]

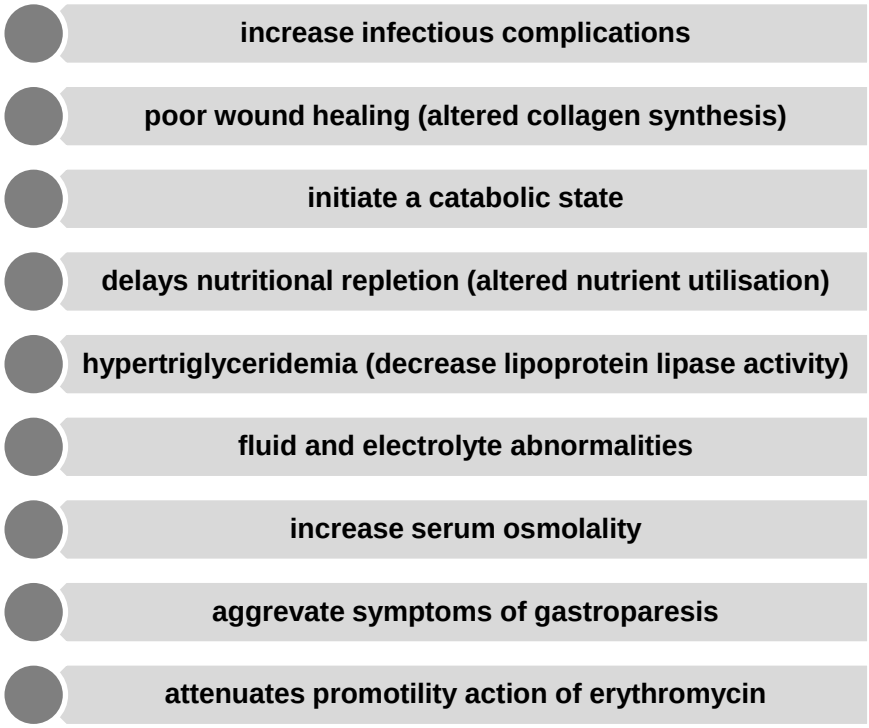


Figure 1.3: Physiological effects of hyperglycaemia

Although there is limited evidence, nutrition support plays an integral part in glucose control. There are no large multicentre randomised controlled trials of different nutrition parameters on glucose control. Recommendations for nutrition support practice are extracted from limited trials and tempered with feedback from clinical experience. Strategies for improving glucose control include:

- avoiding prolonged fasting before surgery,
- providing preoperative CHO beverages,
- avoiding overfeeding,
- ensuring continuous enteral feeding,
- providing a mixed fuel source for parenteral nutrition,
- considering hypocaloric feeding for obese patients,
- providing hypocaloric feeding initially for patients in the acute phase response or those at increased risk of hyperglycaemia,
- using of insulin to maintain glucose control is likely to be a better approach when compared to CHO restriction that causes starvation.[144,145]

1.4 CARBOHYDRATE LOADING CONCEPT

1.4.1 Route of carbohydrate loading

Traditionally, in the morning after waking up, most people have a breakfast consisting of a mixed meal, which causes insulin release and change in the metabolism from the fasted to the fed state. The most obvious way to change the metabolism from the fasted to the fed state is to give a CHO

load. The hypothesis of being in the fed and not the fasted state at the onset of surgery was first verified using an overnight intravenous (IV) infusion of glucose to achieve an endogenous insulin response.[161] The insulin response to glucose infusion is dose dependent and it was necessary to give a very high dose (5 mg/kg/min) and concentration (20%) of glucose infusion so that the quantity of glucose given was about 300 g in 1500 ml. A high dose of glucose infusion increases endogenous insulin release to serum insulin levels seen after the consumption of a standard mixed meal (60–70 µU/ml) and consequently, the patient enters the theatre in a state of normoglycaemia and hyperinsulinaemia, representing a fed metabolic state. This intervention has the desired metabolic effect, but in practice, the use of IV glucose and insulin infusions necessitate access to large veins, frequent control of glucose levels, and adjustment of the glucose infusion rates to maintain glucose levels.[17] These difficulties could be overcome if CHO could be administered through a more physiological route - hence, the oral route of giving CHO was investigated.

1.4.2 Characteristics of oral carbohydrate loading

Preoperative CHO loading can only be given orally in clinical practice if two criteria are fulfilled:

1. the beverage must pass the stomach fast enough to be safe (time specific)
2. the intake of the beverage should induce an endogenous insulin response to cause the desired change in metabolism from the fasted to the fed state (dose specific).[5]

Commercially available oral nutritional supplements (ONS) can change the metabolism from the fasted to the fed state, but they have a relatively slow rate of gastric emptying due to the fat and fibre contents, and are thus theoretically unsafe to use.[17] Another alternative could be clear fluids or sport beverages, which contain mainly CHO with rapid gastric emptying. However, the concentration of CHO is too low (< 8%) to cause an insulin response to switch the metabolism from the fasted to the fed state.[5] A CHO beverage was pioneered, consisting of about 12% (12 g/100 ml) CHO with an osmolality less than 300 mOsm/kg, for preoperative use.[57] The energy content of this beverage is adequate to increase serum insulin levels seen after a standard mixed meal, therefore providing enough energy to switch the patient from the fasted to the fed state before the onset of surgery. The CHO used must be complex, such as maltodextrins rather than glucose or sucrose, to minimise the osmotic load of the beverage to reduce the gastric emptying time.[141] Note that this specific beverage is also protein, fat and fibre free. Upon testing a dose of 400 ml (50 g CHO) of this beverage passed the stomach within 90 minutes.[57] The consumption of 400 ml of this CHO beverage compared to a placebo showed no significant difference in the gastric contents (volume and pH) at the onset of surgery.[162] The intake of up to 400 ml of the CHO beverage also does not contribute to additional adverse events when compared to a similar intake of water.[81,163] Therefore, the intake of a CHO beverage before elective surgery is as safe as the intake of other recommended clear fluids. This formula with about 12% CHO and an osmolality of < 300 mOsm/kg is considered the best method of CHO administration before surgery.[17] There are various

beverages available internationally adhering to these principles that are marketed for preoperative use (Table 1.11).[164]

A new formulation of CHO beverages has been developed containing sources of protein i.e. hydrolysed protein, whey protein and glutamine.[165-167] The composition of the new formulas looks promising since it might reduce insulin resistance, causing decreased loss of lean body mass, and enhance surgical recovery.[9] Whey protein contains essential amino acids that are rapidly used by skeletal muscle during the stress response, it stimulates protein synthesis inducing protein gain, and it is a source of cysteine, which is a precursor of glutathione, which acts as an antioxidant.[168-170] Glutamine is a conditionally essential amino acid and contributes to more than 50% of the body's free amino acid pool.[171] Glutamine attenuates the development of postoperative insulin resistance, increases liver glycogen and enhances the mitochondrial membrane complex activity resulting in fewer cases of hyperglycaemia, decreased insulin requirements, decreased negative nitrogen balance, increased serum glutathione, and decreased inflammatory markers.[165,172-174] Furthermore, whey protein is rapidly digested and absorbed in the small intestine when compared to casein, and supplements containing glutamine are safely emptied from the stomach within two to three hours.[175,176] The overall findings of the potential benefits of whey protein and glutamine-enriching carbohydrate beverages for preoperative use, seems relevant. However, further research is required to establish the clinical benefit. See Table 1.12 for the carbohydrate containing clear beverages available in South Africa.[177-182] The energy supply ranges from 50 kcal to 150 kcal per 100 ml with all of the beverages being fat and lipid free. All beverages contain a source of protein except for the preOp® (Nutricia). All beverages contain at least 12 g CHO per 100 ml that will change the metabolism from the fasted to the fed state. Only the preOp® (Nutricia) adheres to the recommended < 300 mOsm/kg osmolality to ensure rapid gastric emptying. Due to the increased osmolality of the other beverages, the different companies manufacturing these beverages should give evidence that these beverages clear within the recommended time to make it safe for preoperative use. The vitamin, trace element and electrolyte contents of all the beverages differ significantly. From this table it is important to note that not all clear fluid beverages are designed for preoperative use.

Table 1.11: International available carbohydrate beverages for preoperative use[164]

Product	Location	Energy (kcal)	Total Carbohydrate (g)	Maltodextrin (g)	Carbohydrate (%)	Osmolality (mOsm/kg)	Volume (ml)
preOp ® (Nutricia)	Europe, United Kingdom, Canada, South Africa	200	50.4	40	12.5	260 - 285	400
Maxijul ® (Nutricia)	United Kingdom, Europe	190	47.5	43.25	32	420	150
Clearfast ® (BevMD)	United States	200	50	44	14.0	270	355
ONS300 ® (Fresenius Kabi)	Germany	200	50	50	16.6	266	300
ONS400 ® (Fresenius Kabi)	Germany	200	50	50	12.5	266	400
Preload ® (Vitaflo / Nestlé)	United Kingdom	200	52	47.5	13.0	135	400
Arginaid ® H20 (Nestlé)	Japan	300	52	52	18	200	250
Nidex ® (Nestlé)	Brazil	200	50	50	12.5	200	400

*nutritional information per unit

Table 1.12: Carbohydrate containing clear beverages available in South Africa

Product	Provide Xtra (Fresenius Kabi)[177]	Fresubin Jucy (Fresenius Kabi)[178]	preOp (Nutricia)[179]	Fortijuce (Nutricia)[180]	Resource (Nestlé)[181]	Ensure Plus Juce (Abbot)[182]
Energy (kcal)	150	150	50	150	104	150
Protein (g)	4 11% of Energy Pea protein hydrolysate	4 11% of Energy Whey protein	none	4 11% of Energy Whey protein	3.8 10% of Energy Whey protein	4.8 12.8% of Energy
Carbohydates (g)	33.5 89% of Energy Maltodextrin, Saccharose	33.5 89% of Energy Maltodextrin, Saccharose	12.6 100% of Energy Maltodextrin, Fructose	33.5 89% of Energy Maltodextrin, Sucrose	22.6 90% of Energy Maltodextrin, Sucrose	32.7 87.2% of Energy
Electrolytes (mg)						
Sodium	97	6	2.2	19.4	32	Na: 4.8
Potassium	55	7	3.1	19.4	0	K: 4.1
Chloride	50	190	6	356	19.8	Cl: 40.6
Magnesium	30	1	1	4	0	Mg: 3.1
Phosphorous	43	11	1	24	72.2	PO_4: 3.6
Calcium	40	50	6	60	0	Ca: 8
Osmolarity (mOsm/l)	680 - 700	680	260	715 – 750	630	660
Flavour	Apple, Orange	Blackcurrant, Pineapple	Lemon	Blackcurrant, Forest Fruits	Peach, Wildberry	Strawberry
Packaging (ml)	200	200	200	200	237	220
Age Restriction	< 2 years	< 2 years	< 1 year	< 3 years	< 4 years	Unknown
Preoperative Indication	400 ml night before surgery; 200 ml up to 2 hours before surgery	Safe to consume 200 ml up to 2.5 hours before surgery	800 ml night before surgery; 400 ml up to 2 hours before surgery	Indicated for preoperative use	474 ml night before surgery; 237 ml up to 2 hours before surgery	Not specifically indicated for preoperative use

Nutritional analysis per 100ml

1.4.3 Benefits of oral carbohydrate loading

The main objective of preoperative CHO loading is to cause an alteration in metabolism that usually takes place when a patient consumes a light meal – prompting an endogenous insulin release that switches the metabolism from the fasted to the fed state. A 50 g CHO load causes a severe rise in total body insulin sensitivity (approximately 50%) with a marked increase in glucose absorption and a decrease in glucose production.[17] After the consumption of the CHO beverage, the metabolism is in a CHO storing state (anabolism), and when the stress of the surgery occurs, there are mediators released to act in the opposite direction shutting off glucose absorption in muscle and increasing glucose production.[17] If the patient is pretreated with a CHO beverage, the starting point for these reactions are much more anabolic and hence, the stress results in a lower catabolic setting compared with when the patient already has a starting point towards the catabolic state by being fasted overnight.

Numerous studies have shown positive outcomes for POCL with regards to clinical outcomes and patient well-being.[16,74,119-122,164,183] POCL results in approximately 50% less pronounced insulin resistance.[184-186] Muscle function is improved by enhanced protein metabolism after surgery by losing less muscle mass and improved muscle strength.[187,188] Protein breakdown after surgery may be reduced through enhanced insulin action by POCL.[189] Improved nitrogen balance is also observed following POCL.[189] The change in metabolism due to POCL results in a shorter length of stay.[5] The depression of the immune system that takes place in response to surgery is also limited.[190] Thirst is the primary outcome improved by giving oral CHO preoperatively.[17] Other preoperative discomforts like hunger, anxiety, nausea and vomiting are also reduced when POCL is given.[191,192] See figure 1.4 for the potential benefits of preoperative oral CHO treatment.

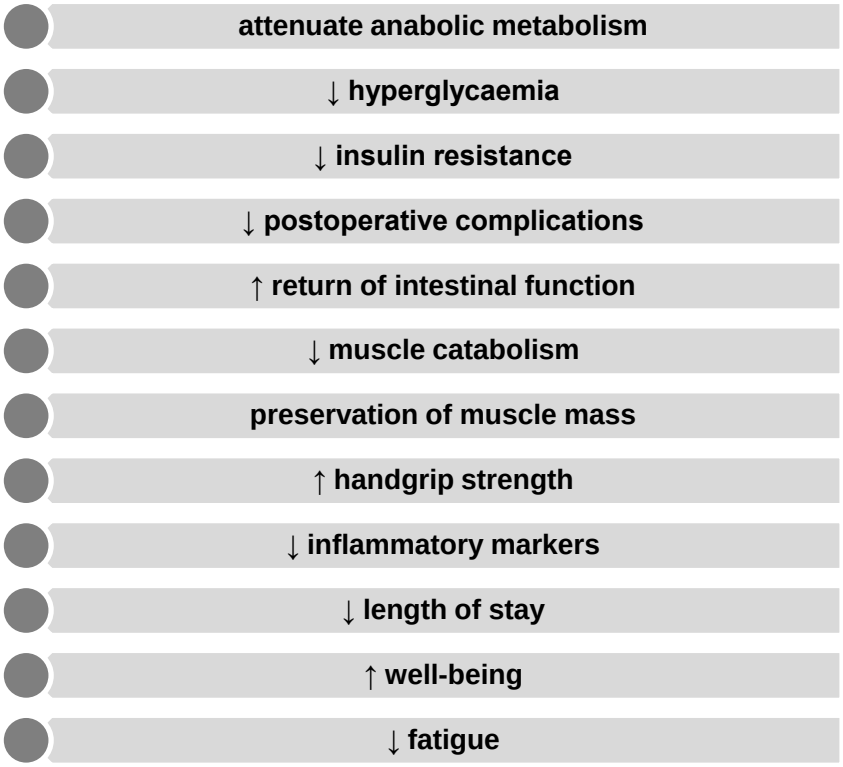


Figure 1.4: Potential benefits of preoperative oral carbohydrate treatment

1.5 ENHANCED RECOVERY AFTER SURGERY

1.5.1 ERAS history

Enhanced Recovery After Surgery (ERAS) is a multimodal perioperative care pathway designed to achieve early recovery for patients undergoing surgery.[193] Although *fast-track surgery* was the first term used to describe this concept, it was misleading and placed too much focus on faster discharge rather than focusing on the patient's recovery. The term ERAS is now an acknowledged term in the medical literature.[193] ERAS is not just a term for a protocol but a continuous movement to develop and improve perioperative care pathways. The ERAS Society has its roots in what was called the ERAS Study Group in 2001, comprisingof a group of surgeons. The intention of the group was to develop the optimal perioperative care pathway by means of literature review and adaption of traditional treatment to optimise patient care since there were a variety of traditions in use in different hospitals and there was great discrepancy between the actual practices and what was already known to be best evidence based practice.

The ERAS Study Group developed and published their first guidelines on elective colonic surgery in 2005, with the elective rectal/pelvic surgery guidelines following in 2009. The international collaboration, together with expanding interest in the ERAS concept, made the ERAS Study Group decide to take this experience to the next level by forming the ERAS Society in Stockholm, Sweden in 2010. The ERAS Society is a multiprofessional, multidisciplinary collaboration with the aim to improve perioperative care through research and education as well as the implementation of best evidence-based practice. The colonic and rectal/pelvic surgery guidelines were updated in

2012; the pancreaticoduodenectomy and cystectomy guidelines followed in 2013; gastrectomy guidelines were published in 2014, gastrointestinal guidelines published in 2015, and gynaecologic guidelines published in 2016. The ERAS Society collaborates with national and international medical societies. The network of centres involved in the development of perioperative care expanded rapidly with centres of excellence in more than 15 countries in Europe, Australia, and North and South America. Africa opened its first centre of excellence in Cape Town, South Africa in 2015.

1.5.2 ERAS principles and recommendations

ERAS represents a paradigm shift in perioperative care in two ways: Firstly, it re-examines traditional practices and replaces them with evidence-base best practices; secondly, it is comprehensive in its scope covering all areas of the patient's journey through the hospital. The mission of ERAS is to develop perioperative care and to improve recovery through research, implementation of evidence-based practices, and audit education. See Figure 1.5 for the patient's journey through the hospital based on the ERAS concept.[193]

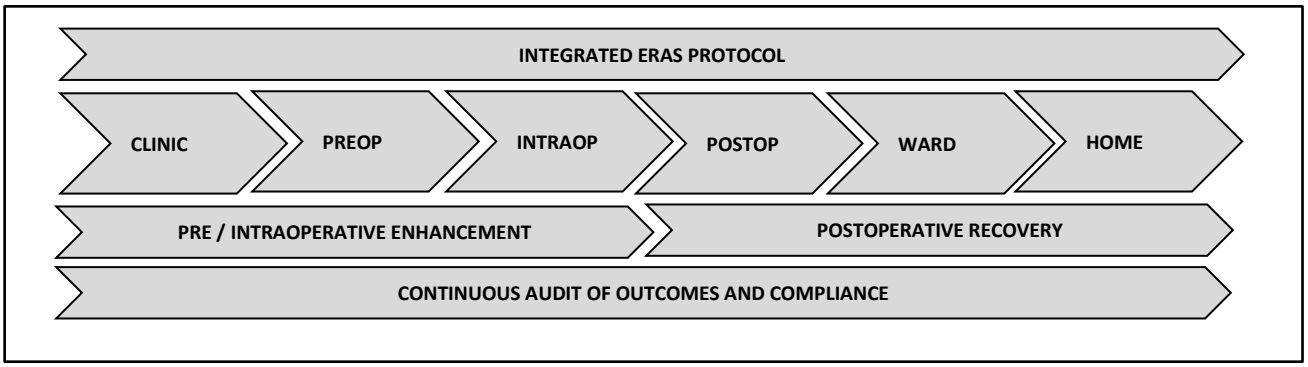


Figure 1.5: The patient's journey through the hospital[193]

The ERAS Protocol is the evidence-based care protocol developed by the ERAS Society. The protocol describes the perioperative care pathway with recommendations for patient care at various steps in the perioperative process (Table 1.13).[193] The ERAS Protocol has to involve the entire team, including surgeons, anaesthetists, intensivists, nurses, dietitians, physiotherapists and psychologists when necessary. The ERAS team forms the basis of the implementation, maintenance, sustainability and further development of the ERAS Protocol. The ERAS Implementation Programme (EIP) is a specific training programme designed and customised for the ERAS care team to implement the ERAS Protocol. The EIP focuses on building well-functioning teams from various units involved in surgical care, introducing highly specific changes to current routines to conform to best-practice, and providing the tools to monitor and analyse the effects of those changes (Figure 1.6).[193] The ERAS Interactive Audit System (EIAS) is an online software tool used to enter patient data related to the patients' journey as well as to ensure that all members of the team conform to the standard ERAS care procedure. The tool consists of two parts: EIAS Data Entry – a module for entering patient data following the patients' journey through the perioperative phase; EIAS Analysis and Report – focused on quality of life for patients by

monitoring the rate of complications and length of stay. EIAS becomes a crucial support in the daily decision-making process and an important quality assurance tool.

Table 1.13: Components of the ERAS Protocol

Preoperative	Intraoperative	Postoperative
• Preadmission counselling • Fluid and carbohydrate loading • No prolonged fasting • No/selective bowel preparation • Antibiotic prophylaxis • Thromboprophylaxis • No premedication	• Short-acting anaesthetic agents • Mid-thoracic epidural anaesthesia/analgesia • No drains • Avoidance of salt and water overload • Maintenance of normothermia (body warmers / warm intravenous fluids)	• Mid-thoracic epidural anaesthesia/analgesia • No nasogastric tubes • Prevention of nausea and vomiting • Avoidance of salt and water overload • Early removal of catheter • Early oral nutrition • Non-opioid oral analgesia/NSAIDs • Early mobilisation • Stimulation of gut motility
Audit of compliance and outcomes		

*NSAID = non-steroidal anti-inflammatory drugs

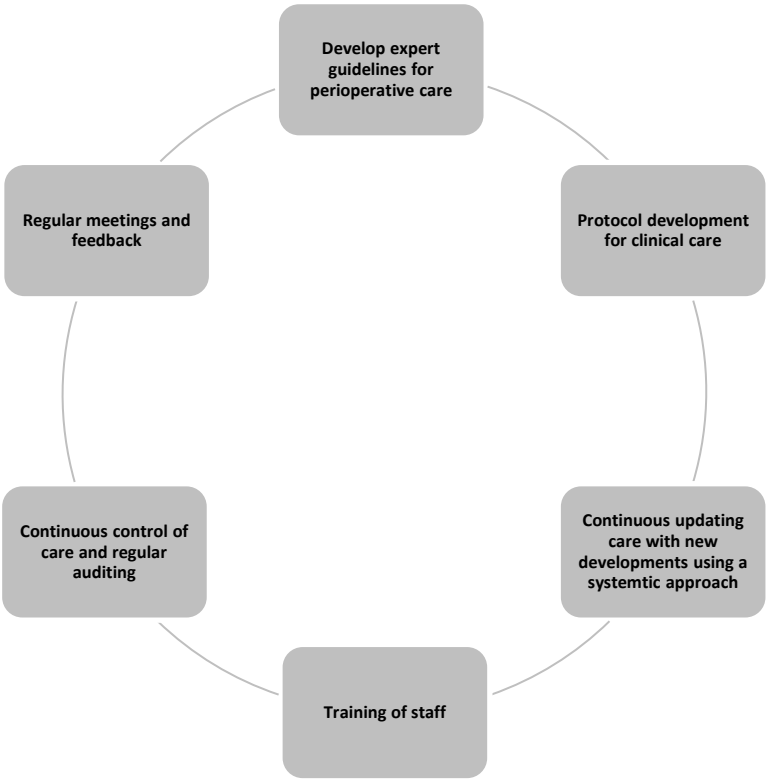


Figure 1.6: Goals of the ERAS Implementation Programme

The ERAS Society, in collaboration with other medical societies, reviews and updates literature for novel guidelines in different surgical procedures including colonic, rectal/pelvic, pancreatic, bladder, gastric, gastrointestinal and gynaecologic surgery.[194-202] Existing guidelines are continuously updated, and the guidelines must also be evaluated to confirm whether the compliance with the ERAS Protocol improves outcomes. The colorectal guidelines were the first

novel guidelines constructed by the expert groups, and after evaluation in a single centre study, it was confirmed that the outcomes were improved substantially when the ERAS Protocol was followed.[194] The intention is to complete the same studies in different surgical procedures as well as in multicentre studies using the EIAS. Expert groups are working on a wide range of procedures to include in the future (including breast and reconstructive surgery, head and neck cancer, thoracic surgery, hepatobiliary surgery and orthopaedic surgery).

1.5.3 ERAS nutrition guidelines

Optimal nutrition forms an integral part of the ERAS Protocol (Table 1.14).[13] Preoperative optimisation is a crucial step in preparation for surgical procedures and should be used to identify patients at risk for morbidity and mortality.[195] Therefore, preoperative screening and assessment is of utmost importance to identify patients at risk of malnutrition. Malnutrition is an independent risk factor for poor outcomes, and has been associated with increased morbidity after surgery. These malnourished patients should receive supplementation. The oral and enteral route seems to be the first choice with parenteral nutrition warranted in cases where enteral nutrition has failed.[203] There is no conferred benefit of supplementation in patients who are not at risk of malnutrition.[203] The ERAS Society recommends an intake of solids up to 6 hours before surgery and clear fluids up to 2 hours before surgery.[194-202] POCL should be used routinely. The clinical effectiveness of POCL as a routine practice in diabetic patients has yet to be established. However, when CHO treatment is given with normal diabetic medication, gastric emptying seems to be normal.[204] In patients where gastric emptying may be delayed specific safety measures should be used at the induction of anaesthesia. Postoperative gum chewing has been shown to be safe and beneficial in reducing time to first bowel movement after gastrointestinal surgery.[205] Normal food intake is the basis for nutrition before and after surgery for most patients according to the ERAS recommendations. Addition of ONS can improve overall intake to meet nutrition requirements. Postoperative patients can drink immediately after recovery from anaesthesia and progress to eating normal food spontaneously as soon as possible. Early feeding reduces the risk of infection and length of stay, and is not associated with an increased risk of anastomotic breakdown; however, the risk of nausea increases without associated vomiting.[206,207] Immunonutrition has been investigated extensively in surgery patients but conclusions are difficult to make since the route of administration (i.e. enteral versus parenteral) is not comparable, patient populations are heterogeneous (i.e. different surgical procedures), at different time periods (i.e. pre- and/or postoperative), in different combinations (i.e. single versus combination), in different dosages, and compared with control groups that are not always isonitrogenous. Therefore, further trials should be conducted in modern perioperative settings and with single immune enhancing products. The ERAS recommendations based on nutrition per surgical procedure are presented in Table 1.15.[194-202]

Table 1.14: Perioperative nutrition interventions as recommended by the ERAS society

PREOPERATIVE	2 – 6 HOURS PREOPERATIVE	INTRAOPERATIVE	POSTOPERATIVE
Screening	Limited fasting		Early intake without restriction
Assessment	(2 hours for fluids and 6 hours for solids)		Chewing gum
Specialised nutrition therapy	Preoperative carbohydrate treatment		Specialised nutrition therapy
Specific requirements			Specific requirements
Route (oral/enteral/parenteral)			Route (oral/enteral/parenteral)
Supplementation			Supplementation
Immunonutrition (formula/dose/timing)			Immunonutrition (formula/dose/timing)

Table 1.15: ERAS recommendation related to nutrition per surgical procedure

COLONIC SURGERY[194]			
Item	**Recommendation**	**Evidence Level**	**Recommendation grade**
Preoperative optimisation	Patients should be screened for nutritional status and if at risk of under nutrition given active nutrition support	extrapolated	strong
Preoperative fasting	Intake of clear fluids up to two hours and solids up to six hours prior to induction of anaesthesia	moderate	strong
Preoperative treatment with carbohydrates	Oral carbohydrate treatment should be used routinely. In diabetic patients treatment can be given along with the diabetic medication.	low (routine) very low (diabetic)	strong (routine) weak (diabetic)
Chewing gum	Chewing gum can be recommended.	moderate	strong
Early oral intake	Patients should be encouraged to take normal food as soon as lucid after surgery.	high	strong
Oral nutrition supplements	ONS may be used to supplement total intake.	low	strong
Immunonutrition	IN could be considered in open colonic resection.	low	weak
RECTAL/PELVIC SURGERY[195]			
Item	**Recommendation**	**Evidence level**	**Recommendation grade**
Preoperative optimisation	Specialised nutrition support should be considered for malnourished patients.	extrapolated	strong
Preoperative fasting	Intake of clear fluids up to two hours and solids up to six hours prior to induction of anaesthesia.	moderate	strong
Preoperative treatment with carbohydrates	Oral carbohydrate loading should be administered to all non-diabetic patients.	low to moderate	strong
Chewing gum	Approach to optimising gut function should include chewing gum.	moderate	strong
Early oral intake	An oral ad-libitum diet four hours after surgery.	moderate	strong
Oral nutrition supplements	In addition to normal food intake, ONS should be offered to maintain adequate intake of protein and energy.	low	strong
Immunonutrition	No recommendation.	none	none

PANCREATIC SURGERY[196]			
Item	**Recommendation**	**Evidence level**	**Recommendation grade**
Preoperative optimisation	Routine use of artificial nutrition is not warranted; malnourished patients should be optimised with ONS or enteral nutrition.	very low	weak
Preoperative fasting	Intake of clear fluids up to two hours and solids up to six hours prior to induction of anaesthesia.	low to high	strong
Preoperative treatment with carbohydrates	Oral carbohydrate loading should be administered to all non-diabetic patients.	low	strong
Chewing gum	Chewing gum is safe and may accelerate gastrointestinal transit.	low	weak
Early oral intake	Patients should be allowed a normal diet after surgery without restrictions; cautioned to begin carefully and increase intake according to tolerance over three to four days;	moderate	strong
Oral nutrition supplements	enteral tube feeding should be given only on specific indication and parenteral nutrition should not be employed routinely.		
Immunonutrition	IN for five to seven days perioperatively should be considered.	moderate	weak

BLADDER SURGERY[197]			
Item	**Recommendation**	**Evidence level**	**Recommendation grade**
Optimisation	Specialised nutrition support should be considered for malnourished patients.	extrapolated	strong
Fasting	Intake of clear fluids up to two hours and solids up to six hours prior to induction of anaesthesia.	moderate	strong
Treatment with carbohydrates	Oral carbohydrate loading should be administered to all non-diabetic patients.	extrapolated	strong
Chewing gum	Optimisation of gut function should involve gum.	moderate	strong
Early oral intake	Early oral nutrition should be started four hours after surgery.	extrapolated	strong
Oral nutrition supplements	No recommendation.	none	none
Immunonutrition	No recommendation.	none	none

GASTRIC SURGERY[198]			
Item	**Recommendation**	**Evidence level**	**Recommendation grade**
Preoperative optimisation	Routine use of artificial nutrition is not warranted; malnourished patients should be optimised with ONS or enteral nutrition.	very low	strong
Preoperative fasting	Intake of clear fluids up to two hours and solids up to six hours prior to induction of anaesthesia.	low to high	strong
Preoperative treatment with carbohydrates	Oral carbohydrate loading should be administered to all non-diabetic patients.	extrapolated	strong

Chewing gum	No recommendation.	none	none
Early oral intake	Patients undergoing total gastrectomy should be offered drink and food at will from postoperative day one; they should be advised to begin cautiously and increase intake according to tolerance. Patients clearly malnourished or those unable to meet 60% of daily requirements by postoperative day six should be given individualised nutrition support.	moderate (total)	weak (total)
Oral nutrition supplements		moderate (malnourished)	strong (malnourished)
Immunonutrition	The benefit shown for major gastrointestinal cancer surgery in general has not been reproduced in dedicated trials on patients undergoing gastrectomy; although benefit cannot be excluded, there is presently insufficient evidence for this patient group.	moderate	weak
GASTROINTESTINAL SURGERY[199,200]			
Item	**Recommendation**	**Evidence level**	**Recommendation grade**
Preoperative optimisation	Optimisation of nutritional status should follow international guidelines.	none	none
Preoperative fasting	Intake of clear fluids should be allowed until two hours before induction of anaesthesia. Solids should be allowed until six hours.		strong
Preoperative treatment with carbohydrates	Preoperative treatment with oral carbohydrates should be routinely administered except in patients with documented delayed gastric emptying or slow gastrointestinal motility and as well as in patients undergoing emergency surgery.		strong (routine use) weak (diabetic/obese)
Chewing gum	Recommended to improve stimulatory effect.	unknown	unknown
Early oral intake	Recommended for the anabolism, stimulatory effect and to decrease insulin resistance.	unknown	unknown
Oral nutrition supplements	No recommendation.	none	none
Immunonutrition	No recommendation.	none	none
GYNAECOLOGIC/ONCOLOGY SURGERY[201,202]			
Item	**Recommendation**	**Evidence level**	**Recommendation grade**
Preoperative optimisation	No recommendation.	none	none
Preoperative fasting	Clear fluids should be allowed up to two hours and solids up to six hours prior to induction of anaesthesia.	high	strong
Preoperative treatment with carbohydrates	Carbohydrate loading reduces postoperative insulin resistance and should be used routinely.	moderate	strong
Chewing gum	The use of chewing gum should be considered.	moderate	weak
Early oral intake	A regular diet within the first 24 hours after surgery is recommended.	high	strong
Oral nutrition supplements	No recommendation.	none	none
Immunonutrition	No recommendation.	none	none

** ONS = Oral nutrition supplements; IN = Immunonutrition*

The problem with trials comparing ERAS with traditional care is that it is very hard to blind the studies; hence, the level of the evidence cannot be the highest. There is no uniformity in the elements that are actually tested since some investigators may see certain elements as standard while others do not. The ERAS guidelines use the Grade of Recommendation, Assessment, Development and Evaluation (GRADE) system for rating the level of the evidence and the strength of the recommendation.[1]

The GRADE system for rating quality of evidence:

- high quality: further research is unlikely to change the confidence in estimate effect,
- moderate quality: further research is likely to have an important impact on the confidence in estimate of effect,
- low quality: further research is very likely to have an important impact on the confidence in estimate of effect,
- very low quality: any estimate of effect is very uncertain.

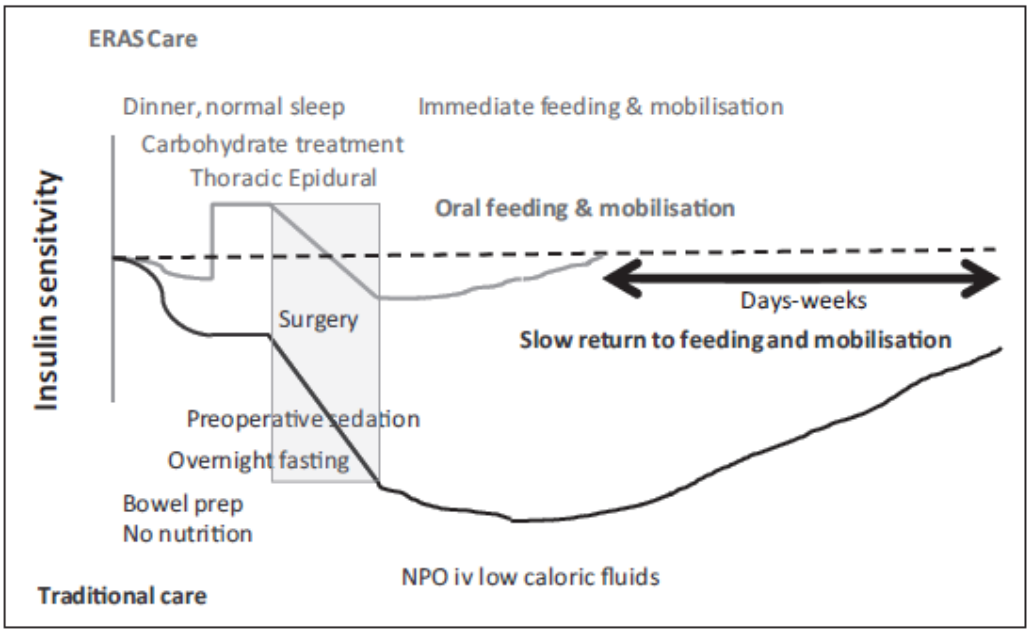
GRADE system for rating strength of recommendation:

- strong: when desirable effects of the intervention clearly outweigh the undesirable effects, or clearly do not,
- weak: when trade-offs are less certain – either because of low quality evidence or because there is a balance between the desirable and undesirable effects.

Despite the drawbacks of the methodology, it does become evident that ERAS Protocols have major benefit for outcomes.

1.5.4 Benefits of ERAS

The mechanism behind the effectiveness of the ERAS Protocol can be attributed to the reduction in metabolic stress and maintenance of fluid homeostasis to reduce the length of stay in the hospital as well as complications associated with surgery. A recent meta-analysis showed that ERAS protocols in major surgery reduced recovery time and length of stay by two to three days and complications by 30 to 50%.[208] The development of insulin resistance as a consequence of the stress of surgery sets off a catabolic response where all parts of the metabolism are disrupted.[193] Protein is being lost from the muscles, causing loss of muscle mass and decreased strength, resulting in difficulty in mobilisation. Further hyperglycaemia develops, which is associated with increased postoperative complications. By reducing metabolic stress and insulin resistance, protein and energy consumed will be utilised in an anabolic fashion, hyperglycaemia can be prevented, and lean body mass can be conserved to promote early mobilisation. Figure 1.7 shows the influence of ERAS versus traditional care on insulin sensitivity.[15]



ERAS = enhanced recovery after surgery; iv = intravenous; NPO = nil per os, prep = preparation

Figure 1.7: Influence of different perioperative treatment on insulin sensitivity[15]

Fluid homeostasis also plays an important role in the recovery process since fluid overload results in a delayed return of bowel function as well as postoperative complications. The literature on the effect of ERAS on the quality of life is heterogeneous since health-specific quality of life instruments for perioperative care are unavailable and investigators use generic quality of life instruments or instruments developed for certain specific diagnosis. There is limited evidence on the cost benefit of ERAS but the fact that it reduces the incidence of complications and decrease length of stay in the hospital, it indirectly lends itself to support the cost benefit.[194] Interventions like the ERAS concept are prone to show significant Hawthorne or trial effects, meaning that the collateral effect on the infrastructure and management culture to implement such a comprehensive programme will have beneficial consequences in addition to those caused by the protocol items themselves or their synergistic effect.[209] Nevertheless, there is a benefit to the use of the ERAS concept (Figure 1.8).[194-202] However, further multicentre and multinational research is required to validate and unify the overall benefits of the comprehensive ERAS protocol.

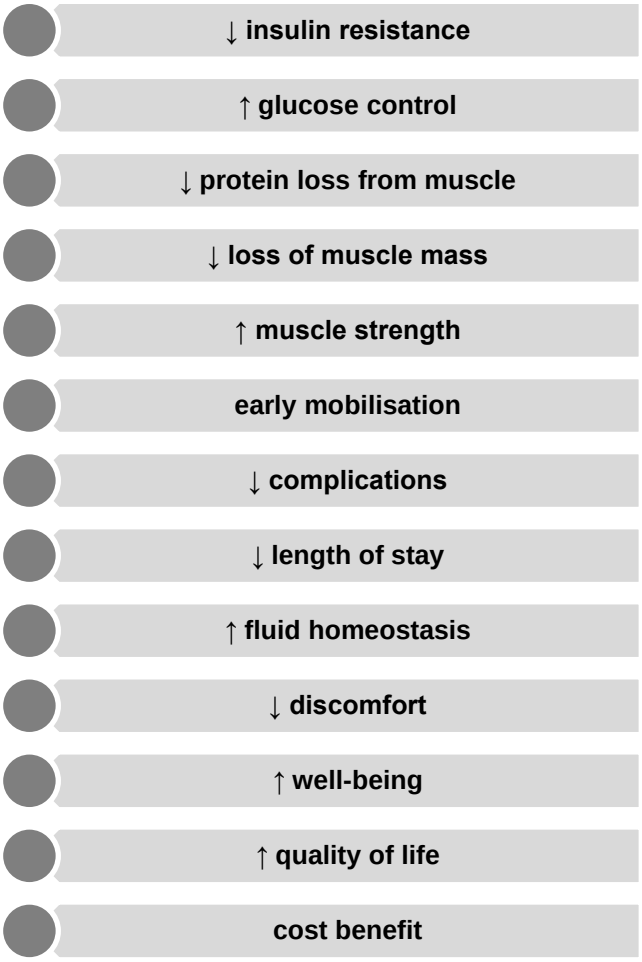


Figure 1.8: Potential benefits of the ERAS protocol[194-202]

1.6 MOTIVATION FOR THE STUDY

Evidence-based medicine (EBM) is an important focus in health care since it provides the potential for healthcare practitioners to close the gap between theory and practice.[11] A systematic review is a complete collection and objective analysis of all available relevant studies in a specific area to answer a specific question; whereas a meta-analysis is the use of statistical methods to summarise the results of independent studies.[210] Both systematic reviews and meta-analyses are used in EBM since they allow for standardised methods of compiling evidence in a systematic approach. According to the quality of evidence, systematic reviews of randomised controlled trials are the best quality of evidence available with meta-analyses ranked as very strong evidence.[211]

The concept of evidence-based nutrition (EBN) can be defined as the application of the best available systematically assembled evidence in setting nutrition policy and practice.[212] A tremendous need arose for the massive volume of research to be compact, accessible, and able to be applied by healthcare practitioners. Nutrition is an evolving paradigm in the medical field and is in definite need for evidence-based guidelines. Nutrition guidelines can be developed based on a systematic review of the relevant scientific literature to ensure that the available scientific evidence

is accurately reflected. Guidelines based on evidence have led to improved performance and better outcomes.[11] From a nutritional point of view, it is our duty to advocate optimal nutrition for all and to emphasise the implementation of best clinical practice accordingly to EBN.

Inappropriate preoperative fasting is a subject that necessitates attention. Virtually all patients for elective surgery are admitted a few days in advance, and the medical personnel still write 'NPO from midnight' on the patient's chart. This practice was established by tradition, and traditions are not easy to break. Bridging the gap between evidence-based medicine and its implementation in practice is of utmost importance in refining the quality of care and improving patient safety.[11] Quality of care is seen as the element that can most increase the possibility of positive outcomes.[213] The importance of this challenge is clear, since the quality of health care provided will increase patient well-being and in return, provide increased clinical outcomes, less discomfort and cost reductions for the patient and healthcare system.[13]

Recent insight taught us that together with surgical techniques, metabolic control is as important to achieve optimal patient care – therefore nutrition care should be seen as an integral part of the optimal management of the surgical patients.[15] Nutrition is no substitute for poor surgery or anaesthesia or shortcomings in other aspects of care. Optimisation of the metabolic state prior to major surgery, however, leads to improved surgical outcomes. Strategies to minimise hyperglycaemia and insulin resistance by aggressive preoperative nutrition and CHO loading may promote maintenance of a perioperative anabolic state, improving healing, reducing complications, and shortening the time to recovery of bowel function and hospital discharge. The ERAS concept establishes a multiprofessional and multidisciplinary approach toward patient care with regards to evidence that aims to form a platform to simplify communication, enhance novel treatments, update and implement guidelines. One of the main nutrition-related elements of the ERAS recommendations is that CHO-containing clear fluids should be allowed up to two hours prior to the induction of anaesthesia.[193]

POCL has been introduced, but has not, so far, been widely implemented into clinical practice. Several systematic reviews have been done on this topic – published between 2010 and 2015, which included studies up to 2014.[16,74,119-122,164,183] Lately, several studies have been published examining the effects of POCL in different elective surgical situations and the results have been conflicting with some showing benefit and others no benefit. A systematic review on this topic will give the investigator an opportunity to explore the question once more by summarising the latest available data up to 2015 with the aim of motivating healthcare practitioners to believe in the intervention. The results will help facilitate the implementation of up-to-date guidelines for healthcare practitioners to reach the therapeutic goal for the patient of rapid recovery to normal function and well-being, the minimum complications and early discharge home. POCL provides a

simple and practical intervention, reflecting good clinical practice and economics that may improve the outcome for many elective surgery patients.

It is often said that it takes up to 15 years for a proven medical treatment to become common practice – this shows how hard it is to move evidence into practice.[193] Implementing the ERAS concept in a hospital requires commitment since it involves changing the way some things have been done in the past. The first clinical centre of excellence in Africa was opened in Cape Town, South Africa in 2015 and may aid in the implementation of the concept on the African continent. In collaboration with the ERAS recommendations, this systematic review will be used to emphasise the importance of the modern fasting guidelines in the clinical setting with regards to biochemistry and clinical events, length of stay, adverse events and patient wellbeing. The focus will be to advocate evidence-based nutrition through changing guidelines as part of the ERAS concept by decreasing prolonged fasting and implementing POCL into practice.

CHAPTER 2: METHODOLOGY

2.1 STUDY OBJECTIVES

2.1.1 Purpose of the study

This systematic review assessed the effects of providing preoperative oral CHO treatment compared to standard fasting, placebo treatment, a combination of oral CHO treatment and IV fluids, and/or IV CHO administrations in adult patients undergoing elective surgery in terms of perioperative complications.

2.1.2 Specific objectives

The primary objectives of this review were to examine the effect of preoperative oral CHO treatment in adult patients on:

- biochemistry and clinical events
- length of stay
- adverse events

(Meta-analysis)

The secondary objectives were to briefly describe the effects of preoperative oral CHO treatment in adult patients with regards to other patient-reported psychosomatic perioperative events.
(Descriptive approach)

2.2 CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

2.2.1 Types of studies

All RCTs that compared the effect of preoperative oral CHO treatment to standard fasting, placebo treatment, a combination of oral CHO treatment and IV fluids, and/or IV CHO administration were included. Trials were included regardless of the lack of blinding or placebo treatment. All other less robust study designs and publication types (including quasi-controlled trials, abstracts, comments, review articles, editorials and letters) and unpublished data were excluded. Cross-over trials were also excluded as this methodology is not suitable for evaluating an intervention that must be given at a specific point in time.

2.2.2 Types of participants

Participants included were male and female human adult patients[1] undergoing elective surgery[2] and receiving general and/or spinal or epidural anaesthesia[3]. This review included trials that

[1] *18 years and above* [214]
[2] *Planned, non-emergency surgical procedure* [215]
[3] *Anaesthesia is the loss of the ability to feel pain; caused by the administration of a drug or other medical interventions. General anaesthesia is the induction of a balanced state of unconsciousness, accompanied by the absence of pain sensation and the paralysis of skeletal muscle over the entire body; produced by the administration of anesthetic agents by inhalation, intravenously, intramuscularly, rectally or via the gastrointestinal tract. Spinal anaesthesia is a regional anaesthesia caused by injection of a local anesthetic into the subarachnoid space around the spinal cord. Epidural anaesthesia is a regional anaesthesia caused by the injection of a local anesthetic into the extradural space, either between the vertebral spines or into the sacral hiatus.*[215]

evaluated the evidence of high-risk anaesthetic patients[4]; however this review excluded patients with diabetes mellitus type 1 and type 2[5], patients with abnormal blood glucose values prior to surgery[6], patients with insulin resistance syndrome[7], and emergency non-elective cases.

2.2.3 Types of interventions

Figure 2.1 shows the types of interventions employed in the studies reviewed. The experimental intervention consisted of a CHO-rich beverage for oral consumption containing ≥ 12% (45 g) CHO to achieve a rise in insulin levels to change the metabolism from a fasted to a fed state, and a low osmolality (< 300 mOsm/kg) to move through the stomach fast enough to ensure that it is perfectly safe to use preoperatively. Trials were eligible if the oral CHO treatment was administered within the following dosage and time: 400 ml within 90–300 minutes (1.5–5 hours) before the induction of anaesthesia (with or without 800 ml the evening before surgery). Co-interventions [≥ 12% (45 g) CHO beverages with different macronutrient profiles] were also eligible for inclusion in the systematic review.

The systematic review focused on the safety and effects of giving oral CHO treatment before elective surgery compared to inactive controls [standard fasting i.e. no oral intake for 6–8 hours before the induction of anaesthesia, and a placebo consisting of a beverage containing < 12% (45 g) CHO] and an active control (IV fluids containing ≥ 12% CHO). The inactive control groups may have received IV fluid therapy during the five hours before surgery start time as long as the total combined dose of CHO given remained <12% (45 g).

[4] *High-risk anaesthetic patients include: pregnant (second trimester or later), postpartum, obese, elderly and those patients with gastric disorders or disease.*[74]

[5] *Criteria used for diagnosis of diabetes mellitus are as follows: symptoms of diabetes mellitus plus random plasma glucose > 11.1 mmol/l (200 mg/dl) OR fasting plasma glucose >7.0 mmol/l (126 mg/dl) OR 2-hour plasma glucose >11.1 mmol/l (200 mg/dl) during the oral glucose tolerance test.* [51-53]

[6] *Normal Glucose Values: fasting plasma glucose of 4.0 – 5.6 mmol/l (72 – 100 mg/dl) and 2-hour post prandial value < 7.8 mmol/l (140 mg/dl).* [51-53]

[7] *Insulin Resistance Syndrome: fasting plasma glucose between 6.5 – 7.0 mmol/l (100 – 126 mg/dl) and two-hour post-prandial values of 7.8 – 11.1 mmol/l (140 – 200mg/dl) during the oral glucose tolerance test.* [51-53]

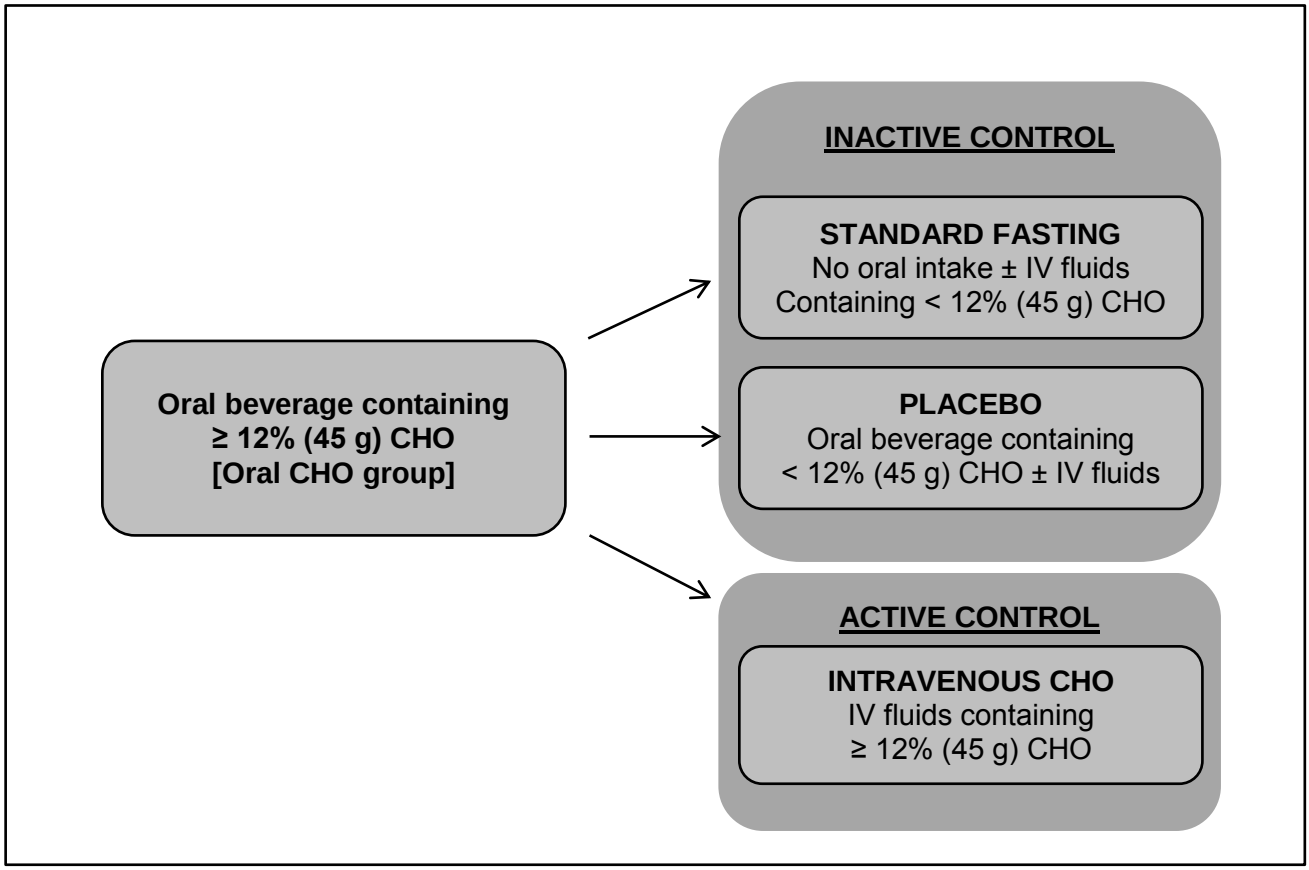


Figure 2.1: Type of interventions

2.2.4 Types of outcome measures

2.2.4.1 Primary outcomes

The primary outcomes of this review were to examine the effect of preoperative oral CHO treatment in adult patients on:

- Biochemistry and clinical events (glucose, insulin, insulin resistance, intestinal function, protein status, immune response)
- Length of stay (intensive care unit, hospital)
- Adverse events (regurgitation, aspiration and any related morbidity or mortality)

2.2.4.2 Secondary outcomes

The secondary outcomes were to briefly describe the effect of preoperative oral CHO treatment in adult patients with regards to other perioperative events (patient-reported psychosomatic outcomes):

- Discomfort/wellbeing (including thirst, hunger, nausea, vomiting, anxiety, pain)
- Fatigue (including weakness, tiredness, malaise)

2.3 SEARCH METHODS FOR IDENTIFICATIONS OF STUDIES

2.3.1 Data sources

Several electronic databases were searched from inception up to May 2015 to locate articles for inclusion in the systematic review. The electronic search included the following major databases to identify potential citations:

- Pubmed - MEDLINE
- Cochrane Library, including:
    - Cochrane Database of Systematic Reviews (CDSR; Cochrane Reviews)
    - Cochrane Central Register of Controlled Trials (CENTRAL; Clinical Trials)
    - Database of Abstracts of Reviews of Effects (DARE; Other Reviews)
- EBSCO Host, including:
    - Academic Search Premier
    - Cumulative Index to Nursing & Allied Health Literature (CINAHL)
    - Africa Wide
    - CAB Abstracts
- ISI Web of Knowledge – Web of Science
- Scopus Abstracts
- ProQuest Medical Library
- Science Direct
- Springerlink
- Google Scholar
- SABINET

In addition, reference lists from relevant studies were reviewed and personal files searched to identify additional publications. Unpublished trials were searched using “Dissertations Abstracts International”, “Database of African Theses and Dissertations” and “Proceedings First”. Databases of ongoing trials (such as Current Controlled Trials, Clinical Trials.gov and the World Health Organization’s Clinical Trials Registry Platform) were also searched and documented so that when this review is updated, these trials can be assessed for possible inclusion (see Chapter 5).

2.3.2 Keywords for searching

The above-mentioned databases were searched using specific search strategies identified with the assistance of a qualified healthcare librarian with experience in systematic reviews. English language restriction was not placed on the searches. The research period was not restricted to include all relevant studies. The latest version of the citations was included.

The following keywords and strings were compiled and searched:

1. preoperative
2. oral carbohydrate*
3. treatment*
4. therap*
5. nutrition
6. load*
7. beverage*
8. drink*
9. solution*
10. supplement*
11. human*
12. adult*
13. trial*
14. 1 AND 2
15. 1 AND 2 AND (3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10)
16. 1 AND 2 AND (3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10) AND 11
17. 1 AND 2 AND (3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10) AND 11 AND 12
18. 1 AND 2 AND (3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10) AND 11 AND 12 AND 13
19. 1 AND 2 AND 11
20. 1 AND 2 AND 11 AND 12
21. 1 AND 2 AND 11 AND 12 AND 13

[* all terms beginning with this root was searched (e.g. searching with the root load will included terms such as loads, loading and loaded).]

2.4 DATA COLLECTIONS AND ANALYSIS

2.4.1 Selection of studies

The selection of studies was divided into three separate phases (Figure 2.2). Phase 1 was conducted by the investigator with the assistance of a healthcare librarian to implement the initial search for studies, applying the relevant resources and search strings (Table 2.1). The initial search used very broad search criteria and was purposefully not very specific to allow the maximum number of potentially relevant studies to be identified. After the initial screening process, further assessment (phase 2) based on pre-specified inclusion and exclusion criteria (Table 2.2) was applied to the titles and abstracts of all the studies for inclusion in the systematic review. The titles and abstracts were examined by the investigator and independent reviewer for inclusion of eligible studies. If there was insufficient information in the title and abstract, the full text article was obtained for clarification. All searches failing to meet the inclusion criteria were excluded. The full

text articles of all potentially eligible studies were retrieved by the investigator. Studies were excluded if no full-text article was available. Multiple reports of the same study were linked together, and data were included only if multiple publications of the same study existed or if multiple studies presented the same data from the same participant. Phase 3 consisted of the investigator and independent reviewer examining the full text articles for compliance of studies with the eligible criteria using a pilot-tested eligibility form (Appendix 6.1). Eligibility was assessed so that the first 'no' response was used as the primary reason for exclusion of the study. The reference lists of review articles were reviewed to ensure that all eligible studies were included.

The reviewer was a registered dietitian trained by the investigator in terms of the methodological processes of a systematic review. The investigator was knowledgeable in the area under review, but the independent reviewer was not a content expert. The review process was blinded (the investigator and reviewer independently reviewed the articles) to ensure that all eligible studies were included. Differences of opinions were settled by a discussion between the investigator and the reviewer, or arbitration by a third person (one of the review authors).

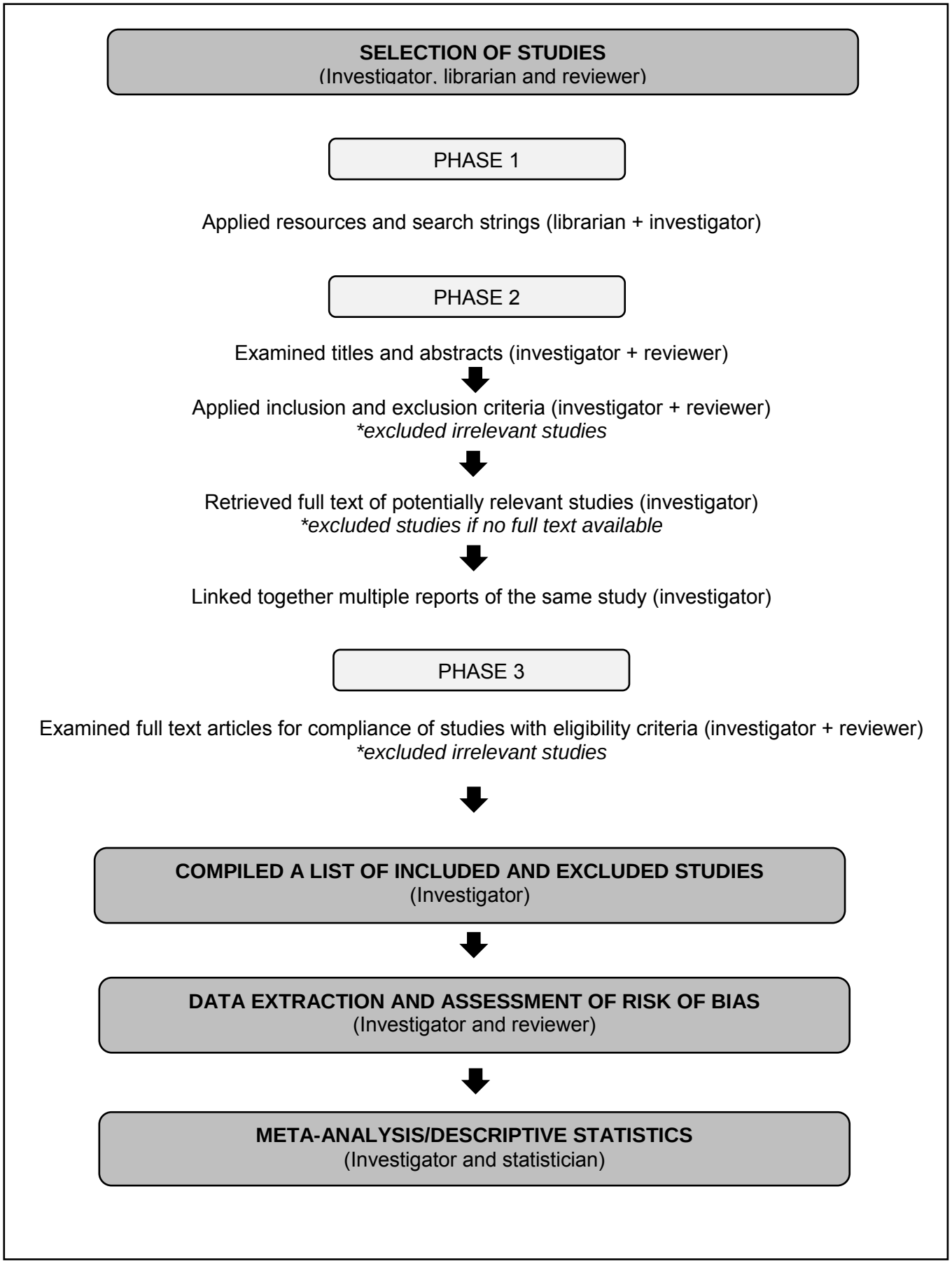


Figure 2.2: Process for selecting studies and collecting data

Table 2.1: Initial search criteria (Phase 1)

Study participants	Human adults
Study intervention	Oral CHO treatment and related terms
Study design	Randomised controlled trials
Language	All
Search period	All

Table 2.2: Inclusion and exclusion criteria (Phase 2)

Inclusion criteria	Exclusion criteria
Human studies	Animal studies
Adults (≥ 18 years)	Neonates, paediatric patients, adolescents
Male and female	None
Experimental interventions includes patients receiving CHO treatment: • Oral consumption • CHO content ≥ 12% (12 g/100 ml); ≥ 45 g • < 300 mOsm/kg osmolality • 800 ml the evening before surgery plus another 400 ml 90–300 minutes before the induction of anaesthesia, or only 400 ml 90–300 minutes before the induction of anaesthesia • Beverages (complying to above mentioned inclusion criteria) with different macronutrient profiles	Criteria not considered in the inclusion criteria
Control interventions includes patients receiving the following: • no oral intake for 6–8 hours before the induction of anaesthesia with or without additional IV fluids containing < 12% CHO (standard fasting) • oral CHO beverage containing < 12% CHO with or without additional IV fluids (placebo) • IV fluids containing ≥ 12% CHO (IV CHO)	Criteria not considered in the inclusion criteria
Low and high risk anaesthetic patients	None
Normal blood glucose values (before surgery): *fasting plasma glucose of 4.0–5.6 mmol/l (72–100 mg/dl) and 2-hour post prandial value < 7.8 mmol/l (140 mg/dl)*	Diabetes Mellitus Type 1 and 2 Abnormal blood glucose values prior to surgery, insulin resistance syndrome
Elective Surgery Cases	Emergency cases No surgery
All studies reporting on 1 or more of the following: • Glucose • Insulin • Insulin resistance • Hyperglycaemia • Intestinal function (flatus/movement) • Muscle function • Muscle strength • Muscle mass • Lean body mass • Nitrogen balance • Total body protein • Immune response • Length of intensive care unit stay • Length of hospital stay	Outcomes not considered in the objectives

Inclusion criteria	Exclusion criteria
• Time until fit for discharge • Regurgitation • Aspiration • Morbidity • Mortality • Thirst • Hunger • Nausea • Vomiting • Pain • Anxiety • Fatigue • Weakness • Tiredness • Malaise	
English language studies	Foreign language studies
Randomised controlled trials	All other study designs and publication types: • Cross-over trials • Quasi-randomised controlled trials • Review articles • Unpublished trials • Abstracts/editorials/comments/letters
Full text available of the study	Unavailable full text of the study

2.4.2 Data extraction and management

Details of the eligible studies were independently extracted by the investigator and a reviewer. The investigator was knowledgeable in the area under review, but the independent reviewer was not a content expert. The reviewer was trained regarding the data extraction process. A data extraction form was designed following the Cochrane Collaboration's checklist of items.[216] The data extraction form was pilot tested; after consensus had been reached between the review authors, the form was modified as required (Appendix 6.2). For trials that were published more than once, the data extraction utilised all sources to retrieve the maximum amount of data and the information was reported directly onto a single data extraction form. The review authors were not blinded to information in an article and had access to all the information. Disagreement between the investigator and reviewer were resolved by discussion, arbitration by a third party, or by contacting the study authors. No disagreements were unresolved.

2.4.3 Assessment of risk of bias in included studies

The risk of bias was assessed based on the updated domain-based evaluation, 'Cochrane risk of bias assessment tool' (Table 2.3).[217] Assessment of risk of bias forms (Appendix 6.3) were completed for each eligible study to critically assess the different domains. Each of the domains had a description and received a judgement of 'low risk of bias', 'high risk of bias or 'unclear risk of bias'. The data was entered into the Review Manager 5.3 (RevMan 5.3) software program, and a risk of bias table was completed for each study to generate a risk of bias graph and/or summary figure. The overall risk of bias of all included studies were assessed and included in the review as

part of 'table of characteristic of included studies' (see Chapter 3), and the overall outcomes is addressed in the results of included studies (see Chapter 3).

The investigator and one reviewer assessed the risk of bias of all eligible studies independently. The reviewer was trained in collecting information for assessments of risk of bias. The risk of bias tool was pilot tested by the investigator and reviewer prior to assessment to ensure consistency and consensus. Blinded assessment did not take place as this method is time consuming and the articles were well-known to the investigator. Disagreement was resolved by consensus and/or arbitration by a third person (one of the review authors). The authors of studies with incomplete reporting were contacted, and open-ended questions were used to avoid the risk of overly positive answers. Data was documented as 'not reported' if the authors of the studies did not respond.

Table 2.3: Domains assessed in the Cochrane Risk of Bias Tool[217]

Domain	Description	Judgement
Sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Was the allocation sequence adequately generated?
Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	Was allocation adequately concealed?
Blinding of participants, personnel and outcomes	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Was knowledge of the allocated intervention adequately prevented during the study?
Incomplete outcome data	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomised participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.	Were incomplete outcomes data adequately addressed?
Selective outcome reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Are reports of the study free of suggestion of selective outcome reporting?
Other sources of bias	State any important concerns about bias not addressed in the other domains in the tool.	Was the study apparently free of other problems that could put it at a high risk of bais?

2.4.4 Data synthesis/analysis of data

2.4.4.1 Measure of treatment effects

Risk ratios were calculated for dichotomous outcomes and mean difference (MD) for continuous outcomes. Results are presented with 95% confidence intervals (CI). Continuous outcomes reported in terms of medians and ranges are presented in a table (see Chapter 3).

2.4.4.2 Unit of analysis issues

The level at which randomisation occurred was taken into account. The following was considered in each study: Whether groups of individuals were randomised together to the same intervention (cluster-randomised trials) or whether there were multiple observations for the same outcome. However, there were no cluster-randomised trials included in this systematic review. Cross-over trials were excluded as this methodology is not suitable for evaluating an intervention that must be given at a specific point in time. In cases where a multi-arm study contributed multiple comparisons in a meta-analysis, treatment groups were either combined or the shared group was split as appropriate. This was done to ensure that 'double counting' was avoided.

2.4.4.3 Dealing with missing data

The original authors of included studies were contacted (via electronic mail by the primary investigator) where data was found to be missing. No method of imputing missing data was used. The impact that the missing data had on the review will be addressed in the discussion section (see Chapter 4). Intention-to-treat analysis was performed to estimate the intervention effect if there was no missing data. In the case of missing data, an available case analysis was carried out.

2.4.4.4 Assessment of heterogeneity

Statistical heterogeneity was assessed by applying the Chi-squared test (Chi^2 test) where a p-value < 0.10 was considered statistically significant, and also by I^2 statistics where a value of greater than 50% represents substantial heterogeneity.[218] The Chi^2 test assesses the statistical significance of heterogeneity and the I^2 statistics quantifies the percentage of the variability in effect estimates that is due to heterogeneity rather than chance.[218]

2.4.4.5 Assessment of reporting biases

Reporting biases in general include publication, time lag, multiple publication, location, citation, language and outcome reporting biases. The authors planned to include funnel plots would there have been any evidence of publication bias (if there were more than 10 studies included in the meta-analysis). As a rule of thumb, tests for funnel plot asymmetry should be used only when there are at least 10 studies included in the analysis, because when there are fewer studies the power of the test is too low to distinguish chance from real asymmetry. [219]

2.4.4.6 Data synthesis

The investigator was responsible for the preparation of the data for statistical analysis, and a statistician trained in systematic reviews performed the actual data synthesis. RevMan 5.3 was used to perform data synthesis. Analyses were done separately for different comparisons. A meta-analysis was only conducted if there were sufficient data and studies reporting similar comparisons for the same outcome measures.

Where substantial methodological or statistical heterogeneity existed, study results were not pooled in a meta-analysis and reported separately. A meta-analysis was used to establish whether there was evidence of an effect; it estimated the size of the effect and the uncertainties surrounding that size; and investigated whether the effect was consistent across studies. A random effects model of meta-analysis was used in the presence of moderate heterogeneity of treatment effects and a fixed effect model in the absence of heterogeneity.

2.4.4.7 Subgroup analysis and investigation of heterogeneity

Subgroup analysis was only conducted in the presence of statistical heterogeneity. The following factors were considered for subgroup analysis: dose and duration of the experimental intervention, study quality (blinding or not), studies that used a placebo treatment or not, macronutrient profile of the experimental intervention, type of surgery (abdominal surgery or not), type of anaesthesia (general, neuraxial or combined), anaesthetic risk (high or low), funding of the study, and between the different control interventions. However, due to insufficient data, most of these factors could not be assessed in subgroup analyses. RevMan 5.3 was used to perform the subgroup analysis.

2.4.4.8 Sensitivity analysis

Providing there were sufficient trials per meta-analysis, a sensitivity analysis to assess the influence of potential factors on the findings were performed. We performed a sensitivity analysis in cases where there was a clear outlying study (or studies) by excluding them from the meta-analysis.

2.5 ETHICS AND LEGAL ASPECTS

The research protocol for the study was approved (S12/06/152) by the Health Research Ethics Committee, Faculty of Medicine and Health Sciences, Stellenbosch University (Appendix 6.4). The protocol was also registered at the Prospective Register of Ongoing Systematic Reviews (PROSPERO) to receive a unique identifying number (CRD42012002313) to record the existence of the protocol and systematic review (Appendix 6.5).

CHAPTER 3: RESULTS

3.2 DESCRIPTION OF STUDIES[8]

3.2.1 Results of the search

The initial search (phase 1) produced 2140 citations, of which 266 were selected by the investigator as potentially relevant citations (Table 3.1). These citations were selected by applying the relevant resources and search strings (see Chapter 2). Additional citations were added as obtained from ongoing trials (n = 9), unpublished trials (n = 2), and article reference lists and personal files (n = 30). All citations were corrected for duplicates/multiple citations (n = 162), providing a total of 145 citations for further assessment in phase 2 (Appendix 6.6).

Table 3.1: Summary of databases searched (phase 1)

Searches	Period Searched	Total Citations	Included Citations
PUBMED/MEDLINE	1950 – 20/05/2015	34	28
COCHRANE (INLUCING CLINICAL TRIALS/CENTRAL, REVIEWS/CDSR, ABSTRACTS/DARE)	1800 – 20/05/2015	58	20
EBSCO HOST (INCLUDING CINAHL, ACADEMIC SEARCH PREMIER, CAB ABSRACTS, AFRICA WIDE)	1865 – 20/05/2015	155	30
ISI WEB OF KNOWLEDGE	1987 – 20/05/2015	98	53
SCOPUS ABSTRACTS	1996 – 20/05/2015	257	56
PROQUEST MEDICAL LIBRARY	1986 – 20/05/2015	108	21
SCIENCE DIRECT	1823 – 20/05/2015	44	9
SPRINGERLINK	1842 – 20/05/2015	201	15
GOOGLE SCHOLAR	2004 – 20/05/2015	1185	34
SABINET	2002 – 20/05/2015	0	0
Sub-Total		2140	266
Ongoing trials			(+) 9
Unpublished trials			(+) 2
Reference lists/Personal files			(+) 30
Sub-Total			307
Correction for duplicates/multiple citations			(-) 162
Phase 1 TOTAL Citations			145

[8] Please note that in chapter 3 the referencing of the included studies will be as per the unique code given in Addendum 6.10.

The 145 citations were independently reviewed by the investigator and the reviewer using pre-specified inclusion and exclusion criteria. Of the 145 citations identified, 59 were excluded (Appendix 6.7). The main reasons for exclusion in phase 2 are summarised in Figure 3.1. Only English language studies were included, but all potentially eligible studies in non-English languages were documented to include in future systematic reviews (see Chapter 5). Eighty-six citations remained for in-depth assessment in phase 3.

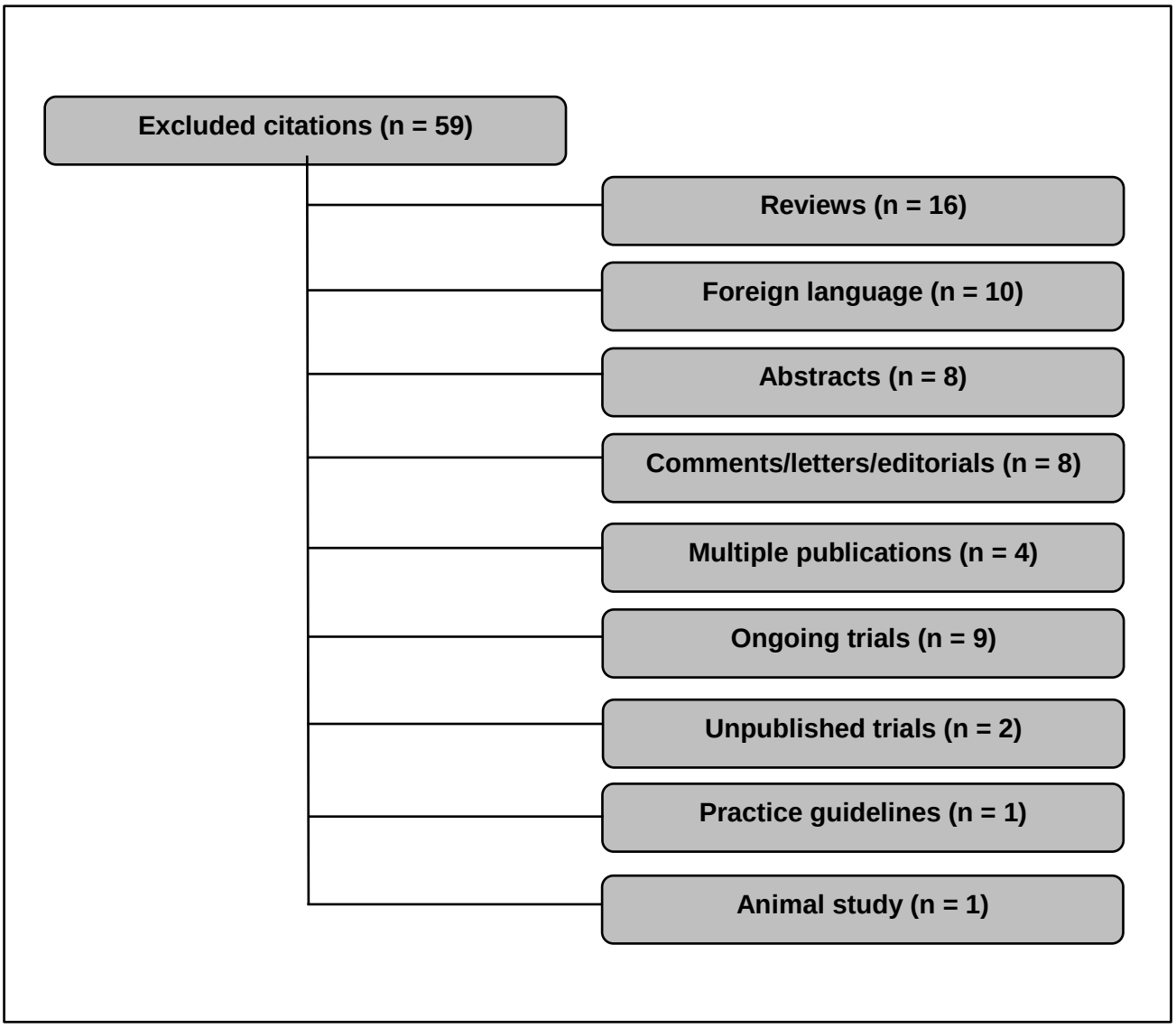


Figure 3.1: Reasons for exclusion of citations (phase 2)

The 86 citations were independently reviewed by the investigator and the reviewer using pre-designed sheets to evaluate eligibility (Appendix 6.8). Another 62 publications were excluded (Appendix 6.9) and 24 were included in this systematic review (Appendix 6.10). The main reasons for study exclusion at this stage included study design and incorrect dosage (see Figure 3.2 for summary). The Prisma flow diagramme provides a diagrammatic representation of the full process followed in identifying and selecting studies (Figure 3.3).

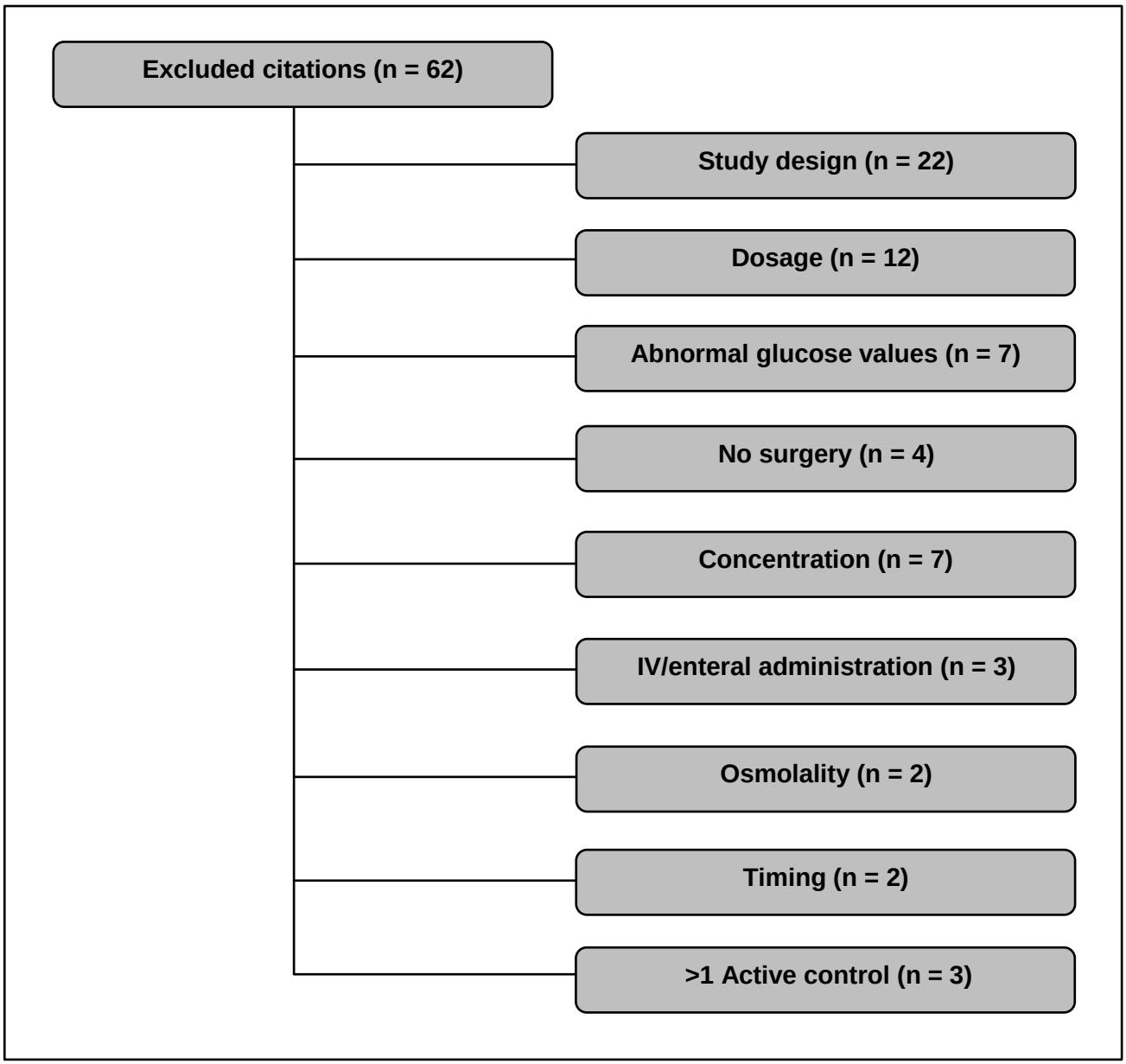


Figure 3.2: Reasons for exclusion of citations (phase 3)

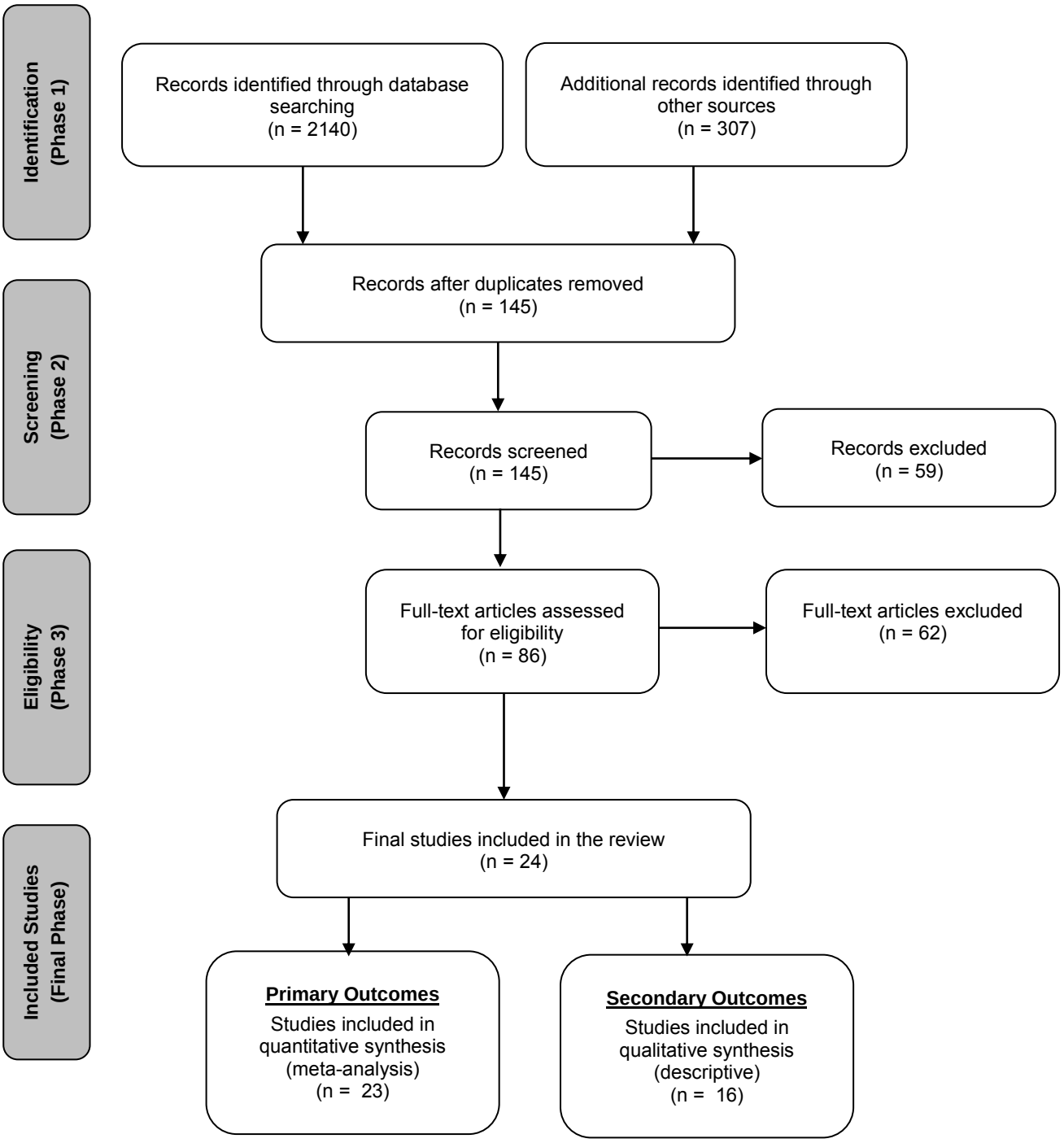


Figure 3.3: Study identification and selection (Phase 1 to 3)

3.2.2 General description of included studies

Twenty-four trials met the criteria for inclusion in this review, and were published between 1995 and 2014. The trials were conducted in a number of different countries: Canada (1 trial; 38 participants), [A74] Croatia (1 trial; 70 participants), [A15] China (1 trial; 48 participants), [A64] Czech Republic (2 trials; 299 participants), [A68, A75] Denmark (1 trial; 86 participants), [A115] Finland (2 trials; 311 participants), [A71, A90] Netherlands (1 trial; 19 participants), [A94] New Zealand (1 trial; 142 participants), [A66] Sweden (7 trials; 526 participants), [A3, A19, A105, A110, A121, A125, A131] Turkey (5 trials; 264 participants) [A6, A14, A16, A52, A84] and the United Kingdom (2 trials; 100 participants). [A101, A106] Figure 3.4

gives a representation of the number of included participants per country. The majority of the trials included were from developed and emerging countries (not classified as developing countries). [A3, A15, A19, A66, A68, A71, A74, A75, A90, A94, A101, A105, A106, A110, A115, A121, A125, A131]

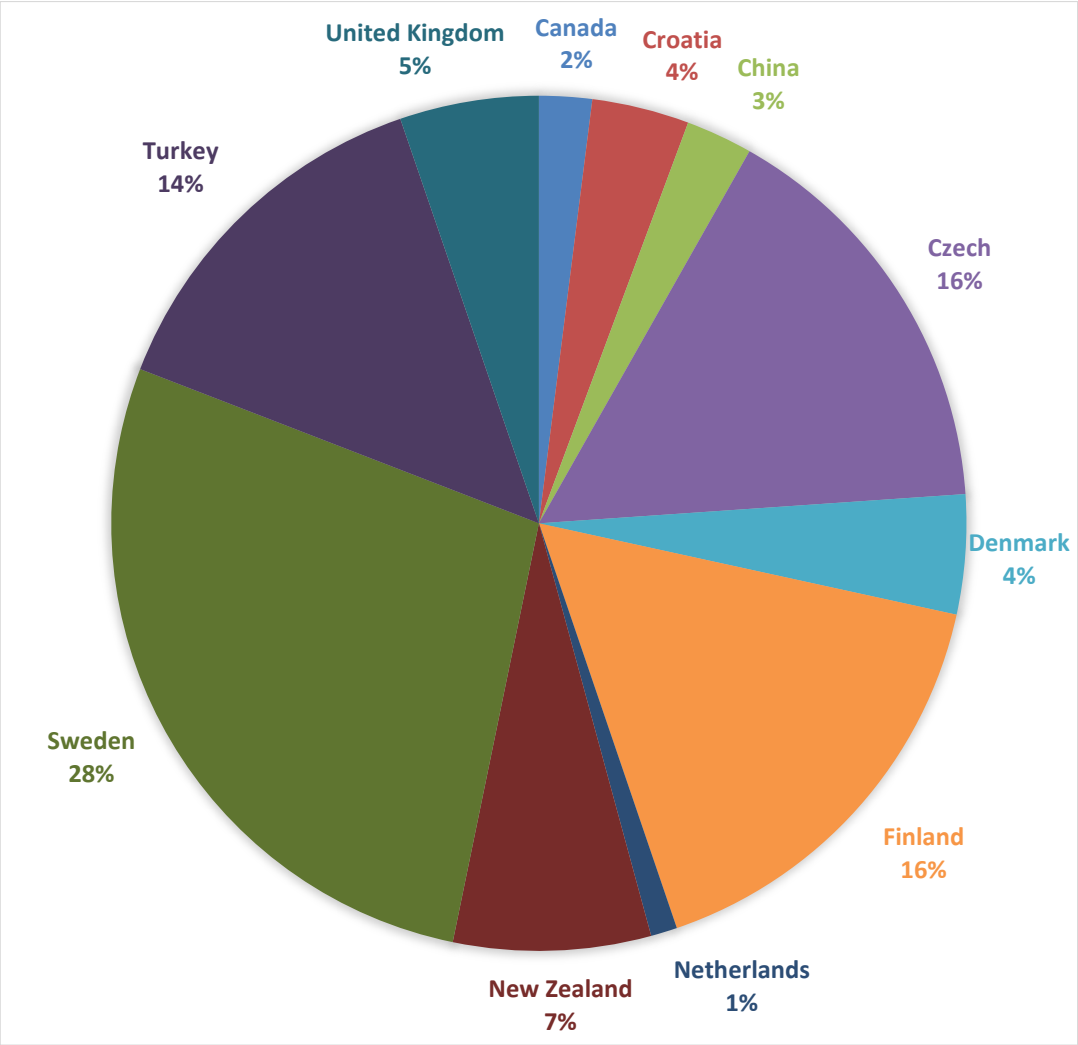


Figure 3.4: Participant distribution per country

In total, these trials included 1903 participants; eleven of the trials included less than 50 participants, [A3, A14, A19, A52, A64, A74, A94, A101, A110, A125, A131] six of the trials included 50 to 100 participants, [A6, A15, A16, A84, A106, A115] three trials included 100 to 150 participants, [A66, A75, A90] two trials included 150 to 200 participants [A68, A105] and two trials included more than 200 participants (Figure 3.5). [A71, A121] Five trials did not report on the gender of the participants, [A6,A14,A19,A68,A101] and in the remaining trials, more female participants (56%) were recruited than male participants (44%). All participants included were 18 years or older with the majority of participants being older than 50 years.

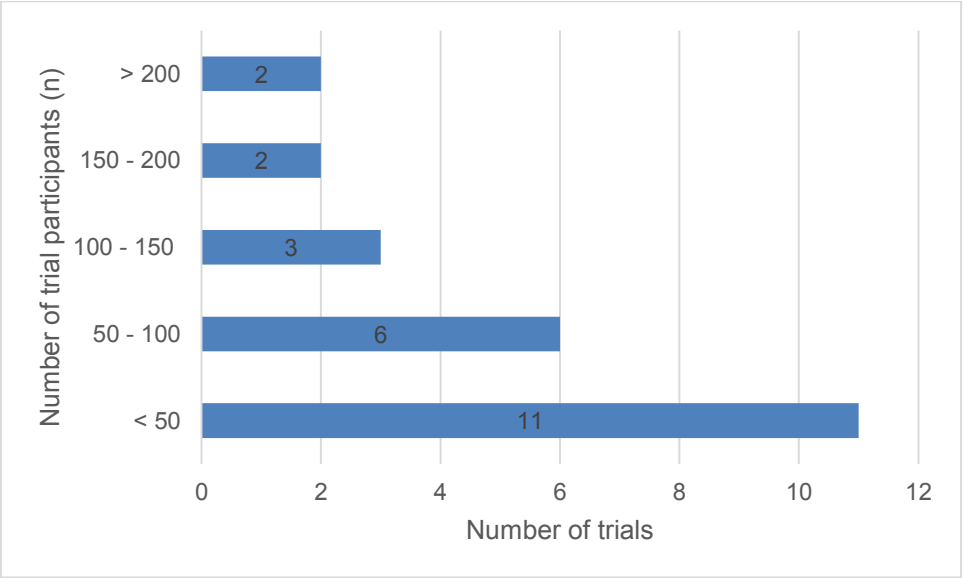


Figure 3.5: The number of trials by number of included participants

High risk anaesthetic patients were not excluded from this systematic review. However, most trials included were based on healthy participants classified by the American Society of Anesthesiologists physical status classification system (ASA score)[9] as ASA I – II (1240 participants), [A6, A14, A15, A16, A52, A64, A68, A75, A84, A101, A105, A110, A115, A121] except for four trials recruiting ASA I – III participants (413 participants) [A3, A19, A66, A71] and one trial recruiting ASA I – IV participants (101 participants) [A90] with the rest of the trials not reporting on the ASA scores. Six trials did not indicate the BMI of the participants [A6, A14, A15, A16, A19, A101] but the rest of the included participants had a BMI below 30 kg/m^2. All participants with diabetes mellitus type 1 and type 2, patients with abnormal blood glucose values prior to surgery, and patients with insulin resistance syndrome were excluded from this review. All trials reported that participants were undergoing elective surgery. Sixteen trials included participants that went for abdominal surgery (1605 participants) [A14, A15, A16, A52, A64, A66, A68, A71, A75, A84, A101, A105, A106, A115, A121, A131] with the remaining going for orthopaedic (109 participants) [A3, A19, A94, A110, A125] and other surgeries including cardiac, urology and spinal surgery (189 participants) [Figure 3.6]. [A6, A74, A90] Where reported, the mean duration of abdominal and orthopaedic surgery seemed to be shorter than for cardiac surgery. [A3, A19, A52, A64, A66, A68, A71, A74, A75, A90, A94, A105, A110, A115, A125] Most participants received general anaesthesia (n = 995) [A14, A16, A64, A68, A71, A84, A90, A101, A105, A106] with the rest receiving spinal (n = 83), [A19, A52] epidural (n = 29), [A110, A125] or a combination of general and neuraxial anaesthesia (n = 785) [Figure 3.7]. [A3, A66, A74, A75, A94, A115, A121, A131]

[9] ASA score is the subjective assessment of a patient's physical health that is based on five classes (I – V): I = patient is completely healthy and fit, II = patient has mild systemic disease, III = patient has severe systemic disease that is not incapacitating, IV = patient has incapacitating disease that is a constant threat to life, V = moribund patient who is not expected to live 24 hours with or without surgery.[220]

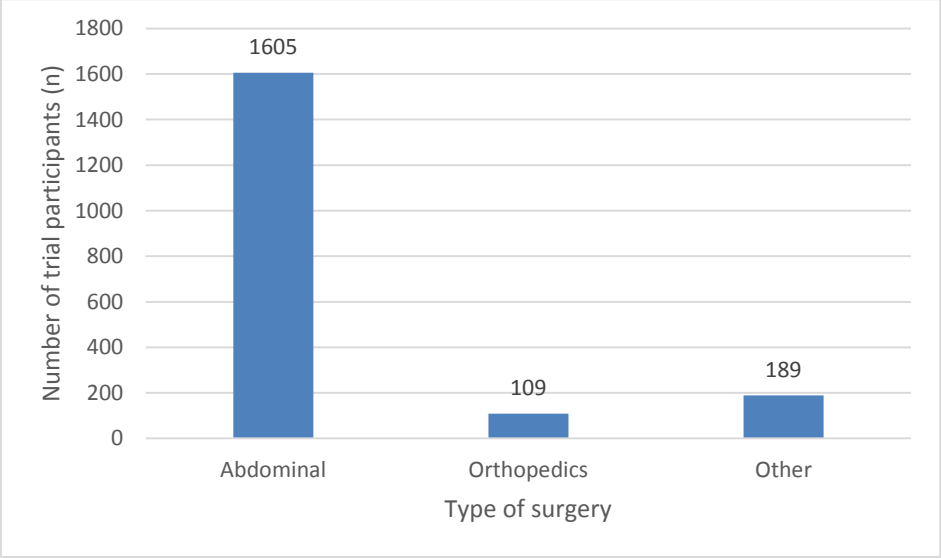


Figure 3.6: Type of surgery by number of included participants

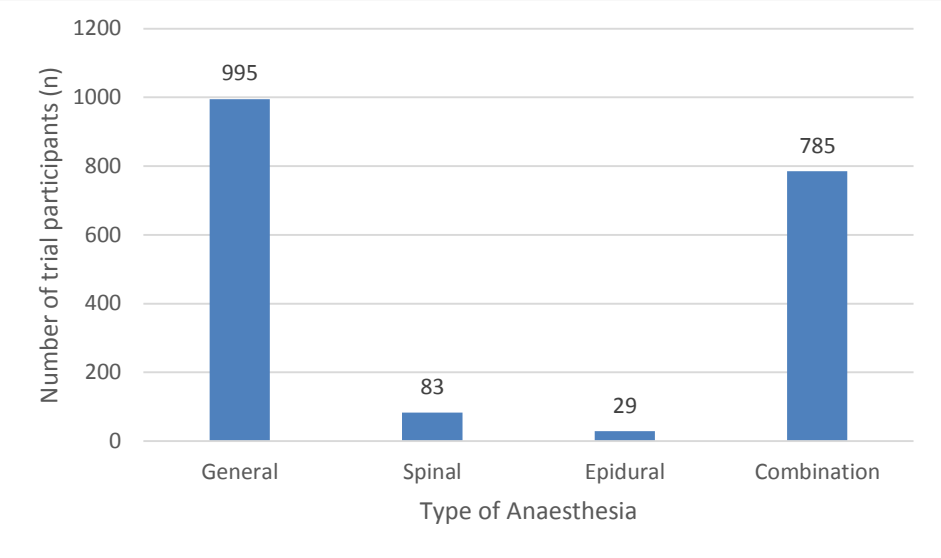


Figure 3.7: Type of anaesthesia by number of included participants

All participants in the experimental group (n = 788) received 400 ml of a 12% CHO-containing beverage at least 2 hours before induction of anaesthesia – most participants (n = 583) also received 400 to 800 ml of the beverage the evening before surgery. [A3, A6, A14, A15, A16, A19, A52, A66, A68, A74, A84, A101, A105, A106, A110, A115, A121, A125] The majority of the trials used Nutricia Preop® as the oral CHO beverage (one trial used Nutricia AS that has the same nutritional analysis as Nutricia Preop®), [A131] except one trial that used Vitajoule as the oral CHO beverage. [A101] The actual time from ingestion of beverage to induction of anaesthesia and to the start of the surgery was unclear in most trials; however, it was stipulated that the beverage was consumed at least 2 hours before the induction of anaesthesia and the start of surgery. A placebo was used as an inactive control in 11 of the trials (310 participants) consisting of water, [A3, A101, A131] sweetened water, [A110, A125] flavoured water, [A64, A66, A105, A115, A121] and fluid and electrolytes. [A106] All the trials using standard fasting as an inactive control fasted their patients from the evening before surgery (673 participants). [A6, A14, A15,

[A16, A19, A52, A64, A68, A71, A74, A75, A84, A90, A94, A101, A105, A121] Two trials included IV CHO administration as an active control (132 participants). [A68, A71] Even though some of the ERAS elements were used in most of the trials, only one trial indicated that an ERAS protocol was followed.[A75] The details of the included trials are summarised in Appendix 6.11 and Appendix 6.12, and other trial characteristics are discussed under the relevant results sections.

3.3 RISK OF BIAS IN INCLUDED STUDIES AND METHODOLOGICAL QUALITY

The Cochrane Risk of Bias assessment tool was completed for each of the included trials to assess the methodological quality and to enable data entry into RevMan 5.3 (Appendix 6.13). The full details of the methodological quality of the trials are provided in Appendix 6.14.

The quality assessments of the trial methodology were reported as a summary (Figure 3.8) and a graph (Figure 3.9). All trials included in this review were RCTs, and the sequence generation was not indicative of bias. More than half of the trials (16 of 24) [A3, A6, A14, A15, A16, A19, A66, A68, A71, A75, A90, A94, A101, A110, A115, A125] confirmed allocation concealment with the remaining trials not clearly reporting on the method of concealment. Eleven trials reported to be double blinded; [A3, A15, A19, A64, A66, A105, A106, A110, A115, A121, A125] seven trials were single blinded; [A14, A16, A74, A84, A90, A94, A101] one trial did not blind the participants or personnel; [A75] four trials did not indicate the blinding of participants and personnel. [A6, A52, A68, A131] In the majority of the trials it was unclear whether the outcomes were blinded except for four trials were it was clearly stated that the outcomes were blinded. [A3, A64, A66, A71] Seventeen of the 24 trials had incomplete outcome data, [A3, A6, A14, A16, A64, A66, A68, A71, A74, A75, A90, A94, A101, A105, A110, A121, A131] indicating a high risk of bias for this domain. Intention to treat analysis was not reported in any trial**.** There was no clear evidence of selective reporting. High risk of bias was detected in the 'other' category which included unclear eligibility criteria, uneven baseline comparability, loss to follow-up and funding of trials. The methodological graph (Figure 3.9) indicates no risk of bias with regards to sequence generation and low risk with regards to allocation concealment (selection bias). Uncertainty (unclear risk of bias) was found in especially the blinding of outcome assessment (detection bias) and the selective reporting (reporting bias) categories. High risk of bias was detected with blinding of participants and personnel (performance bias), incomplete outcome data (attrition bias) as well as other bias (including funding).

The GRADE approach defines the quality of evidence for each outcome reported in a systematic review as the extent to which one can be confident that an estimate of effect is close to the quantity of specific interest. GRADE assessment was not completed for this review as it is a relative new initiative from the Cochrane Collaboration and this is not a Cochrane Review. Quality was not used to weigh the trials in the meta-analyses of this review but will be commented on, as appropriate, within this and the discussion chapter. Furthermore, the GRADE assessment will be incorporated into the systematic review before publishing the results.

Figure 3.8: Methodological quality summary – judgement about each methodological quality item for each included study

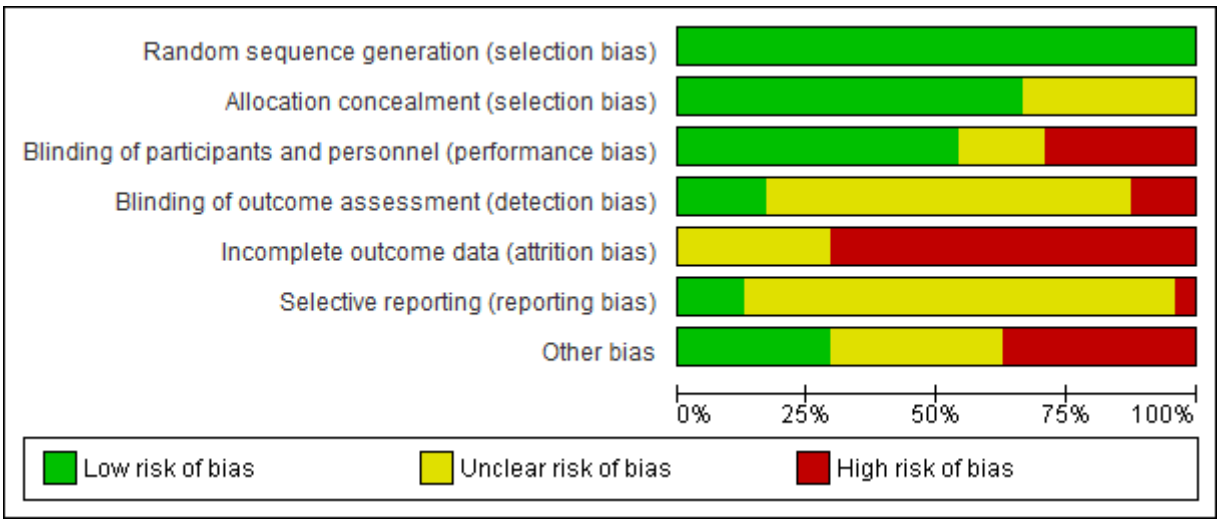


Figure 3.9: Methodological quality graph – judgement about each methodological quality item presented as percentages across all included studies

3.4 EFFECTS OF INTERVENTION

The primary and secondary outcomes addressed in this systematic review are summarised in Table 3.2. The primary outcomes, as stated, were reported by 23 of the trials (n = 1841), with 16 trials (n = 1449) reporting on the patients' psychosomatic experience with reference to the secondary outcomes. The outcomes addressed per trial are summarised in Appendix 6.15. The results of the primary outcomes will be presented per comparison in Chapter 3 but will be discussed per time interval in Chapter 4 (see Appendix 6.16 for a detailed explanation). The results of the secondary outcomes will be presented using a descriptive approach. Please note that four comparison groups were investigated per outcome, including:

- comparison 1: oral CHO versus inactive control (fasting + placebo) *[referred to as the inactive control]*
- comparison 2: oral CHO versus inactive control (fasting) *[referred to as the fasting control]*
- comparison 3: oral CHO versus inactive control (placebo) *[referred to as the placebo control]*
- comparison 4: oral CHO versus active control (intravenous) *[referred to as the active control]*

Table 3.2: Outcomes addressed in the systematic review

PRIMARY OUTCOMES

BIOCHEMISTRY: GLUCOSE (HOMA-IR + QUICKI)*

Comparison 1: Oral CHO versus inactive control

- Baseline
- Before anaesthesia
- Day 0 post-surgery
- Day 1 post-surgery

Comparison 2: Oral CHO versus fasting

- Baseline
- Before anaesthesia
- Day 0 post-surgery
- Day 1 post-surgery

Comparison 3: Oral CHO versus placebo

- Baseline
- Before anaesthesia
- Day 0 post-surgery
- Day 1 post-surgery

Comparison 4: Oral CHO versus active control

- Baseline
- Before anaesthesia
- Day 0 post-surgery
- Day 1 post-surgery

BIOCHEMISTRY: INSULIN (HOMA-IR + QUICKI)*

Comparison 1: Oral CHO versus inactive control

- Baseline
- Before anaesthesia
- Day 0 post-surgery
- Day 1 post-surgery

Comparison 2: Oral CHO versus fasting

- Baseline
- Before anaesthesia
- Day 0 post-surgery
- Day 1 post-surgery

Comparison 3: Oral CHO versus placebo

- Baseline
- Before anaesthesia
- Day 0 post-surgery
- Day 1 post-surgery

Comparison 4: Oral CHO versus active control

- Baseline
- Before anaesthesia
- Day 0 post-surgery
- Day 1 post-surgery

BIOCHEMISTRY: INSULIN RESISTANCE*

- HOMA-IR
- QUICKI
- HEC

PROTEIN STATUS: TOTAL BODY PROTEIN

Comparison 1: Oral CHO versus inactive control

- Baseline
- Day 3 post-surgery
- Day 7 post-surgery
- Day 28 post-surgery

Comparison 2: Oral CHO versus fasting

- Baseline
- Day 3 post-surgery

- Day 7 post-surgery
- Day 28 post-surgery

Comparison 3: Oral CHO versus placebo

- Baseline
- Day 3 post-surgery
- Day 7 post-surgery
- Day 28 post-surgery

Comparison 4: Oral CHO versus active control

- Baseline
- Day 3 post-surgery
- Day 7 post-surgery
- Day 28 post-surgery

PROTEIN STATUS: MUSCLE STRENGTH

Comparison 1: Oral CHO versus inactive control

- Baseline
- Day 1 post-surgery
- Day 3 post- surgery
- Day 7 post-surgery
- Day 28 post-surgery

Comparison 2: Oral CHO versus fasting

- Baseline
- Day 1 post-surgery
- Day 3 post- surgery
- Day 7 post-surgery
- Day 28 post-surgery

Comparison 3: Oral CHO versus placebo

- Baseline
- Day 1 post-surgery
- Day 3 post- surgery
- Day 7 post-surgery
- Day 28 post-surgery

Comparison 4: Oral CHO versus active control

- Baseline
- Day 1 post-surgery
- Day 3 post- surgery
- Day 7 post-surgery
- Day 28 post-surgery

IMMUNE STATUS: C-REATIVE PROTEIN

Comparison 1: Oral CHO versus inactive control

- Baseline
- Before anaesthesia
- Day 1 post-surgery
- Day 3 post-surgery
- Day 7 post-surgery

Comparison 2: Oral CHO versus fasting

- Baseline
- Before anaesthesia
- Day 1 post-surgery
- Day 3 post-surgery
- Day 7 post-surgery

Comparison 3: Oral CHO versus placebo

- Baseline
- Before anaesthesia
- Day 1 post-surgery
- Day 3 post-surgery
- Day 7 post-surgery

Comparison 4: Oral CHO versus active control

- Baseline
- Before anaesthesia
- Day 1 post-surgery

- Day 3 post-surgery
- Day 7 post-surgery

RETURN OF INTESTINAL FUNCTION

- Flatus/stool
- Bowel movement

LENGTH OF STAY: INTENSIVE CARE UNIT

- Intensive care unit
- Hospital
- Fit for discharge

ADVERSE EVENTS

- Regurgitation
- Aspiration
- Morbidity
- Mortality

SECONDARY OUTCOMES
preoperative versus postoperative versus perioperative; intragroup versus intergroup

THIRST

HUNGER

NAUSEA

VOMITING

ANXIETY

PAIN

FATIGUE

WEAKNESS

TIREDNESS

MALAISE

***** The glucose and insulin results for the trials using the homeostatic model assessment (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI) method were combined when analysing the glucose and insulin results respectively; whereas the results of the trials using the hyperinsulinaemic-euglycaemic clamp (HEC) method will be presented separately in the insulin resistance section. The glucose and insulin results of the trials using the HEC method to measure insulin resistance cannot be combined with the trials using the HOMA-IR and QUICKI methods since the HEC method is not physiologically the same as the other methods due to fact that insulin is infused to create a hyperinsulinaemic state whilst glucose is concomitantly infused to maintain euglycaemia. The HOMA-IR and QUICKI methods are based on physiological levels of glucose and insulin. Therefore, the biochemical results were grouped as follows:

- Glucose (HOMA-IR and QUICKI)
- Glucose (HEC) – will be presented in a table in the insulin resistance section
- Insulin (HOMA-IR and QUICKI)
- Insulin (HEC) – will be presented in a table in the insulin resistance section
- Insulin resistance (HOMA-IR)
- Insulin resistance (QUICKI)
- Insulin resistance (HEC)

** Day 0 Postoperative = within 24 hours postoperative; Day 1 Postoperative = 24 to 48 hours postoperative

3.4.1 Primary outcomes

3.4.1.1 Glucose (HOMA-IR and QUICKI)

There were eight trials (864 participants) assessing glucose (HOMA-IR and QUICKI) as an outcome.[A52,A66,A68,A71,A74,A84,A90,A106] The unit of measurement for glucose is mmol/l. The results that were pooled in meta-analyses for glucose (HOMA-IR and QUICKI) are summarised in Table 3.3. Note that Table 3.3 only provides results for the pooled data. The results of the trials reporting the outcomes as median (interquartile range) are presented in Appendix 6.17. There were five trials with missing or no data and could, therefore, not be included.[A6,A16,A64,A121,A131]

Table 3.3: Results of trials evaluating glucose (HOMA-IR and QUICKI) that were pooled in a meta-analysis

COMPARISON / TIME INTERVAL	NUMBER OF STUDIES*	PARTICIPANTS	MEAN DIFFERENCE	p	HETEROGENEITY	
					Chi^2	I^2
COMPARISON 1: Oral CHO versus inactive control (fasting + placebo)						
Glucose at baseline	5	408	-0.03 [-0.15, 0.09]	0.62	6.68	40%
Glucose before anaesthesia	4	456	0.34 [0.01, 0.68]	0.04**	6.37	53%
Glucose at day 0 post surgery	1	101	0.10 [-0.49, 0.69]	0.74	Not applicable	
Glucose at day 1 post surgery	2	207	0.32 [-0.20, 0.85]	0.23	0.86	0%
COMPARISON 2: Oral CHO versus fasting						
Glucose at baseline	3	287	-0.09 [-0.20, 0.02]	0.09	1.84	0%
Glucose before anaesthesia	3	314	0.51 [0.24, 0.77]	0.0002**	0.99	0%
Glucose at day 0 post surgery	1	101	0.10 [-0.49, 0.69]	0.74	Not applicable	
Glucose at day 1 post surgery	Results reported as median (interquartile range) *					
COMPARISON 3: Oral CHO versus placebo						
Glucose at baseline	2	207	-0.13 [-0.38, 0.13]	0.33	0.28	0%
Glucose before anaesthesia	1	142	-0.10 [-0.54, 0.34]	0.65	Not applicable	
Glucose at day 0 post surgery	Not reported by any of the trials					
Glucose at day 1 post surgery	2	207	0.32 [-0.20, 0.85]	0.23	0.86	0%
COMPARISON 4: Oral CHO versus active control (IV CHO)						
Glucose at baseline	1	137	0.10 [-0.28, 0.48]	0.60	Not applicable	
Glucose before anaesthesia	1	137	-0.20 [-0.70, 0.30]	0.44	Not applicable	
Glucose at day 0 post surgery	Results reported as median (interquartile range) *					
Glucose at day 1 post surgery	Results reported as median (interquartile range) *					

* see Appendix 6.17 for results reported as median (interquartile range); all results showed no statistically significant difference between groups

** Statistical significant result ($p < 0.05$)

CHO = oral carbohydrate treatment group; IV = intravenous; p = p-value

3.4.1.1.1 Comparison 1: Oral CHO versus inactive control (fasting + placebo)

a. Glucose (HOMA-IR and QUICKI) at baseline

Eight trials reported results on glucose at baseline. [A52,A66,A68,A71,A74,A84,A90,A106] Results from six trials were pooled in a meta-analysis but the results cannot be reported because of significant heterogeneity between the trials (Chi^2 = 11.56, df = 5, p = 0.04, I^2 = 57%). An investigation of the source of heterogeneity was carried out using both subgroup analysis and sensitivity analysis. Heterogeneity remained significant after subgroup analyses with respect to dose and duration of experimental intervention, type of surgery, type of anaesthesia and anaesthetic risk. Since the forest plot clearly shows that the trial by Yagci 2008 had outlying results compared to all the other trial results, a sensitivity analysis was carried out to determine the effect of removing this one trial from the meta-analysis on heterogeneity.[A84] After removing this trial from the meta-analysis, heterogeneity between studies was no longer significant (Chi^2 = 2.19, df = 4, p = 0.70, I^2 = 40%, Appendix 6.18 Analysis 1.1) but there was no significant difference in glucose levels at baseline between the oral CHO and the inactive control (fasting or placebo) groups (MD -0.10, 95%CI: -0.20 to 0.00, 495 participants, 5 trials, Appendix 6.18 Analysis 1.1). The results of Yagci 2008 showed a significantly higher glucose level at baseline in the oral CHO group compared to the fasting group (MD 0.67, 95%CI: 0.19 to 1.15, 70 participants, 1 trial, Appendix 6.18 Analysis 1.1).[A84] Kaska 2010 and Tran 2009 reported results as median (interquartile range) but there was no significant difference in glucose at baseline between the oral CHO and fasting groups in the two studies (Appendix 6.17).[A68,A74]

b. Glucose (HOMA-IR and QUICKI) before anaesthesia

Four trials reported results on glucose before anaesthesia and their meta-analysis showed significantly (p = 0.04) higher glucose levels in the oral CHO group compared to the fasting or placebo groups (MD 0.34, 95% CI: 0.01 to 0.68, 456 participants, 4 trials, Appendix 6.18 Analysis 1.2).[A66,A71,A84,A90] No significant heterogeneity was detected between the trials (Chi^2 = 6.37, df = 3, p = 0.10, I^2 = 53%, Appendix 6.18 Analysis 1.2). Two trials had missing data and could not be included.[A16,A52]

c. Glucose (HOMA-IR and QUICKI) at day 0 postoperative

Three trials reported results on glucose at day 0 post surgery.[A68,A74,A90] Results from Järvelä 2008 showed no significant difference in glucose levels between the oral CHO and fasting groups (MD 0.10, 95%CI: -0.49 to 0.69, 101 participants, 1 trial, Appendix 6.18 Analysis 1.3).[A90] Kaska 2010 and Tran 2009 presented results as median (interquartile range) and the authors reported a significantly higher glucose level in the oral CHO group compared to the fasting group in the two trials (Appendix 6.17).[A68,A74] One trial had missing data and could not be included.[A52]

d. Glucose (HOMA-IR and QUICKI) at day 1 postoperative

Three trials reported results on glucose at day 1 post surgery.[A66,A68,A106] Results from two trials were pooled in a meta-analysis but there was no significant difference in glucose levels between the oral CHO and placebo groups (MD 0.32, 95%CI: -0.20 to 0.85, 207 participants, 2 trials, Appendix 6.18 Analysis 1.4).[A66,A106] There was no significant heterogeneity detected between the trials (Chi^2 = 0.86, df = 1, p = 0.35, I^2 = 0%, Appendix 6.18 Analysis 1.4). Kaska 2010 reported results as median (interquartile range) but there was no significant difference between the oral CHO and fasting groups (Appendix 6.17).[A68]

3.4.1.1.2 Comparison 2: Oral CHO versus fasting

a. Glucose (HOMA-IR and QUICKI) at baseline

Six trials reported results on glucose at baseline.[A52,A66,A71,A74,A84,A90] Results from four trials were pooled in a meta-analysis but the results cannot be reported because of significant heterogeneity between the trials (Chi^2 = 11.01, df = 3, p = 0.01, I^2 = 73%).[A52,A71,A84,A90] An investigation of the source of heterogeneity was carried out using both subgroup analysis and sensitivity analysis. Heterogeneity remained significant after subgroup analyses with respect to dose and duration of experimental intervention, type of surgery, type of anaesthesia and anaesthetic risk. Since the forest plot clearly shows that the trial by Yagci 2008 had outlying results compared to the other three trial results, a sensitivity analysis was carried out to determine the effect of removing this trial from the meta-analysis on heterogeneity.[A84] After removing this trial from the meta-analysis, heterogeneity between studies was no longer significant (Chi^2 = 1.84, df = 2, p = 0.40, I^2 = 0%, Appendix 3.18 Analysis 2.1) but there was no significant difference in glucose levels at baseline between the oral CHO and the inactive control (fasting or placebo) groups (MD -0.09, 95%CI: -0.20 to 0.02, 287 participants, 3 trials, Appendix 3.16 Analysis 2.1). The results of Yagci 2008 showed a significantly higher glucose level at baseline in the oral CHO group compared to the fasting group (MD 0.67, 95%CI: 0.19 to 1.15, 70 participants, 1 trial, Appendix 3.18 Analysis 2.1). Mathur 2010 and Tran 2009 reported results as median (interquartile range) but there was no significant difference between the oral CHO and fasting groups in the two trials (Appendix 3.17).[A66,A74]

b. Glucose (HOMA-IR and QUICKI) before anaesthesia

Three trials reported results on glucose before anaesthesia and their results were pooled in a meta-analysis which showed significantly higher (p = 0.0002) glucose levels in the oral CHO group compared to the fasting group (MD 0.51, 95%CI: 0.24 to 0.77, 314 participants, 3 trials, Appendix 3.18 Analysis 2.2).[A71,A84, A90] No significant heterogeneity was detected between the trials (Chi^2 = 0.99, df = 2, p = 0.61, I^2 = 0%, Appendix 3.18 Analysis 2.2). Two trials had missing data and could not be included.[A16,A52]

c. Glucose (HOMA-IR and QUICKI) at day 0 postoperative

Three trials reported results on glucose at Day 0 post surgery.[A68,A74,A90] Results from Järvelä 2008 showed no significant difference in glucose levels between the oral CHO and fasting groups (MD 0.10, 95%CI: -0.49 to 0.69, 101 participants, 1 trial, Appendix 3.18 Analysis 2.3).[A90] Kaska 2010 and Tran 2009 reported results as median (interquartile range) and there was a significantly higher glucose level in the oral CHO group compared to the fasting group in the two trials (Appendix 3.17).[A68,A74] One trial had missing data and could not be included.[A52]

d. Glucose (HOMA-IR and QUICKI) at day 1 postoperative

One trial reported results as median (interquartile range) but there was no significant difference between the oral CHO and fasting groups (Appendix 3.17).[A68]

3.4.1.1.3 Comparison 3: Oral CHO versus placebo

a. Glucose (HOMA-IR and QUICKI) at baseline

Results from two trials were pooled in a meta-analysis but there was no significant difference in glucose levels at baseline between the oral CHO and placebo groups (MD -0.13, 95%CI: -0.38 to 0.13, 207 participants, 2 trials, Appendix 3.18 Analysis 3.1).[A66,A106] No significant heterogeneity was detected between the trials ($Chi^2 = 0.28$, df = 1, p = 0.59, $I^2 = 0\%$, Appendix 3.18 Analysis 3.1).

b. Glucose (HOMA-IR and QUICKI) before anaesthesia

Results from one trial showed no significant difference in glucose levels before anaesthesia between the oral CHO and the placebo groups (MD -0.10, 95%CI: -0.54 to 0.34, 142 participants, 1 trial, Appendix 3.18 Analysis 3.2).[A66]

c. Glucose (HOMA-IR and QUICKI) at day 0 postoperative

This outcome was not reported by any of the trials assessing this comparison.

d. Glucose (HOMA-IR and QUICKI) at day 1 postoperative

Results from two trials were pooled in a meta-analysis but there was no significant difference in glucose levels at Day 1 post surgery between the oral CHO and placebo groups (MD 0.32, 95%CI: -0.20 to 0.85, 207 participants, 2 trials, Appendix 3.18 Analysis 3.3).[A66,A106] There was no significant heterogeneity detected between the trials ($Chi^2 = 0.86$, df = 1, p = 0.35, $I^2 = 0\%$, Appendix 3.18 Analysis 3.3).

3.4.1.1.4 Comparison 4: Oral CHO versus active control

a. Glucose (HOMA-IR and QUICKI) at baseline

Two trials reported results on glucose at baseline.[A68,A71] Results from Helminen 2009 showed no significant difference in glucose levels between the oral CHO and IV CHO groups (MD 0.10, 95%CI: -0.28 to 0.0.48, 137 participants, 1 trial, Appendix 3.18 Analysis 4.1).[A71] Kaska 2010 reported results for glucose at baseline as median (interquartile range) but there was no significant difference between the oral CHO and IV CHO groups (Appendix 3.17).[A68]

b. Glucose (HOMA-IR and QUICKI) before anaesthesia

Helminen 2009 showed no significant difference in glucose levels before anaesthesia between the oral CHO and IV CHO groups (MD -0.20, 95%CI: -0.70 to 0.30, 137 participants, 1 trial, Appendix 3.18 Analysis 4.2).[A71]

c. Glucose (HOMA-IR and QUICKI) at day 0 postoperative

Kaska 2010 reported results for glucose at day 0 post surgery as median (interquartile range) but there was no significant difference between the oral CHO and IV CHO groups (Appendix 3.17).[A68]

d. Glucose (HOMA-IR and QUICKI) at day 1 postoperative

Kaska 2010 reported results for glucose at Day 1 post surgery as median (interquartile range) but there was no significant difference between the oral CHO and IV CHO groups (Appendix 3.17).[A68]

3.4.1.2 Insulin (HOMA-IR and QUICKI)

There were six trials (569 participants) assessing insulin (HOMA-IR and QUICKI) as an outcome.[A52,A66,A71,A74,A84,A106] The unit of measurement for insulin is microunits/l. The results that were pooled in meta-analyses for glucose (HOMA-IR and QUICKI) are summarised in Table 3.4. Note that Table 3.4 only provides results for the pooled data. The results of the trials reporting the outcomes as median (interquartile range) are presented in Appendix 6.17. There were six trials with missing or no data that could not be included.[A6,A64,A68,A90,A121,A131]

Table 3.4: Results of trials evaluating insulin (HOMA-IR and QUICKI) that were pooled in a meta-analysis

COMPARISON / TIME INTERVAL	NUMBER OF STUDIES *	PARTICIPANTS	MEAN DIFFERENCE	P	HETEROGENEITY	
					Chi^2	I^2
COMPARISON 1: Oral CHO versus inactive control (fasting + placebo)						
Insulin at baseline	2	89	-1.84 [-3.28, -0.40]	0.01**	0.51	0%
Insulin before anaesthesia	2	115	1.64 [-1.53, 4.82]	0.22	1.48	32%
Insulin at day 0 post surgery	Results reported as median (interquartile range)					
Insulin at day 1 post surgery	1	65	7.70 [5.97, 9.43]	< 0.00001**	Not applicable	
COMPARISON 2: Oral CHO versus fasting						
Insulin at baseline	2	89	-1.84 [-3.28, -0.40]	0.01**	0.51	0%
Insulin before anaesthesia	2	115	1.64 [-1.53, 4.82]	0.31	1.48	32%
Insulin at day 0 post surgery	Results reported as median (interquartile range)					
Insulin at day 1 post surgery	Not reported by any of the trials					
COMPARISON 3: Oral CHO versus placebo						
Insulin at baseline	1	65	3.90 [1.17, 6.63]	0.005**	Not applicable	
Insulin before anaesthesia	Results reported as median (interquartile range)*					
Insulin at day 0 post surgery	Not reported by any of the trials					
Insulin at day 1 post surgery	1	65	7.70 [5.97, 9.43]	< 0.00001**	Not applicable	
COMPARISON 4: Oral CHO versus active control (IV CHO)						
Insulin at baseline	1	41	2.90 [-1.39, 7.19]	0.19	Not applicable	
Insulin before anaesthesia	1	41	0.40 [-5.38, 6.18]	0.89	Not applicable	
Insulin at day 0 post surgery	Not reported by any of the trials					
Insulin at day 1 post surgery	Not reported by any of the trials					

* see Appendix 6.17 for results reported as median (interquartile range); all results showed no statistically significant difference between groups

** Statistical significant result ($p < 0.05$)

CHO = oral carbohydrate treatment group; IV = intravenous; p = p-value

3.4.1.2.1 Comparison 1: Oral CHO versus inactive control (fasting + placebo)

a. Insulin (HOMA-IR and QUICKI) at baseline

Six trials reported results on insulin at baseline.[A52,A66,A71,A74,A84,A106] Results from four trials were pooled in a meta-analysis but the results cannot be reported because of significant heterogeneity between the trials ($Chi^2 = 124.64$, df = 3, $p < 0.00001$, $I^2 = 98\%$).[A52,A71,A84,A106] An investigation of the source of heterogeneity was carried out using both subgroup analysis and sensitivity analysis. Heterogeneity remained significant after subgroup analyses with respect to dose and duration of experimental intervention, type of surgery, type of anaesthesia and anaesthetic risk. Since the forest plot clearly shows that two of the trials (Yagci 2008, Yuill 2005) had outlying results compared to the other results, a sensitivity analysis was carried out to determine the effect of removing these two trials from the meta-analysis on heterogeneity.[A84,A106] After removing the two trials from the meta-analysis, heterogeneity between studies was no longer significant ($Chi^2 = 0.51$ df = 1, p = 0.47, $I^2 = 0\%$, Appendix 6.19 Analysis 1.1) and the meta-analysis showed significantly lower insulin levels at baseline in the oral CHO group compared to the inactive control (fasting or placebo) groups (MD -1.84, 95%CI: -3.28 to -0.40, 89 participants, 2 trials, Appendix 6.18 Analysis 1.1).[A52,A71] However, the results of both Yagci 2008 (MD 13.78, 95%CI: 11.43 to 16.13, 70 participants, 1 trial, Appendix 6.19 Analysis 1.1)[A84] and Yuill 2005 (MD 3.90, 95%CI: 1.17 to 6.63, 65 participants, 1 trial, Appendix 6.19 Analysis 1.1)[A106] showed significantly higher insulin levels at baseline in the oral CHO group compared to the inactive (fasting or placebo) groups. Mathur 2010 and Tran 2009 reported results as median (interquartile range) but there was no significant difference between the oral CHO and placebo groups in the two trials (Appendix 6.17).[A66,A74]

b. Insulin (HOMA-IR and QUICKI) before anaesthesia

Three trials reported results on insulin before anaesthesia,[A66,A71,A84] and results from two trials were pooled in a meta-analysis but there was no significant difference in insulin levels between the oral CHO and inactive control groups (MD 1.64, 95%CI: -1.53 to 4.82, 115 participants, 2 trials, Appendix 6.19 Analysis 1.2).[A71,A84] No significant heterogeneity was detected between the trials ($Chi^2 = 1.48$, df = 1, p = 0.22, $I^2 = 32\%$, Appendix 6.19 Analysis 1.2). Mathur 2010 reported results as median (interquartile range) but there was also no significant difference between the oral CHO and placebo groups (Appendix 6.17).[A66]

c. Insulin (HOMA-IR and QUICKI) at day 0 postoperative

Tran 2009 reported results as median (interquartile range) but there was no significant difference between the oral CHO and fasting groups (Appendix 6.17).[A74]

d. Insulin (HOMA-IR and QUICKI) at day 1 postoperative

Two trials reported results on insulin at Day 1 post surgery.[A66,A106] Results from Yuill 2005 showed significantly higher insulin levels in the oral CHO group compared to the placebo group (MD 7.70, 95%CI: 5.97 to 9.43, 65 participants, 1 trial, Appendix 3.19 Analysis 1.3).[A106] Mathur 2010 reported results as median (interquartile range) but there was no significant difference between the oral CHO and placebo groups (Appendix 3.17).[A66]

3.4.1.2.2 Comparison 2: Oral CHO versus fasting

a. Insulin (HOMA-IR and QUICKI) at baseline

Four trials reported results on insulin at baseline,[A52,A71,A74,A84] and three trials were pooled in a meta-analysis but the results cannot be reported because of significant heterogeneity between the trials ($Chi^2 = 123.72$, $df = 2$, $p < 0.00001$, $I^2 = 98\%$).[A52,A71,A84] An investigation of the source of heterogeneity was carried out using both subgroup analysis and sensitivity analysis. Heterogeneity remained significant after subgroup analyses with respect to dose and duration of experimental intervention, type of surgery, type of anaesthesia and anaesthetic risk.

Since the forest plot clearly shows that one of the trials *(*Yagci 2008*)* had outlying results compared to the other two trial results,[A84] a sensitivity analysis was carried out to determine the effect of removing this one trial from the meta-analysis on heterogeneity. After removing this trial from the meta-analysis, heterogeneity between studies was no longer significant ($Chi^2 = 0.51$, $df = 1$, $p = 0.47$, $I^2 = 0\%$, Appendix 6.19 Analysis 2.1) and the meta-analysis showed significantly lower insulin levels at baseline in the oral CHO group compared to the fasting group (MD -1.84, 95%CI: -3.28 to -0.40, 89 participants, 2 trials, Appendix 6.19 Analysis 2.1).[A52,A71] However, the results of Yagci 2008 showed significantly higher insulin levels at baseline in the oral CHO group compared to the fasting group (MD 13.78, 95%CI: 11.43 to 16.13, 70 participants, 1 trial, Appendix 6.19 Analysis 2.1). Tran 2009 reported results as median (interquartile range) and there was no significant difference between the oral CHO group compared to the fasting group (Appendix 6.17).[A74]

b. Insulin (HOMA-IR and QUICKI) before anaesthesia

Two trials reported results on insulin before anaesthesia and were pooled in a meta-analysis but there was no significant difference in insulin levels between the oral CHO and fasting groups (MD 1.64, 95%CI: -1.53 to 4.82, 115 participants, 2 trials, Appendix 3.19 Analysis 2.2).[A71,A84] No significant heterogeneity was detected between the trials ($Chi^2 = 1.48$, $df = 1$, $p = 0.22$, $I^2 = 32\%$, Appendix 6.19 Analysis 2.2).

c. Insulin (HOMA-IR and QUICKI) at day 0 postoperative

Tran 2009 reported results as median (interquartile range) and there was no significant difference between the oral CHO group compared to the fasting group (Appendix 3.17).[A74]

d. Insulin (HOMA-IR and QUICKI) at day 1 postoperative

This outcome was not reported by any of the trials assessing this comparison.

3.4.1.2.3 Comparison 3: Oral CHO versus placebo

a. Insulin (HOMA-IR and QUICKI) at baseline

Two trials reported this outcome.[A66,A106] In Yuill 2005, the oral CHO group had higher insulin levels compared to the placebo group (MD 3.90, 95%CI: 1.17 to 6.63, 65 participants, 1 trial, Appendix 3.19 Analysis 3.1).[A106] However, results from Mathur 2010, which were reported as median (interquartile range), found no significant difference between the oral CHO and placebo groups (Appendix 6.17).[A66]

b. Insulin (HOMA-IR and QUICKI) before anaesthesia

Mathur 2010 reported results as median (interquartile range) but there was no significant difference between the oral CHO and placebo groups (Appendix 3.17).[A66]

c. Insulin (HOMA-IR and QUICKI) at day 0 postoperative

This outcome was not reported by any of the trials assessing this comparison.

d. Insulin (HOMA-IR and QUICKI) at day 1 postoperative

Two trials reported results on insulin at Day 1 post surgery.[A66,A106] Results from Yuill 2005 showed significantly higher insulin levels in the oral CHO group compared to the placebo group (MD 7.70, 95% CI: 5.97 to 9.43, 65 participants, 1 trial, Appendix 3.19 Analysis 3.2).[A106] Mathur 2010 reported results as median (interquartile range) but there was no significant difference between the oral CHO and placebo groups (Appendix 3.17).[A66]

3.4.1.2.4 Comparison 4: Oral CHO versus active control (IV CHO)

a. Insulin (HOMA-IR and QUICKI) at baseline

Helminen 2009 showed no significant difference in insulin levels at baseline between the oral CHO and IV CHO groups (MD 2.90, 95%CI: -1.39 to 7.19, 41 participants, 1 trial, Appendix 3.19 Analysis 4.1).[A71]

b. Insulin (HOMA-IR and QUICKI) before anaesthesia

Helminen 2009 showed no significant difference in insulin levels before anaesthesia between the oral CHO and IV CHO groups (MD 0.40, 95%CI: -5.38 to 6.18, 41 participants, 1 trial, Appendix 3.19 Analysis 4.2).[A71]

c. Insulin (HOMA-IR and QUICKI) at day 0 postoperative

This outcome was not reported by any of the trials assessing this comparison.

d. Insulin (HOMA-IR and QUICKI) at day 1 postoperative

This outcome was not reported by any of the trials assessing this comparison.

3.4.1.3 Insulin resistance

Six trials (270 participants) assessed insulin resistance as an outcome.[A3,A19,A66,A74,A110,A125] The different methods to measure insulin resistance included the HOMA-IR, QUICKI and HEC methods. Results for the different methods will be reported separately. The results of the trials reporting the outcomes as median (interquartile range) are presented in Appendix 6.17. Three trials had missing or no data, and could not be included.[A6,A64,A68]

3.4.1.3.1 Insulin resistance: HOMA-IR

Only two trials assessed insulin resistance as measured by the HOMA-IR method.[A66,A74] Mathur 2010 compared oral CHO intake to placebo with no significant difference at baseline (MD 0.29, 95%CI: -0.22 to 0.80, 142 participants, 1 trial), before anaesthesia (MD 0.17, 95%CI: -0.15 to 0.49, 142 participants, 1 trial) or day 1 postoperative (MD 0.15, 95%CI: -0.54 to 0.84, 142 participants, 1 trial) [Appendix 6.20].[A66] Tran 2009 reported results as median (interquartile range) when comparing oral CHO intake to standard fasting with no significant difference between groups at baseline or day 0 postoperative (Appendix 6.17).[A74]

3.4.1.3.2 Insulin resistance: QUICKI

Ljunggren 2012 included both the HEC and QUICKI method but the QUICKI method was excluded since the HEC method is the golden standard and glucose and insulin levels were kept at a certain level;[A19] Kaska 2010 had missing data.[A68] Therefore, no data was analysed for this outcome.

3.4.1.3.3 Insulin resistance: HEC

Four trials assessed insulin resistance by the HEC method.[A3,A19,A110,A125] The comparison between the different trials using the HEC method to calculate insulin resistance is challenging because there is no fixed consensus on the important parameters, including optimal procedure duration, infusion rate of insulin to create a hyperinsulinaemic state, glucose infusion rate to maintain euglycaemia, and reporting of results. Descriptive statistics were used to presents the studies

utilising the 'gold standard' method for determining insulin resistance (Table 3.5). Note that a greater reduction in insulin sensitivity indicates a greater development of insulin resistance.

Table 3.5: Insulin resistance as measured by the HEC method

Study	Number of Participants	Groups	Time Interval	Results	p-value
Ljunggren 2014	22	Oral CHO versus placebo	Day before surgery to first postoperative day.	Insulin sensitivity decreased by 51% (35–61) after ingesting the CHO beverage compared to 39% (21–51) after ingesting water.	p > 0.05
Ljunggren 2012	39	Oral CHO versus fasting	Day before surgery to first postoperative day.	Insulin sensitivity decreased by 51% (0–74) after ingesting the CHO beverage compared to 43% (19–77) after fasting.	p > 0.05
Soop 2004	14	Oral CHO versus placebo	1 week preoperatively and on the third day postoperative.	Insulin sensitivity decrease by 36% (±10%) in the oral CHO group versus 49% (±7%) in the placebo group.	p > 0.05
Soop 2001	15	Oral CHO versus placebo	1 week preoperatively to immediate postoperative.	Insulin sensitivity decreased by 18% (±6%) in the oral CHO group versus 43% (±9%) in the placebo group.	p < 0.05*

* Statistical significant result (p < 0.05)

CHO = oral carbohydrate treatment group; HEC = hyperinsulinaemic euglycaemic clamp; p = p-value

3.4.1.4 Total body protein

Two trials (45 participants) assessed total body protein as an outcome.[A66,A110] None of the trials assessed oral CHO intake to standard fasting or IV CHO administration. Mathur 2010 and Soop 2004 compared oral CHO intake to a placebo at different time intervals with no significant difference between groups at any of the time points (Table 3.6) [Appendix 6.21]. [A66,A110]

Table 3.6: Results of trials evaluating total body protein

Study	Number of Participants	Time Interval	Mean Difference (95% Confidence Interval)	p-value
		Oral CHO versus Placebo		
Mathur 2010	31	Baseline (Preoperative)	-0.33 (-1.77; 1.11)	p = 0.65
Soop 2004	14	Day 3 Postoperative	2.24 (-8.47; 12.95)	p = 0.68
Mathur 2010	31	Day 7 Postoperative	-0.07 (-0.42; 0.28)	p = 0.70
Mathur 2010	31	Day 28 Postoperative	0.03 (-0.42; 0.28)	p = 0.90

3.4.1.5 Muscle strength

One trial assessed muscle strength as an outcome.[A66] None of the trials assessed oral CHO intake to standard fasting or IV CHO administration. Mathur 2010 compared oral CHO intake to a placebo

with no difference between groups at any of the time points (Table 3.7) [Appendix 6.22]. Two trials were excluded due to missing data.[A68,A101]

Table 3.7: Results of trials evaluating muscle strength

Study	Number of Participants	Time Interval	Mean Difference (95% Confidence Interval)	p-value
		Oral CHO versus Placebo		
Mathur 2010	142	Baseline (Preoperative)	Missing data	Missing data
Mathur 2010	142	Day 1 Postoperative	-2.22 (-7.75;3.31)	p = 0.43
Mathur 2010	142	Day 3 Postoperative	-1.11 (-5.97;3.75)	p = 0.65
Mathur 2010	142	Day 7 Postoperative	-3.16 (-10.23;3.91)	p = 0.38
Mathur 2010	142	Day 28 Postoperative	0.07 (-6.82;6.96)	p = 0.98

3.4.1.6 C-reactive protein

Three trials with 406 participants assessed C-reactive protein (CRP) as an outcome.[A15,A66,A68] Mathur 2010 reported results as median (interquartile range); Kaska 2010 also reported results as median (interquartile range) except CRP at day 1 postoperative was reported as a mean (standard deviation); Zelic 2013 reported results as a mean (standard deviation). There were no significant differences between the comparisons except at day 1 postoperative the oral CHO group had a significant lower CRP than the fasting group (Appendix 6.23 Analysis 1.3 Analysis 2.3). The results are summarised in Table 3.8. One trial was excluded due to missing data.[A74]

Table 3.8: Results of trials evaluating CRP

COMPARISON / TIME INTERVAL	MEDIAN (INTERQUARTILE RANGE)				MEAN (STANDARD DEVIATION)			
	Number of Studies	Number of Participants	Mean Difference	p-value	Number of Studies	Number of Participants	Mean Difference	p-value
COMPARISON 1: Oral CHO versus inactive control (fasting + placebo)								
CRP at baseline	2	291	NS**		0	0	NR	
CRP before anaesthesia	2	291	NS**		0	0	NR	
CRP at Day 1 postoperative	2	291	NS**		2	219	-8.77 (-15.05,-2.50)	p = 0.006*
CRP at Day 3 postoperative	2	291	NS**		0	0	NR	
CRP at Day 7 postoperative	2	291	NS**		0	0	NR	
COMPARISON 2: Oral CHO versus fasting								
CRP at baseline	1	149	NS**		0	0	NR	
CRP before anaesthesia	1	149	NS**		0	0	NR	
CRP at Day 1 postoperative	0	0	NR		2	219	-8.77 (-15.05,-2.50)	p = 0.006*
CRP at Day 3 postoperative	1	149	NS**		0	0	NR	
CRP at Day 7 postoperative	1	149	NS**		0	0	NR	
COMPARISON 3: Oral CHO versus placebo								
CRP at baseline	1	142	NS**		0	0	NR	
CRP before anaesthesia	1	142	NS**		0	0	NR	
CRP at Day 1 postoperative	1	142	NS**		0	0	NR	
CRP at Day 3 postoperative	1	142	NS**		0	0	NR	
CRP at Day 7 postoperative	1	142	NS**		0	0	NR	
COMPARISON 4: Oral CHO versus active control (IV CHO)								
CRP at baseline	1	149	NS**		0	0	NR	
CRP before anaesthesia	1	149	NS**		0	0	NR	
CRP at Day 1 postoperative	0	0	NR		0	0	NR	
CRP at Day 3 postoperative	1	149	NS**		0	0	NR	
CRP at Day 7 postoperative	1	149	NS**		0	0	NR	

* Statistical significant result ($p < 0.05$)
** see Appendix 6.17 for results reported as median (interquartile range); all results showed no statistically significant difference between groups

CHO = oral carbohydrate treatment group; CRP = C-reactive protein; IV = intravenous; NR = not reported; NS = not significant

3.4.1.7 Return of intestinal function

Two trials (140 participants) assessed return of intestinal function as an outcome.[A75,A101] The outcome was measured by the length in days from surgery to first flatus/stool or bowel movement. Serclova 2009 reported the results as means (standard deviations) while Noblett 2006 reported the results as median (without indicating the interquartile range). The results are summarised per comparison: flatus/stool (Table 3.9) and bowel movements (Table 3.10). Results from Šerclová 2009, showed that the oral CHO group had significantly fewer days for the return of intestinal function than the fasting group (inactive control) [stool/flatus: Appendix 6.24; bowel movement Appendix 6.25].[A75] Noblett 2006 reported that there was no significant difference between the oral CHO and the inactive control (fasting or placebo groups) [Appendix 6.17].[A101] None of the trials assessed oral CHO intake to the active control (i.e. IV CHO administration).

Table 3.9: Results of trials evaluating flatus / stool (days)

Comparison	Trial	Number of Participants	Mean Difference	p-value	Trial	Number of Participants	Median**
COMPARISON 1 *Oral CHO versus inactive control*	Serclova 2009	103	-1.80 (-2.22;-1.38)	p < 0.00001*	Noblett 2006	35	Oral CHO: 2 Fasting: 3 Placebo: 3
COMPARISON 2 *Oral CHO versus fasting*	Serclova 2009	103	-1.80 (-2.22;-1.38)	p < 0.00001*	Noblett 2006	35	Oral CHO: 2 Fasting: 3
COMPARISON 3 *Oral CHO versus placebo*	NR				Noblett 2006	35	Oral CHO: 2 Placebo: 3
COMPARISON 4 *Oral CHO versus active control*	NR				NR		

* Statistical significant result (p < 0.05)
** Results reported as median without indicating the interquartile range
CHO = oral carbohydrate treatment group; NR = not reported by any of the trials

Table 3.10: Results of trials evaluating bowel movements (days)

Comparison	Trial	Number of Participants	Mean Difference	p-value	Trial	Number of Participants	Median**
COMPARISON 1 *Oral CHO versus inactive control*	Serclova 2009	103	-1.80 (-2.15;-1.45)	p < 0.00001*	Noblett 2006	35	Oral CHO: 2 Fasting: 3.5 Placebo: 5
COMPARISON 2 *Oral CHO versus fasting*	Serclova 2009	103	-1.80 (-2.15;-1.45)	p < 0.00001*	Noblett 2006	35	Oral CHO: 2 Fasting: 3.5
COMPARISON 3 *Oral CHO versus placebo*	NR				Noblett 2006	35	Oral CHO: 2 Placebo: 5
COMPARISON 4 *Oral CHO versus active control*	NR				NR		

* Statistical significant result (p < 0.05)
** Results reported as median without indicating the interquartile range
CHO = oral carbohydrate treatment group; NR = not report by any of the trials

3.4.1.8 Length of stay

Ten trials (885 participants) reported on length of stay.[A19,A66,A68,A74,A75,A90,A105,A106,A110,A125] Length of stay was divided into the days in the ICU, days in the hospital and the days until fit for discharge. The results are summarised in Table 3.11.

Table 3.11: Results of length of stay that were pooled in a meta-analysis

	ICU				HOSPITAL				FIT FOR DISCHARGE			
	NUMBER OF TRIALS	n	EFFECTS ESTIMATE	p-VALUE	NUMBER OF TRIALS	n	EFFECTS ESTIMATE	p-VALUE	NUMBER OF TRIALS	n	EFFECTS ESTIMATE	p-VALUE
COMPARISON 1	1	101	-2.10 (4.84, 0.64)	0.13	2	187	-0.04 (-0.27, 0.19)	0.37	1	142	*median (interquartile range)***	
Oral CHO versus inactive control					4	439	*median (interquartile range)***					
COMPARISON 2	1	101	-2.10 (-4.84, 0.64)	0.13	1	113	-0.10 (-0.40, 0.20)	> 0.05	Not reported by any of the trials			
Oral CHO versus fasting					1	103	-3.00 (-3.92, 2.08)	< 0.05*				
					2	232	*median (interquartile range)***					
COMPARISON 3	NR				2	129	0.01 (-0.23, 0.25)	0.95	1	142	*median (interquartile range)***	
Oral CHO versus placebo					2	207	*median (interquartile range)***					
COMPARISON 4	NR				NR				NR			
Oral CHO versus active control												

* Statistical significant result ($p < 0.05$)
** see Appendix 6.17 for results reported as median (interquartile range)
*** Results could not be pooled due to significant heterogeneity between the studies ($Chi^2 = 34.92$, $df = 1$, $p < 0.00001$, $I^2 = 97\%$)
CHO = oral carbohydrate treatment group; ICU = intensive care unit; n = number of participants; NR = not reported by any of the trials

3.4.1.8.1 Length of ICU stay

a. Comparison 1: Oral CHO versus inactive control (fasting + placebo)

Järvelä 2008 assessed the length of stay in ICU (days) but there was no difference between the oral CHO and fasting groups (MD -2.10, 95%CI: -4.84 to 0.64, 101 participants, 1 trial, Appendix 6.26).[A90]

b. Comparison 2: Oral CHO versus fasting

Järvelä 2008 assessed the length of stay in ICU (days) but there was no difference between the oral CHO and fasting groups (MD -2.10, 95%CI: -4.84 to 0.64, 101 participants, 1 trial, Appendix 6.26). [A90]

c. Comparison 3: Oral CHO versus placebo

This outcome was not reported by any of the trials assessing this comparison.

d. Comparison 4: Oral CHO versus active control (IV CHO)

This outcome was not reported by any of the trials assessing this comparison.

3.4.1.8.2 Length of hospital stay

a. Comparison 1: Oral CHO versus inactive control (fasting + placebo)

Eight trials reported results on length of hospital stay.[A66,A68,A74,A75,A105,A106,A110,A125] Results from Hausel 2005, Serclova 2009 and Soop 2001 were pooled in a meta-analysis but the results could not be reported because of significant heterogeneity between the trials (Chi^2 = 38.07, df = 2, p < 0.00001, I^2 = 95%).[A75,A105,A125] An investigation of the source of heterogeneity was carried out using both subgroup analysis and sensitivity analysis. Heterogeneity remained significant after subgroup analyses with respect to dose and duration of experimental intervention, type of surgery, type of anaesthesia and anaesthetic risk. Since the forest plot clearly shows that one of the trials (Šerclová 2009) had outlying results compared to the other two trial results, a sensitivity analysis was carried out to determine the effect of removing this one trial from the meta-analysis on heterogeneity.[A75] After removing this trial from the meta-analysis, heterogeneity between studies was no longer significant (Chi^2 = 0.97, df = 1, p = 0.60, I^2 = 0%, Appendix 6.27) but there was no significant difference in the length of hospital stay between the oral CHO and the inactive control (fasting or placebo) groups (MD -0.04, 95%CI: -0.27 to 0.19, 187 participants, 2 trials, Appendix 6.27). However, the results of Šerclová 2009 showed significantly shorter hospital stay in the oral CHO group compared to the fasting group (MD 10.40, 95%CI 11.32 to 9.48, 103 participants, 1 trial, Appendix 6.27). Soop 2004 reported results as mean (standard deviation) but since the standard deviations for the two groups were both zeros, no treatment effect could be calculated.[A110] The trial authors reported no significant difference between the oral CHO and the

placebo group. The remaining four trials reported results as median (interquartile range).[A66,A68,A74,A106] In three of these trials there was no significant difference between the oral CHO and the inactive control (fasting or placebo) groups (Appendix 6.17).[A66,A68,A106] Results from Tran 2009 showed a significantly shorter hospital stay in favour of the oral CHO group (p = 0.008) (Appendix 6.17).[A74]

b. Comparison 2: Oral CHO versus fasting

Four trials reported results on length of hospital stay.[A68,A74,A75,A105] Results from two trials were pooled in a meta-analysis but the results could not be reported because of significant heterogeneity (Chi^2 = 34.92, df = 1, p < 0.00001, I^2 = 97%). No investigation of the source of heterogeneity was carried out because there were only two trials in the meta-analysis. Results are therefore reported separately for the two trials. Although the results of the Hausel 2005 study showed no significant difference in hospital stay between the two groups (MD -0.10, 95%CI: -0.40 to 0.20, 113 participants, 1 trial, Appendix 6.27),[A105] the results from Šerclová 2009 showed significantly shorter hospital stay in the oral CHO group compared to the fasting group (MD -3.00, 95%CI: -3.92 to -2.08, 103 participants, 1 trial, Appendix 6.27).[A75] Two trials reported results as median (interquartile range).[A68,A74] In Kaska 2010 there was no significant difference between the oral CHO and fasting groups (Appendix 6.17).[A68] However, results from Tran 2009 showed a significantly shorter hospital stay in favour of the oral CHO group (p = 0.008) compared to the fasting group (Appendix 6.17).[A74]

c. Comparison 3: Oral CHO versus placebo

Five trials reported results on length of hospital stay.[A66,A105,A106,A110,A125] Results from two trials were pooled in a meta-analysis but there was no significant difference in length of hospital stay between the oral CHO and the placebo groups (MD 0.01, 95%CI: -0.23 to 0.25, 129 participants, 2 trials, Appendix 6.27).[A105,A125] No significant heterogeneity was detected between the trials (Chi^2 = 0.21, df = 1, p = 0.64, I^2 = 0%, Appendix 6.27). Soop 2004 reported results as mean (standard deviation) but since the standard deviations for the two groups were both zeros, no treatment effect could be calculated.[A110] The trial authors reported no significant difference between the oral CHO and the placebo group. The remaining two trials reported results as median (interquartile range) but there was no significant difference between the oral CHO and placebo groups (Appendix 6.17).[A66,A106]

d. Comparison 4: Oral CHO versus active control (IV CHO)

This outcome was not reported by any of the trials assessing this comparison.

3.4.1.8.3 Fit for discharge

a. Comparison 1: Oral CHO versus inactive control (fasting + placebo)

Mathur 2010 reported the number of days until fit for discharge as median (interquartile range) but there were no significant difference between the oral CHO and placebo groups (Appendix 6.17).[A66]

b. Comparison 2: Oral CHO versus fasting

This outcome was not reported by any of the trials assessing this comparison.

c. Comparison 3: Oral CHO versus placebo

One trial reported the number of days until fit for discharge as median (interquartile range) but there were no significant difference between the oral CHO and placebo groups (Appendix 6.17).[A66]

d. Comparison 4: Oral CHO versus active control (IV CHO)

This outcome was not reported by any of the trials assessing this comparison.

3.4.1.9 Adverse events

The majority of trials reported on one or more of the adverse events of the intervention (i.e. regurgitation, aspiration, morbidity and mortality). The major adverse events associated with the intervention are summarised in Table 3.12 using descriptive statistics. Adverse events were accounted for by the number of patients experiencing an event. According to the available data there were no regurgitation (n = 1345; 13 trials),[A16,A64,A68,A71,A74,A84,A90,A101,A105,A106,A110,A115,A121] aspiration (n = 1509; 16 trials),[A14,A16,A64,A68,A71,A74,A75,A84,A90,A94,A101,A105,A106,A110,A115,A121] morbidity (n = 1178; 13 trials)[A16,A19,A64,A68,A74,A75,A84,A101,A105,A106,A110,A115,A121] or mortality (n = 1697; 22 trials)[A3,A6,A14,A15,A16,A19,A52,A64,A66,A71,A74,A75,A84,A90.A94,A101,A105,A106,A110,A115,A121,A125] directly as a result of the intake of the oral CHO beverage.

Table 3.12: Adverse events per trial

TRIAL	n	REGURGITATION	ASPIRATION	MORBIDITY	MORTALITY
LJUNGGREN 2014 (A3)	22	NR	NR	NR	No*
CANBY 2014 A6)	50	NR	NR	NR	No*
YILMAZ 2013 (A14)	40	NR	No	NR	No*
ZELIC 2013 (A15)	70	NR	NR	NR	No*
YILDIZ 2013 (A16)	60	No	No	No	No
LJUNGGREN 2012 (A19)	39	NR	NR	No^	No
YAGMURDUR 2011 (A52)	44	NR	NR	NR	No*
WANG 2010 (A64)	48	No	No	No	No*
MATHUR 2010 (A66)	142	NR	NR	NR	No*
KASKA 2010 (A68)	194	No	No	No^	NR
HELMINEN 2009 (A71)	210	No	No	NR	No*
TRAN 2009 (A74)	38	No	No	No^	No*
SERCLOVA 2009 (A75)	105	NR	No	No^	No
YAGCI 2008 (A84)	70	No	No	No	No
JARVELA 2008 (A90)	101	No	No	NR	No*
MELIS 2006 (A94)	19	NR	No	NR	No*
NOBLETT 2006 (A101)	35	No	No	No^	No*
HAUSEL 2005 (A105)	172	No	No	No^	No*
YUILL 2005 (A106)	65	No	No	No^	No*
SOOP 2004 (A110)	14	No	No	No	No*
BISGAARD 2003 (A115)	86	No	No	No	No*
HAUSEL 2001 (A121)	252	No	No	No	No*
SOOP 2001 (A125)	15	NR	NR	NR	No*
NYGREN 1995 (A131)	12	NR	NR	NR	NR

^ no complications directly related to the intake of the oral CHO beverage (i.e. allergic reaction, intolerability requiring discontinuation of the beverage, or clinical signs of electrolyte abnormalities); complications related to surgery; psychosomatic complications will be discuss separately as secondary outcomes

** trial did not indicate mortality but it was extrapolated that there was no mortality if the same number of participants that started the trial finished the trial (excluding the participants that were lost to follow up due to not meeting inclusion criteria)*

n = number of participants; NR = not reported

3.4.2 Secondary outcomes

Sixteen trials assessed the secondary outcomes as stated (n = 1449). [A6, A14, A15, A16, A52, A64, A66, A71, A74, A75, A90, A94, A105, A115, A121, A131] Not one of the trials defined the terms as it is self-evident. The results of the trials indicated considerable variability in terms of type of data (continuous versus dichotomous), unit of measurement (visual analogue scale, verbal descriptive scale, ordinal scale, state-trait anxiety inventory), time of measurements (preoperative and/or postoperative), interventions (oral CHO versus standard fasting versus placebo versus IV CHO) and comparisons (intragroup versus intergroup). Continuous data refers to the severity of the outcomes while dichotomous data refers to the number of participants experiencing the outcomes. Given the wide variety of methodologies used to evaluate these measures and the subjective nature of their report, a descriptive approach was adopted.

3.4.2.1 Thirst

Eleven trials assessed thirst as an outcome (932 participants). [A6, A15, A16, A52, A64, A66, A71, A74, A94, A121, A131] All the trials reported on the severity of thirst experienced (continuous data). Ten of the trials used a 100 mm Visual Analogue Scale (VAS) while one trial made use of a 4-point Likert scale.[A6] Only four of the trials indicated that they made use of self-reporting; [A52, A64, A66, A131] one trial indicated that the nurse administered the score; [A121] and the rest did not comment on the scoring method. Eight trials assessed thirst in the preoperative phase only; [A6, A52, A64, A71, A74, A94, A121, A131] one trial assessed thirst in the postoperative phase only; [A15] two trials assessed thirst both in the preoperative and postoperative phase. [A16, A66] Six trials compared oral CHO intake to standard fasting only; [A6, A15, A16, A52, A74, A94] two trials compared oral CHO intake to placebo only; [A66, A131] two trials compared oral CHO intake to both fasting and placebo; [A64, A121] and one trial compared oral CHO intake to both fasting and IV CHO. [A71] Three of the trials had incomplete data. [A66, A94, A121] The main findings of the trials assessing thirst are summarised in Table 3.13 (see Appendix 6.29 for comparison of results).

Table 3.13: Trials assessing thirst – secondary outcomes

STUDY ID	n	UNIT OF MEASUREMENT	TYPE OF DATA		TIME OF MEASUREMENT		INTERVENTION				MAIN FINDINGS
			CONTINUOUS	DICHOTOMOUS	PREOP	POSTOP	CHO	FASTING	PLACEBO	IV	
Canby, 2014 (A6)	50	Likert scale	✓		✓		✓	✓			CHO group less thirsty preop than fasting group ($p < 0.05$)*
Zelic, 2013 (A15)	70	100 mm VAS	✓			✓	✓	✓			CHO group less thirsty postop than fasting group ($p > 0.05$)
Yildiz, 2013 (A16)	60	100 mm VAS	✓		✓	✓	✓	✓			CHO group less thirsty preop than fasting group ($p < 0.05$)*; CHO group less thirsty 2 hours postop than fasting group ($p < 0.05$)*; No difference between groups at 24 hours postop ($p > 0.05$)
Yagmurdur, 2011 (A52)	44	100 mm VAS (self-reported)	✓		✓		✓	✓			CHO group less thirsty from baseline to preop ($p < 0.05$)*; Fasting group more thirsty from baseline to preop ($p < 0.05$)*; CHO group less thirsty preop than fasting group ($p < 0.05$)*
Wang, 2010 (A64)	48	100 mm VAS (self-reported)	✓		✓		✓	✓	✓		CHO group no change from 18 hours to 1 hour preop ($p = 0.921$); Fasting group more thirst from 18 hours to 1 hour preop ($p = 0.001$)*; Placebo group more thirst from 18 hours to 1 hour preop ($p = 0.015$)*; @18 hours preop: no difference in thirst between groups ($p = 0.967$);

									@1 hour preop: difference in thirst between the groups (p = 0.005)*; CHO vs placebo group @ 1 hour preop: no difference in thirst (p = 0.970)
Mathur, 2010 (A66)	142	100 mm VAS (self-reported)	✓	✓	✓	✓		✓		All between group comparisons before anaesthesia and postop were not different (p > 0.05)
Helminen, 2009 (A71)	210	100 mm VAS	✓	✓		✓	✓		✓	CHO group: thirst increased before intake of beverage (p < 0.05)* with decrease in thirst after intake of beverage (p < 0.05)*; Fasting group: increase in thirst from evening before surgery until anaesthesia the following day (p < 0.05)*; IV group: increase in thirst from evening before surgery until anaesthesia the following day (p < 0.05)*
Tran, 2009 (A74)	25	100 mm VAS	✓	✓		✓	✓			CHO group less thirsty preop than fasting group (p = 0.01)*
Melis, 2006 (A94)	19	100mm VAS	✓	✓		✓	✓			CHO group less thirsty preop than other groups (p value missing)
Hausel, 2001 (A121)	252	100 mm VAS (nurse reported)	✓	✓		✓	✓	✓		Fasting group: increase in thirst preop (p < 0.001)*; Placebo group: no consistent trend; CHO group less thirsty preop compared to fasting group (p < 0.001)*
Nygren, 1995 (A131)	12	100 mm VAS (self-reported)	✓	✓		✓		✓		CHO group thirst reduced for 60 minutes (p < 0.01)*; Placebo group thirst reduced for 40 minutes (p < 0.05)*

* Statistical significant result (p < 0.05)

CHO = oral carbohydrate treatment group; IV = intravenous carbohydrate treatment group; n = number of participants; postop = postoperative; preop = preoperative; VAS = visual analogue scale

3.4.2.2 Hunger

Ten trials assessed 862 participants' severity of hunger (continuous data). [A6, A16, A52, A64, A66, A71, A74, A94, A121, A131] Nine of the trials used a 100 mm VAS; one of the trials made use of a 4-point Likert scale.[A6] Only four of the studies indicated that they made use of self-reporting; [A52, A64, A66, A131] one study indicated that the nurse administered the score; [A121] and the rest did not comment on the scoring method. Seven trials assessed hunger in the preoperative phase; [A6, A52, A64, A71, A74, A94, A121, A131] none of the trials assessed hunger in the postoperative phase only; two trials assessed hunger both in the preoperative and postoperative phase.[A16, A66] Five trials compared oral CHO intake to standard fasting only; [A6, A16, A52, A74, A94] two trials compared oral CHO intake to placebo only; [A66, A131] two trials compared oral CHO intake to both fasting and placebo; [A64, A121] one trial compared oral CHO intake to both fasting and IV CHO. [A71] Two of the trials had incomplete data. [A94, A121] The main findings of the trials assessing hunger are summarised in Table 3.14 (see Appendix 6.30 for comparison of results).

Table 3.14: Trials assessing hunger – secondary outcomes

STUDY ID	n	UNIT OF MEASUREMENT	TYPE OF DATA		TIME OF MEASUREMENT		INTERVENTION				MAIN FINDINGS
			CONTINUOUS	DICHOTOMOUS	PREOP	POSTOP	CHO	FASTING	PLACEBO	IV	
Canby, 2014 (A6)	50	Likert scale	✓		✓		✓	✓			CHO group less hungy preop than fasting group ($p < 0.05$)*
Yildiz, 2013 (A16)	60	100 mm VAS	✓		✓	✓	✓	✓			CHO group less hungry preop than fasting group ($p < 0.05$)*; CHO group less hungry 2 hours postop than fasting group ($p < 0.05$)*; No difference between groups at 24 hours postop ($p > 0.05$)
Yagmurdur, 2011 (A52)	44	100 mm VAS (self-reported)	✓		✓		✓	✓			CHO group less hungry from baseline to preop ($p < 0.05$)*; Fasting group more hungry from baseline to preop ($p < 0.05$)*; CHO group less hungry preop than fasting group ($p < 0.05$)*
Wang, 2010 (A64)	48	100 mm VAS (self-reported)	✓		✓		✓	✓	✓		CHO group no change from 18 hours to 1 hour preop ($p = 0.147$); Fasting group more hungry from 18 hours to 1 hour preop ($p = 0.006$)*; Placebo group no change from 18 hours to 1 hour preop ($p = 0.291$); @18 hours preop: no difference in hunger between groups ($p = 0.968$); @1 hour preop: difference in hunger between the groups ($p = 0.041$)*;

									CHO vs Placebo group @ 1 hour preop: no difference in hunger (p = 0.146)
Mathur, 2010 (A66)	142	100 mm VAS (self-reported)	✓	✓	✓	✓		✓	All between group comparisons before anaesthesia and postop were not different (p > 0.05).
Helminen, 2009 (A71)	210	100 mm VAS	✓	✓		✓	✓		✓ CHO group: decrease in hunger after intake of beverage (p < 0.05)*; Fasting group: increase in hunger preop (p < 0.05)*; IV group: no change in hunger preop (p > 0.05) CHO group less hungry than fasting group preop (p < 0.05)*
Tran, 2009 (A74)	25	100 mm VAS	✓	✓		✓	✓		CHO group less hungry preop than fasting group (p = 0.04)*
Melis, 2006 (A94)	19	100 mm VAS	✓	✓		✓	✓		CHO group less hungry preop than other groups (p value missing)
Hausel, 2001 (A121)	252	100 mm VAS (nurse reported)	✓	✓		✓	✓	✓	Fasting group: increase in hunger preop (p < 0.05)*; Placebo group: no consistent trend; CHO group less hungry preop compared to fasting group (p < 0.05)
Nygren, 1995 (A131)	12	100 mm VAS (self-reported)	✓	✓		✓		✓	CHO group no change in hunger (p = 0.1); Placebo group hunger reduced for 20 minutes (p < 0.05)*

* Statistical significant result (p < 0.05)

CHO = oral carbohydrate treatment group; IV = intravenous carbohydrate treatment group; n = number of participants; postop = postoperative; preop = preoperative; VAS = visual analogue scale

3.4.2.3 Nausea

Twelve trials assessed nausea as an outcome (1 139 participants); [A14, A15, A16, A52, A64, A66, A75, A90, A94, A105, A115, A121] Seven trials reported on continuous data (i.e. the severity of nausea experienced); [A14, A16, A52, A64, A66, A94, A121] two trials reported on dichotomous data (i.e. number of patients experiencing nausea and number of episodes per patients); [A75, A90] three trials reported on both continuous and dichotomous data. [A15, A105, A115] All trials reporting on the severity of nausea used a VAS; [A15, A16, A52, A64, A66, A94, A105, A121] except one trial using a verbal descriptive scale (VDS) [A14] and one trial using an ordinal scale. [A115] Four of the trials indicated that they made use of self-reporting; [A52, A64, A66, A105] two trials indicated that the nurse administered the score; [A15, A121] the rest of the trials did not report on the scoring method. Nausea was assessed in four of the trials in the preoperative period only; [A52, A64, A94, A121] five of the trials assessed nausea in the postoperative period only; [A14, A15, A75, A90, A115] two trials assessed nausea in both the preoperative and postoperative period; [A16, A66, A105] one trial assessed the severity of nausea experienced in both the preoperative and postoperative period, and the number of patients experiencing nausea only in the postoperative period.[A105] Seven trials compared oral CHO intake to standard fasting; [A14, A15, A16, A52, A75, A90, A94] two trials compared oral CHO intake to a placebo; [A66, A115] three trials compared oral CHO intake to both standard fasting and a placebo; [A64, A105, A121] none of the trials compared oral CHO intake to IV CHO administration. One of the trials had incomplete data. [A94] The main findings of the trials assessing nausea are summarised in Table 3.15 (see Appendix 6.31 for comparison of results).

Table 3.15: Trials assessing nausea – secondary outcomes

STUDY ID	n	UNIT OF MEASUREMENT	TYPE OF DATA		TIME OF MEASUREMENT		INTERVENTION				MAIN FINDINGS
			CONTINUOUS	DICHOTOMOUS	PREOP	POSTOP	CHO	FASTING	PLACEBO	IV	
Yilmaz, 2013 (A14)	40	VDS	✓			✓	✓	✓			*CHO group less nauseous postop than fasting group ($p < 0.001$) **
Zelic, 2013 (A15)	70	100 mm VAS (nurse reported)	✓			✓	✓	✓			CHO group overall less nauseous postop than fasting group ($p > 0.05$)
		Number of episodes		✓		✓	✓	✓			
Yildiz, 2013 (A16)	60	100 mm VAS	✓		✓	✓	✓	✓			No difference between groups ($p > 0.05$)
Yagmurdur, 2011 (A52)	44	100 mm VAS (self reported)	✓		✓		✓	✓			No difference between groups ($p > 0.05$)
Wang, 2010 (A64)	48	100 mm VAS (self reported)	✓		✓		✓	✓	✓		CHO group no change from 18 hours to 1 hour preop ($p = 0.139$); Fasting group no change from 18 hours to 1 hour preop ($p = 0.116$); Placebo group no change from 18 hours to 1 hour preop ($p = 0.135$); @18 hours preop: no difference in nausea between groups ($p = 0.984$); @1 hour preop: no difference in nausea between the groups ($p = 0.995$); CHO vs placebo group @ 1 hour preop: no difference in nausea ($p = 0.788$)
Mathur, 2010 (A66)	142	100 mm VAS (self reported)	✓		✓	✓	✓		✓		All between group comparisons before anaesthesia and postop were not different ($p > 0.05$).
Šerclová, 2009 (A75)	105	Number of patients		✓		✓	✓	✓			Fewer patients experienced nausea in the CHO group than the fasting group on day 2 to 4 postoperative ($p < 0.05$)**

Järvelä, 2008 (A90)	101	Number of patients		✓		✓	✓	✓		More patients experienced nausea in the CHO group than the fasting group on day 1 postoperative (p = 0.044)**
Melis, 2006 (A94)	19	100 mm VAS	✓		✓		✓	✓		CHO group less nauseous preop than other groups (p value missing)
Hausel, 2005 (A105)	172	100 mm VAS (self reported)	✓		✓	✓	✓	✓	✓	Fasting group more nauseous postop than preop (p = 0.018)** Placebo group more nauseous postop than preop (p < 0.001)** No difference between groups (p > 0.05)
		Number of patients		✓		✓	✓	✓	✓	*CHO group: fewer patients experienced nausea as time passed (p < 0.001)** *Placebo group: fewer patients experienced nausea as time passed (p = 0.006)** *Fasting group: no difference in number of patients experiencing nausea (p = 0.067) *No difference between groups (p = 0.305)
Bisgaard, 2003 (A115)	86	Ordinal scale	✓			✓	✓		✓	No difference between groups (p = 0.871)
		Number of episodes		✓		✓	✓		✓	No difference between groups (p = 1.000)
Hausel, 2001 (A121)	252	100 mm VAS (nurse reported)	✓		✓		✓	✓	✓	CHO group: no change in nausea preop (p > 0.05) Fasting group: no change in nausea preop (p > 0.05); Placebo group: more nausea preop (p < 0.0001)**

* Results combined for postoperative nausea and vomiting

** Statistical significant result (p < 0.05)

CHO = oral carbohydrate treatment group; IV = intravenous carbohydrate treatment group; n = number of participants; postop = postoperative; preop = preoperative; VAS = visual analogue scale; VDS = verbal descriptive scale

3.4.2.4 Vomiting

Six trials assessed vomiting as an outcome (574 participants). [A14, A15, A75, A90, A105, A115] Three trials reported on dichotomous data (i.e. number of patients vomiting and number of episodes per patient); [A75, A90, A105] one trial reported on continuous data; [A14] two trials reported on both continuous and dichotomous data. [A15, A115] The different scales used include: VDS, [A14] VAS, [A15] and an ordinal scale. [A115] Only one trial indicated that the nurse administered the score; [A15] all the other trials did not comment on the scoring method. All the trials assessed vomiting only in the postoperative period. Four trials compared oral CHO intake to standard fasting; [A14, A15, A75, A90] one trial compared oral CHO intake to a placebo; [A115] one trial compared oral CHO intake to both standard fasting and a placebo; [A105] none of the trials compared oral CHO intake to IV CHO administration. The main findings of the trials assessing vomiting are summarised in Table 3.16 (see Appendix 6.32 for comparison of results).

Table 3.16: Trials assessing vomiting – secondary outcomes

STUDY ID	n	UNIT OF MEASUREMENT	TYPE OF DATA		TIME OF MEASUREMENT		INTERVENTION				MAIN FINDINGS
			CONTINUOUS	DICHOTOMOUS	PREOP	POSTOP	CHO	FASTING	PLACEBO	IV	
Yilmaz, 2013 (A14)	40	VDS	✓			✓	✓	✓			*CHO group less vomiting postop than fasting group (p < 0.001)**
Zelic, 2013 (A15)	70	100 mm VAS (nurse reported)	✓			✓	✓	✓			CHO group overall less vomiting postop than fasting group (p > 0.05)
		Number of episodes		✓		✓	✓	✓			
Šerclová, 2009 (A75)	105	Number of patients		✓		✓	✓	✓			Fewer patients experienced vomiting in the CHO group than the fasting group on day 2 postoperative (p < 0.05)**
Järvelä, 2008 (A90)	101	Number of patients		✓		✓	✓	✓			No difference between CHO and fasting groups on day 1 postoperative (p = 0.437)
Hausel, 2005 (A105)	172	Number of patients		✓		✓	✓	✓	✓		*CHO group: fewer patients experienced vomiting as time passed (p < 0.001)** *Placebo group: fewer patients experienced vomiting as time passed (p = 0.006)** *Fasting group: no difference in number of patients experiencing vomiting (p = 0.067) *No difference between groups (p = 0.305)
Bisgaard, 2003 (A115)	86	Ordinal scale	✓			✓	✓		✓		No difference between groups (p = 0.278)
		Number of episodes		✓		✓	✓		✓		No difference between groups (p = 0.336)

* Results combined for postoperative nausea and vomiting

** Statistical significant result (p < 0.05)

CHO = oral carbohydrate treatment group; IV = intravenous carbohydrate treatment group; n = number of participants; postop = postoperative; preop = preoperative; VAS = visual analogue scale; VDS = verbal descriptive scale

3.4.2.5 Anxiety

Eleven trials assessed anxiety as an outcome (902 participants); [A6, A14, A16, A52, A64, A66, A71, A74, A94, A121, A131] All the trials reported on the severity of anxiety experienced (continuous data). Two types of scales were used to measure anxiety: The 100 mm VAS [A16, A52, A64, A66, A71, A74, A94, A121, A131] and the State-Trait Anxiety Inventory (STAI). [A6, A14] Four of the studies indicated that they made use of self-reporting; [A52, A64, A66, A131] one study indicated that the nurse administered the score; [A121] and the rest did not comment on the scoring method. Nine of the trials assessed anxiety only in the preoperative period; [A14, A16, A52, A64, A71, A74, A94, A121, A131] none of the trials assessed anxiety only in the postoperative period; two trials assessed anxiety both in the preoperative and postoperative period. [A6, A66] Six trials compared oral CHO intake to standard fasting; [A6, A14, A16, A52, A74, A94] two trials compared oral CHO intake to aplacebo; [A66, A131] two trials compared oral CHO intake to both fasting and a placebo; [A64, A121] one trial compared oral CHO intake to both fasting and IV CHO administration.[A71] One trial had incomplete outcome data.[A94] The main findings of the trials assessing anxiety are summarised in Table 3.17 (see Appendix 6.33 for comparison of results).

Table 3.17: Trials assessing anxiety – secondary outcomes

STUDY ID	n	UNIT OF MEASUREMENT	TYPE OF DATA		TIME OF MEASUREMENT		INTERVENTION				MAIN FINDINGS
			CONTINUOUS	DICHOTOMOUS	PREOP	POSTOP	CHO	FASTING	PLACEBO	IV	
Canby, 2014 (A6)	50	State-Trait Anxiety Inventory	✓		✓	✓	✓	✓			No difference between CHO and fasting groups ($p > 0.05$)
Yilmaz, 2013 (A14)	40	State-Trait Anxiety Inventory	✓		✓		✓	✓			CHO group less anxious preop than fasting group ($p = 0.035$)*
Yildiz, 2013 (A16)	60	100 mm VAS	✓		✓		✓	✓			No difference between CHO and fasting groups ($p > 0.05$)
Yagmurdur, 2011 (A52)	44	100 mm VAS (self-reported)	✓		✓		✓	✓			CHO group less anxious from baseline to preop ($p < 0.05$)*; CHO group less anxious preop than fasting group ($p < 0.05$)*
Wang, 2010 (A64)	48	100 mm VAS (self-reported)	✓		✓		✓	✓	✓		CHO group no change from 18 hours to 1 hour preop ($p = 0.080$); Fasting group no change from 18 hours to 1 hour preop ($p = 0.278$); Placebo group no change from 18 hours to 1 hour preop ($p = 0.712$); @18 hours preop: no difference in anxiety between groups ($p = 0.442$); @1 hour preop: no difference in anxiety between groups ($p = 0.104$); CHO vs placebo group @ 1 hour preop: no difference in anxiety ($p = 0.940$)
Mathur, 2010 (A66)	142	100 mm VAS (self-reported)	✓		✓	✓	✓		✓		All between-group comparisons were not different ($p > 0.05$)
Helminen, 2009 (A71)	210	100 mm VAS	✓		✓		✓	✓		✓	CHO group: no change in anxiety ($p > 0.05$); Fasting group: increase in anxiety ($p < 0.05$)*; IV group: increase in anxiety ($p < 0.05$)*

Tran, 2009 (A74)	25	100 mm VAS	✓	✓	✓	✓		CHO group less anxious preop than fasting group (p = 0.01)*
Melis, 2006 (A94)	19	100 mm VAS	✓	✓	✓	✓		CHO group less anxious preop than other groups (p-value missing)
Hausel, 2001 (A121)	252	100 mm VAS (nurse reported)	✓	✓	✓	✓	✓	Fasting group: no change (p > 0.05); Placebo group: no change (p > 0.05); CHO group less anxious preop compared to fasting group (p < 0.001)*
Nygren, 1995 (A131)	12	100 mm VAS (self-reported)	✓	✓	✓		✓	CHO group: no change in anxiety for 90 minutes after intake (p = 0.11); Placebo group: anxiety reduced for 90 minutes after intake (p < 0.05)*

* Statistical significant result (p < 0.05)

CHO = oral carbohydrate treatment group; IV = intravenous carbohydrate treatment group; n = number of participants; postop = postoperative; preop = preoperative; VAS = visual analogue scale

3.4.2.6 Pain

Eight trials assessed pain as an outcome (1 081 participants). [A15, A52, A66, A71, A75, A105, A115, A121] All the trials reported on the severity of pain experienced (continuous data) using a 100 mm VAS; three of the trials indicated that they made use of self-reporting; [A52, A66, A105] one trial indicated that the nurse administered the score; [A121] and the other trial did not comment on the scoring method. Three of the trials assessed pain only in the preoperative period; [A52, A71, A121] two trials assessed pain only in the postoperative period; [A15, A75] three trials assessed pain both in the preoperative and postoperative period. [A66 , A105, A115] Three trials compared oral CHO intake to standard fasting; [A15, A52, A75] two trials compared oral CHO intake to placebo; [A66, A115] two trials compared oral CHO intake to both fasting and a placebo; [A105, A121] one trial compared oral CHO intake to both fasting and IV CHO administration.[A71] One trial was excluded due to incomplete data. [A110] The main findings of the trials assessing pain are summarised in Table 3.18 (see Appendix 6.34 for comparison of results).

Table 3.18: Trials assessing pain – secondary outcomes

STUDY ID	n	UNIT OF MEASUREMENT	TYPE OF DATA		TIME OF MEASUREMENT		INTERVENTION				MAIN FINDINGS
			CONTINUOUS	DICHOTOMOUS	PREOP	POSTOP	CHO	FASTING	PLACEBO	IV	
Zelic, 2013 (A15)	70	100 mm VAS	✓			✓	✓	✓			CHO group overall less pain postop than fasting group ($p > 0.05$)
Yagmurdur, 2011 (A52)	44	100 mm VAS (self reported)	✓		✓		✓	✓			No difference between groups ($p > 0.05$)
Mathur, 2010 (A66)	142	100 mm VAS (self reported)	✓		✓	✓	✓		✓		All between-group comparisons before anaesthesia and postop were not different ($p > 0.05$).
Helminen, 2009 (A71)	210	100 mm VAS	✓		✓		✓	✓		✓	No difference between groups ($p > 0.05$)
Šerclová, 2009 (A75)	105	100 mm VAS	✓			✓	✓	✓			CHO group less pain than the fasting group ($p < 0.05$)*
Hausel, 2005 (A105)	172	100 mm VAS (self reported)	✓		✓	✓	✓	✓	✓		No difference between groups ($p > 0.05$)
Bisgaard, 2003 (A115)	86	100 mm VAS	✓		✓	✓	✓		✓		No difference between groups ($p = 0.228$)
Hausel, 2001 (A121)	252	100 mm VAS (nurse reported)	✓		✓		✓	✓	✓		CHO group: no change in pain preop ($p > 0.05$) Fasting group: no change in pain preop ($p > 0.05$); Placebo group: no change in pain preop ($p > 0.05$)

* Statistical significant result ($p < 0.05$)
CHO = oral carbohydrate treatment group; IV = intravenous carbohydrate treatment group; n = number of participants; postop = postoperative; preop = preoperative; VAS = visual analogue scale

3.4.2.7 Fatique

Three trials assessed fatigue as an outcome (288 participants); [A16, A66, A115] All trials reported on the severity of fatigue experienced (continuous data) with two trials using a 100 mm VAS [A16, A66] and one trial using an ordinal scale.[A115] One of the trials indicated that they made use of self-reporting. [A66] All trials assessed fatigue in both the preoperative and postoperative period. One trial compared oral CHO intake to standard fasting; [A16] two trials compared oral CHO intake to a placebo; [A66, A115] none of the trials compared oral CHO intake to IV CHO administration. The main findings of the trials assessing fatigue are summarised in Table 3.19 (see Appendix 6.35 for comparison of results).

Table 3.19: Trials assessing fatigue – secondary outcomes

STUDY ID	n	UNIT OF MEASUREMENT	TYPE OF DATA		TIME OF MEASUREMENT		INTERVENTION				MAIN FINDINGS
			CONTINUOUS	DICHOTOMOUS	PREOP	POSTOP	CHO	FASTING	PLACEBO	IV	
Yildiz, 2013 (A16)	60	100 mm VAS	✓		✓	✓	✓	✓			CHO group less fatigue preop compared to fasting group ($p < 0.05$)*; No difference between groups postop ($p > 0.05$)
Mathur, 2010 (A66)	142	100 mm VAS (self reported)	✓		✓	✓	✓		✓		CHO group increase in fatigue from preop to postop ($p < 0.005$)*; Placebo group increase in fatigue from preop to postop ($p < 0.005$)*; No difference between group ($p > 0.05$)
Bisgaard, 2003 (A115)	86	Ordinal scale	✓		✓	✓	✓		✓		No difference between groups ($p = 0.228$)

* Statistical significant result ($p < 0.05$)
CHO = oral carbohydrate treatment group; IV = intravenous carbohydrate treatment group; n = number of participants; postop = postoperative; preop = preoperative; VAS = visual analogue scale

3.4.2.8 Weakness

Five trials assessed weakness as an outcome (589 participants). [A16, A64, A71, A94, A121] All of the trials reported on the severity of weakness experienced (continuous data), and used a 100 mm VAS. One of the trials indicated that they made use of self-reporting; [A64] one trial indicated that the nurse administered the score; [A121] and the other trials did not comment. Four trials assessed weakness in the preoperative period [A64, A71, A94, A12] with one trial assessing weakness in both the preoperative and postoperative period.[A16] Two trials compared oral CHO intake to standard fasting; [A16, A94] two trials compared oral CHO intake to both fasting and placebo; [A64, A121] one trial compared oral CHO intake to both fasting and IV CHO administration; [A71] none of the trials compared oral CHO intake to only placebo or IV CHO administration. Only one trial had incomplete data.[A94] The main findings of the trials assessing weakness are summarised in Table 3.20 (see Appendix 6.36 for comparison of results).

Table 3.20: Trials assessing weakness – secondary outcomes

STUDY ID	n	UNIT OF MEASUREMENT	TYPE OF DATA		TIME OF MEASUREMENT		INTERVENTION				MAIN FINDINGS
			CONTINUOUS	DICHOTOMOUS	PREOP	POSTOP	CHO	FASTING	PLACEBO	IV	
Yildiz, 2013 (A16)	60	100 mm VAS	✓		✓	✓	✓	✓			CHO group less weak than fasting group preop ($p < 0.05$)* CHO group less week than fasting group postop ($p < 0.05$)*
Wang, 2010 (A64)	48	100 mm VAS (self-reported)	✓		✓		✓	✓	✓		CHO group no change from 18 hours to 1 hour preop ($p = 0.198$); Fasting group no change from 18 hours to 1 hour preop ($p = 0.775$); Placebo group no change from 18 hours to 1 hour preop ($p = 0.868$); @18 hours preop: no difference in weakness between groups ($p = 0.886$); @1 hour preop: no difference in weakness between groups ($p = 0.832$); CHO vs Placebo group @ 1 hour preop: no difference in weakness ($p = 0.584$)
Helminen, 2009 (A71)	210	100 mm VAS	✓		✓		✓	✓		✓	CHO group: no change in weakness ($p > 0.05$); Fasting group: increase in weakness ($p < 0.05$)*; IV group: no change in weakness ($p > 0.05$)
Melis, 2006 (A94)	19	100 mm VAS	✓		✓		✓	✓			CHO group less weak preop than other groups (p-value missing)
Hausel, 2001 (A121)	252	100 mm VAS (nurse reported)	✓		✓		✓	✓	✓		CHO group: no change ($p > 0.05$) Fasting group: increase in weakness ($p < 0.05$)*; Placebo group: no change ($p > 0.05$)

* Statistical significant result ($p < 0.05$)

CHO = oral carbohydrate treatment group; IV = intravenous carbohydrate treatment group; n = number of participants; postop = postoperative; preop = preoperative; VAS = visual analogue scale

3.4.2.9 Tiredness

Five trials assessed tiredness as an outcome (573 participants). [A52, A64, A71, A94, A121] All trials reported on the severity of tiredness (continuous data) by using a 100 mm VAS. Two of the trials indicated that they made use of self-reporting; [A52, A64] one trial indicated that the nurse administered the score; [A121] and the other trials did not comment. All trials assessed tiredness in the preoperative period only. Two trials compared oral CHO intake to standard fasting only; [A52, A94] two trials compared oral CHO intake to both fasting and a placebo; [A64, A121] one trial compared oral CHO intake to both fasting and IV CHO administration; [A71] none of the trials compared oral CHO intake to placebo or IV CHO administration only. Only one trial had incomplete data.[A94] The main findings of the trials assessing tiredness are summarised in Table 3.21 (see Appendix 6.37 for comparison of results).

Table 3.21: Trials assessing tiredness – secondary outcomes

STUDY ID	n	UNIT OF MEASUREMENT	TYPE OF DATA		TIME OF MEASUREMENT		INTERVENTION				MAIN FINDINGS
			CONTINUOUS	DICHOTOMOUS	PREOP	POSTOP	CHO	FASTING	PLACEBO	IV	
Yagmurdur, 2011 (A52)	44	100 mm VAS (self reported)	✓		✓		✓	✓			No difference between CHO and fasting groups (p > 0.05)
Wang, 2010 (A64)	48	100 mm VAS (self reported)	✓		✓		✓	✓	✓		CHO group no change from 18 hours to 1 hour preop (p = 0.150); Fasting group no change from 18 hours to 1 hour preop (p = 0.299); Placebo group no change from 18 hours to 1 hour preop (p = 0.223); @18 hours preop: no difference in tiredness between groups (p = 0.889); @1 hour preop: no difference in tiredness between groups (p = 0.615); CHO vs placebo group @ 1 hour preop: no difference in tiredness (p = 0.509)
Helminen, 2009 (A71)	210	100 mm VAS	✓		✓		✓	✓		✓	CHO group: no change in tiredness (p > 0.05); Fasting group: increase in tiredness (p < 0.05)*; IV group: no change in tiredness (p > 0.05)
Melis, 2006 (A94)	19	100 mm VAS	✓		✓		✓	✓			CHO group less tired preop than other groups (p value missing)
Hausel, 2001 (A121)	252	100 mm VAS (nurse reported)	✓		✓		✓	✓	✓		CHO group: no change in tiredness (p > 0.05) Fasting group: increase in tiredness (p < 0.0001)*; Placebo group: increase in tiredness (p < 0.001)*;

* Statistical significant result (p < 0.05)

CHO = oral carbohydrate treatment group; IV = intravenous carbohydrate treatment group; n = number of participants; postop = postoperative; preop = preoperative; VAS = visual analogue scale

3.4.2.10 Malaise

Five trials assessed malaise as an outcome (584 participants). [A16, A52, A66, A115, A121] All of the trials reported on the severity of malaise experienced by using a 100 mm VAS; two of the trials indicated that they made use of self-reporting; [A52, A66] one trial indicated that the nurse administered the score; [A121] and the other trial did not comment. Three trials assessed malaise in the preoperative period only; [A52, A66, A121] two trials assessed malaise in both the preoperative and postoperative period; [A16, A115] none of the trials assessed malaise in the postoperative period only. Two trials compared oral CHO intake to standard fasting; [A16, A52] two trials compared oral CHO intake to placebo; [A66, A115] one trial compare oral CHO intake to both standard fasting and a placebo; [A121] none of the trials compared oral CHO intake to IV CHO administration. The main findings of the trials assessing malaise are summarised in Table 3.22 (see Appendix 6.38 for comparison of results).

Table 3.22: Trials assessing malaise – secondary outcomes

STUDY ID	n	UNIT OF MEASUREMENT	TYPE OF DATA		TIME OF MEASUREMENT		INTERVENTION				MAIN FINDINGS
			CONTINUOUS	DICHOTOMOUS	PREOP	POSTOP	CHO	FASTING	PLACEBO	IV	
Yildiz, 2013 (A16)	60	100 mm VAS	✓		✓	✓	✓	✓			No difference between group preop ($p > 0.05$); CHO group experienced less malaise than fasting group postop ($p < 0.05$)*
Yagmurdur, 2011 (A52)	44	100 mm VAS (self reported)	✓		✓		✓	✓			CHO group: decrease in malaise ($p < 0.05$)*; CHO group experienced less malaise than fasting group preop ($p < 0.05$)*
Mathur, 2010 (A66)	142	100 mm VAS (self reported)	✓		✓		✓		✓		No difference between group ($p > 0.05$)
Bisgaard, 2003 (A115)	86	100 mm VAS	✓		✓	✓	✓		✓		No difference between group ($p = 0.349$)
Hausel, 2001 (A121)	252	100 mm VAS (nurse reported)	✓		✓		✓	✓	✓		Fasting group: no change ($p > 0.05$); Placebo group: decrease in malaise ($p < 0.01$)*; CHO group experienced less malaise compared to fasting group ($p < 0.01$)*

* Statistical significant result ($p < 0.05$)
CHO = oral carbohydrate treatment group; IV = intravenous carbohydrate treatment group; n = number of participants; postop = postoperative; preop = preoperative; VAS = visual analogue scale

CHAPTER 4: DISCUSSION

4.1 GENERAL

POCL up to two hours before the induction of anaesthesia is one of the main nutrition elements of the ERAS Society's recommendations.[194-202] This review examined data from 24 trials including 1903 participants receiving POCL undergoing various types of anaesthesia (mainly general or a combination of general and neuraxial anaesthesia) and elective surgical procedures (mainly abdominal surgery). POCL was compared to standard fasting and/or placebo in the majority of trials with only two trials examining IV carbohydrate administration. The trials were conducted in a wide geographical setting with most participants from Sweden. The majority of trials included in this systematic review were still relatively small (< 100 participants). More female than male participants were included in the review with the majority of participants being older than 50 years. It is worth mentioning that many trials limited inclusion to otherwise healthy participants with an ASA score of I – II. Trials that included participants with ASA scores of III and IV generally reported smaller numbers due to the fact that these participants were less likely to undergo elective surgery. Amongst trials included in this review, experimental and control groups were well matched with no significant differences between groups at baseline. A combination of heterogeneous surgical procedures and anaesthetic protocols introduced a number of variables that could have diminished the possibility of detecting any clinical benefit of POCL. Also, trials did not clearly indicate which of the ERAS protocol components formed part of the intervention and this could have a direct effect on the outcomes. The results of the trials were conflicting with some trials showing positive results and others negative or no results. The results of the systematic review will be discussed per outcomes (where applicable, results were grouped together to avoid repetition).

4.2 PRIMARY OUTCOMES

Results were reported as mean (standard deviation) and median (interquartile range), and therefore, all results could not be pooled together. Therefore, the discussion will focus on the data that could be pooled together, single trials as well as trials not included in the review but relevant to the topic.

4.2.1 Biochemical status

4.2.1.1 Glucose

Traditionally, hyperglycaemia was considered a normal adaptive response; today based on physiological data, it is evident that glycaemic control is fundamental in reducing postoperative morbidity and mortality.[164] Hyperglycaemia is associated with increased infectious complications (decreased phagocytosis and glycosylation of immune globulins), poor wound healing (altered collagen synthesis), fluid and electrolyte abnormalities, nutritional depletion (preventing optimal nutritional utilisation), hypertriglyceridemia (decreased lipoprotein lipase activity), accelerated catabolic state, and aggravated symptoms of gastroparesis.[144] Even though neurohormonal alterations (i.e. cortisol, catecholamines and glucagon) and cytokine release (i.e. interleukin-1,

interleukin-6 and tumor necrosis factor α) contributes to stress hyperglycaemia, the primary force still remains gluconeogenesis and insulin resistance.[221] While hyperglycaemia must be avoided the questions still remain what is the optimal glucose level that maximises benefit and minimises risk, and do these levels differ between different population groups.

The results of this review showed that there was no significant difference in glucose levels at baseline between groups (one trial with significant heterogeneity was excluded). However, the POCL group had a significant higher glucose level at the induction of anaesthesia (i.e. after the intake of the carbohydrate beverage) when compared to the fasting group (p = 0002). Two trials respectively showed that the glucose levels was significantly increased in the POCL group compared to the fasting group on day 0 postoperative[222,223] with one trial showing no significant difference.[224] Due to standard physiological processes this is a normal appearance that glucose levels will increase when you give oral glucose (i.e. oral carbohydrates) compared to nothing (i.e. standard fasting). Even though the glucose levels were significantly higher in the POCL group it was still within normal physiological range. Unfortunately, none of the trials evaluated POCL to a placebo group on Day 0 postoperative to compare to the effect of fasting on glucose levels. Interestingly, there was no significant difference in glucose levels between groups on day 1 postoperative. Table 4.1 gives a summary of the trials included in the review at different time intervals (see Appendix 6.16 for clarification of the discussion process).

Table 4.1: Summary of trials assessing glucose at different time intervals in this review

TIME INTERVAL	COMPARISON
BASELINE	No significant difference between groups when data pooled together; [A52, A66, A71, A90, A106] one trial was excluded due to heterogeneity and significant higher glucose levels in the POCL group [A84]
BEFORE ANAESTHESIA	Significant difference between POCL and fasting groups (p = 0.0002);* [A71, A84, A90] no difference between POCL, placebo and IV groups
DAY 0 POSTOPERATIVE	One trial reported results as mean (standard deviation) with no significant results between groups; [A90] two trials reported results as median (interquartile range) with significantly higher glucose levels in the POCL group compared to the fasting group [A68, A74]
DAY 1 POSTOPERATIVE	No significant difference between the POCL, fasting, placebo and IV groups

* Statistical significant result (p < 0.05)

IV = intravenous, POCL = preoperative oral carbohydrate loading

4.2.1.2 Insulin

During the metabolic response there is an increase in glucose production with simultaneous increase in insulin secretion. Therefore, theoretically as the glucose levels increase the insulin levels will increase. POCL mimics the intake of breakfast and causes the release of endogenous insulin to levels seen after a normal meal. It was proposed that the postoperative effect of POCL on insulin sensitivity is related to the enhanced insulin levels at the onset of surgery.[121] Data on insulin levels in this review are conflicting with differences at baseline and no trend observed

(Table 4.2). It is of no clinical value to compare the pooled glucose and insulin values in this review since the same trials were not included at the specified time points due to methodological differences and missing data.

Table 4.2: Summary of trials assessing insulin at different time intervals in this review

TIME INTERVAL	COMPARISON
BASELINE	Significant lower insulin levels in the POCL group versus inactive control when data pooled together (two trials were excluded due to significant heterogeneity) [p = 0.01].* The trials comparing the POCL group to fasting showed significant lower insulin levels when pooled (p = 0.01).*In contrast, the single trial evaluating the POCL group to placebo showed significant higher insulin levels in the POCL group (p = 0.005).* Data reported as median did not record any significant difference between POCL and inactive control groups. One trial compared POCL to IV glucose administration with no significant difference between groups.
BEFORE ANAESTHESIA	No significant difference between the POCL, fasting, placebo and IV groups.
DAY 0 POSTOPERATIVE	One trial investigated POCL to fasting at this point with no significant difference between groups. None of the trials compared POCL to placebo or IV glucose administration.
DAY 1 POSTOPERATIVE	One trial investigated POCL to placebo at this point with a significant difference between groups (p < 0.00001).* None of the trials compared POCL to fasting or IV glucose administration.

* Statistical significant result (p < 0.05)

IV = intravenous, POCL = preoperative oral carbohydrate loading

4.2.1.3 Insulin resistance

Due to the antagonistic effects of the stress hormones released during surgery, there is a decrease in insulin sensitivity with subsequent insulin resistance that is characterised by hyperglycaemia. See Figure 4.1 for a diagrammatic representation of the effect of fasting, POCL and numerous ERAS elements on the effect of different biochemical parameters during surgery (as per author's interpretation). Even though the trauma of surgery itself causes insulin resistance the severity of insulin resistance and hyperglycaemia increase even more with open surgical techniques.[15] The type of anaesthesia used also has an impact on the metabolic response since the use of epidural anaesthesia decreases the release of stress hormones opposing less insulin resistance than expected during general anaesthesia.[164] Standard fasting before surgery also poses a metabolic risk by inducing a catabolic state and enhancing the patient's response to trauma. Therefore, theoretically the patient that was fasted before receiving general anaesthesia for open surgery will have the worst metabolic response. See Figure 4.2 for a diagrammatic representation of the effect of various parameters on insulin resistance (as per author's interpretation). The main aim during the perioperative period is to manage glycaemic control by reducing insulin resistance and creating a more anabolic environment to reduce complications. The intake of a preoperative oral carbohydrate beverage containing approximately 12% carbohydrates (in the form of maltodextrin to decrease to osmolality and increase the gastric emptying time) initiates a more anabolic state.[164] The mechanism by which POCL attenuates postoperative insulin resistance is not fully understood (see Chapter 1).

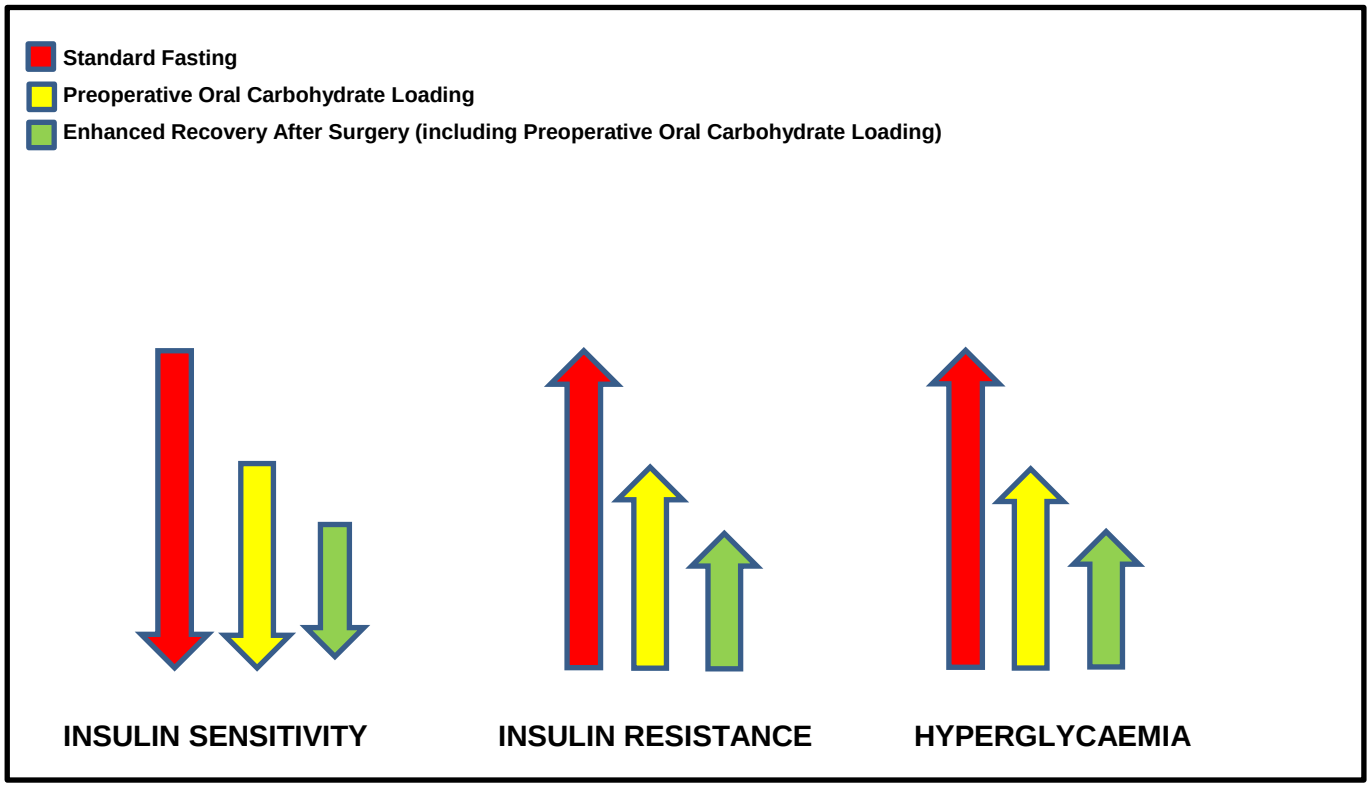


Figure 4.1: Theoretical representation of the effect of POCL and/or multiple ERAS elements on biochemical parameters during surgery

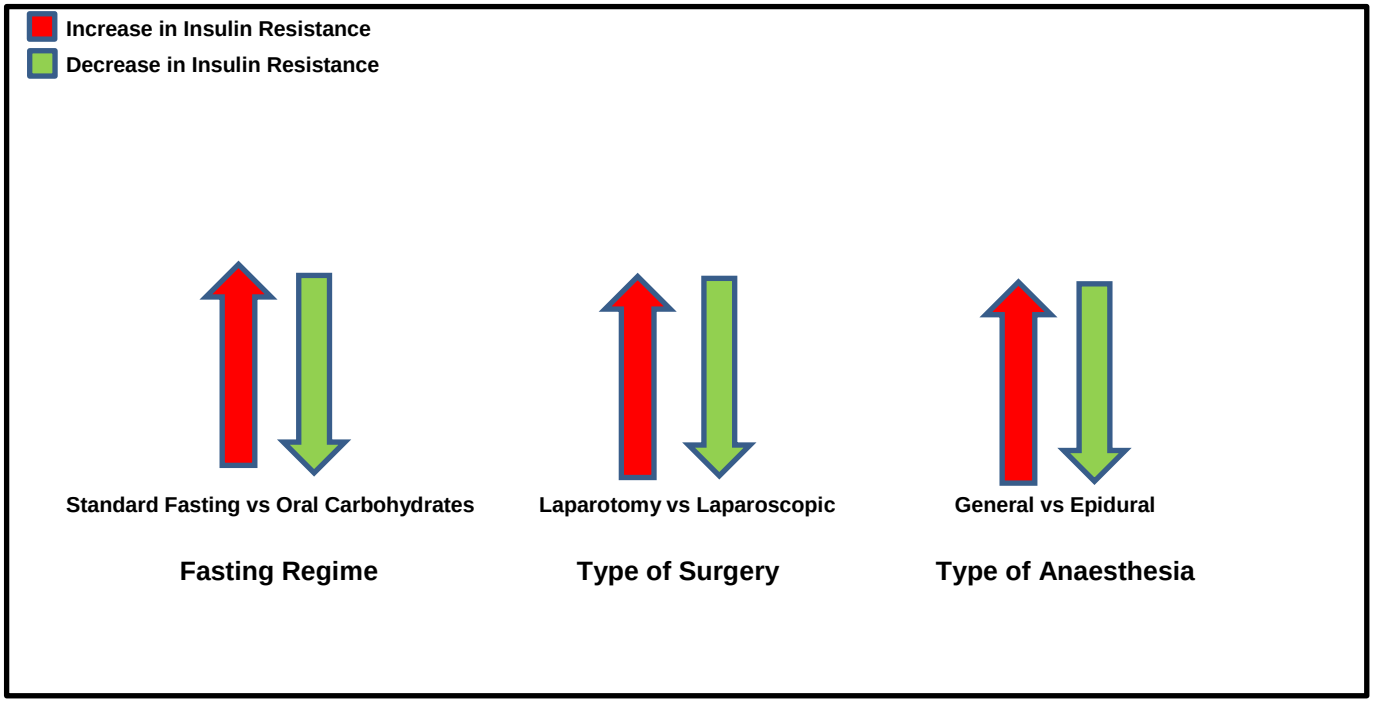


Figure 4.2: Theoretical representation of the effect of various parameters on insulin resistance

Data with regards to insulin resistance should be interpreted with caution since the different methods measure different parameters that are not comparable. The most common methods on this topic include the hyperinsulinaemic euglycaemic clamp (HEC), insulin tolerance test (ITT), homeostatic model assessment – insulin resistance (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI). See Table 4.3 for a comparison of these methods.[16,225] Other methods to measure insulin resistance include the frequently sampled intravenous glucose tolerance test, insulin suppression test, continuous infusion of glucose with model assessment, insulin sensitivity test, oral glucose tolerance test, lipid-based fasting formulae, glucose/insulin ratio, and fasting insulin resistance index. Note that some methods measure insulin resistance while others measure insulin sensitivity; a greater reduction in insulin sensitivity is associated with a greater development of insulin resistance.

The HEC method is the gold standard to measure insulin resistance since it measures insulin resistance in the carbohydrate fed state, and can differentiate between hepatic and peripheral insulin resistance. The HOMA-IR and QUICKI equations measure insulin resistance using the basal glucose and insulin concentrations during the fasted state, making it less sensitive and less accurate.[17] The HOMA-IR and ITT measure different aspects of insulin resistance: HOMA-IR employs simultaneous measures of glucose and insulin to measure insulin resistance whereas ITT uses the rate of glucose disposal in response to insulin to measure insulin sensitivity.[17] The ITT is more reproducible than HOMA-IR, therefore where repetitive measurements are taken for comparison, the ITT should give a more reliable result.[226] A high ITT value indicates benefit by signifying high insulin sensitivity and consequently, reduced insulin resistance whereas a high HOMA-IR value indicates harm by signifying high insulin resistance.

Table 4.3: Methods used to measure insulin resistance[16,225]

Method	Description
HEC *Invasive test*	Insulin is infused intravenously at a constant rate for a specific period while glucose is also infused simultaneously at a variable rate to maintain blood glucose levels at 4.5 mmol/l. Conducted under very controlled circumstances. Entire body glucose disposal calculated (M).
ITT *Invasive test*	Uses the rate of glucose disposal in response to insulin as a measure of insulin sensitivity (the reciprocal of insulin resistance).
HOMA-IR *Non-invasive test*	Equation used to calculate insulin resistance. HOMA-IR = insulin (uu/ml) x blood glucose level (mg/dl) / 405
QUICKI *Non-invasive test*	Crude estimation of insulin sensitivity derived from the inverse of the sum of the decimal logarithms of the fasting insulin and fasting glucose levels.

HEC = hyperinsulinaemic normoglycaemic clamp; ITT = insulin tolerance test; HOMA-IR = homeostatic model assessment – insulin resistance; QUICKI = quantitative insulin sensitivity check index

The number of trials included in this review was limited with only six trials assessing insulin resistance. Four trials used the HEC method and two trials used the HOMA-IR method. None of the included trials used the QUICKI or ITT methods. The trials using the HEC method to measure insulin resistance included a relatively small number of participants.[186,227-229] Interestingly, the four

trials using this method were conducted by only two authors. Descriptive statistics were used to present trials using the HEC method since the comparison between the trials were challenging with regards to comparison groups (i.e. POCL versus placebo, POCL versus fasting), time intervals (i.e. day before surgery to day 1 postoperative, 1 week preoperative to third day postoperative, 1 week preoperative to immediate postoperative), and no fixed consensus on the important parameters (i.e. duration of infusion, infusion rate). Both the trials using the HOMA-IR method to calculate the insulin resistance did not find any significant difference between the POCL, fasting and placebo groups.[223,230] To note is that none of the trials compared POCL to fasting and placebo in the same trial since the emphasis here will be on the amount of oral carbohydrate intake rather than the volume of fluid intake. Table 4.4 gives a summary of numerous trials available in the literature evaluating the effect of POCL on the development of postoperative insulin resistance.

From Table 4.4 it is evident that there is great variability in trials assessing these outcomes:

- Different measurement methods i.e. HEC, HOMA-IR, QUICKI, ITT;
- Sample size i.e. small sample size with HEC method as the gold standard including the least number of participants;
- Type of surgery i.e. minor versus major surgery, laparoscopic versus open surgery;
- Type of anaesthesia i.e. general versus neuraxial versus combination;
- Experimental groups i.e. amount of CHO and volume of POCL, evening dose of POCL;
- Control groups i.e. inactive (standard fasting, placebo), active (IV POCL), no control
- Time of measurement i.e. baseline (one week before surgery to day before surgery), postoperative (immediate after surgery versus a day or two after surgery).

Trials evaluating insulin resistance by the HEC method. Eight trials assessed this outcomes but were conducted by a limited number of authors: two trials were conducted by Ljunggren et al, two trials by Svanfeldt et al, two trials by Soop et al, and Olle Ljungqvist was principal or co-author in six of the trials.[161,185,186,189,227,228,229,231] The majority of trials evaluated insulin resistance at baseline and within the first 24 hours postoperative. Insulin resistance develops within hours after surgery; therefore, results from immediate postoperative compared to 24 hours or more postoperative will be different and cannot be pooled together. Soop 2004 et al evaluated insulin resistance at baseline and at day 3 postoperative, and concluded that the sites of postoperative insulin resistance shifts from mainly or exclusively peripheral tissues in the first 24 hours after surgery to involve also the liver to a substantial degree on day 3 postoperative.[186]

Table 4.4: Trials evaluating the effect of POCL on the development of insulin resistance

Study	n	Type of Surgery	Type of Anaesthesia	Experimental Group	Control Group	Time of Measurement	Findings	p - value
Hyperinsulinaemic Euglycaemic Clamp								
Ljunggren 2014 [227]	22	Hip replacement	General + spinal	POCL 800 ml (pm) + 400 ml (am)	Placebo	Before surgery and on day 1 postoperative	IS decreased by 51% in POCL group compared to 39% in the placebo group	> 0.05
Ljunggren 2012 [228]	57	Hip replacement	Spinal	POCL 800 ml (pm) + 400 ml (am)	Standard fasting placebo	Before surgery and on day 1 postoperative	IS decreased by 51% in POCL group compared to 43% in the fasting group; no significant difference between POCL and placebo	< 0.05 **
Svanfeldt 2007 [189]	12	Colorectal surgery	General + epidural	High POCL (125 mg/ml CHO) – 175 – 200 g CHO	Low POCL (25 mg/ml CHO) – 35 – 40 g CHO	Before surgery and on day 1 postoperative	No effect on postoperative peripheral IS	0.049 **
Svanfeldt 2005 [231]	6	Simulated setting (no surgery)	No anaesthesia	POCL 800 ml (pm) POCL 400 ml (am) POCL 800 ml (pm) + 400 ml (am)	Standard fasting	120 minutes after the morning drink (i.e. onset of 'surgery')	IS increase by 50% three hours after intake of morning drink	< 0.01 **
Soop 2004 [186]	14	Hip replacement	Epidural	POCL 800 ml (pm) + 400 ml (am)	Placebo	1 week preoperative and on day 3 postoperative	IS decreased by 36% in POCL group compared to placebo group	> 0.05
Soop 2001 [229]	15	Hip replacement	Epidural	POCL 800 ml (pm) + 400 ml (am)	Placebo	1 week preoperative to immediately postoperative	IS decreased by 18% in POCL group compared to placebo group	< 0.05 **
Nygren 1999 [185]	30	Colorectal surgery (14); Hip replacement (16)	Colorectal: general + epidural Hip: spinal + epidural	POCL 800 ml (pm) + 400 ml (am)	Standard fasting (colorectal surgery) Placebo (hip replacement)	Colorectal: day before surgery and 24 hours postoperative; Hip Replacement: 1 week before surgery and immediately after surgery	Colorectal: 24% greater reduction in IS in fasted group than in POCL group at 24 hours postoperative; Hip replacement: 37% reduction in IS in placebo group immediately after surgery; no significant reduction in IS in POCL group	< 0.05 **

Ljungqvist 1994 [161]	12	Open cholecystectomy	General	IV glucose infusion	Standard fasting	3 days preoperative and on day 1 postoperative	IS reduced in fasting group compared with IV glucose group	< 0.01 **
Homeostatic model assessment – insulin resistance								
Lidder 2013* [226]	120	Colorectal surgery	General + epidural	POCL + Postop Placebo; Preop Placebo + Postop ONS; POCL + Postop ONS	Preop placebo + Postop placebo	Before surgery and day 1, 2, 3 postoperative	IR lower in group receiving supplements than in group receiving placebo	0.001 **
Pexe-Machado 2013 [167]	22	Gastrointestinal surgery	General + epidural	POCL with pea protein hydrolysate: 400ml (pm) + 200ml (am)	Standard fasting	Before surgery and on day 1 postoperative	No significant difference between groups	0.34
Dock-Nascimento 2012 [174]	48	Laparoscopic cholecystectomy	General	POCL with water + maltodextrin + glutamine	Standard fasting; water (placebo); POCL with water + maltodextrin (POCL)	At induction of anaesthesia and 10 hours postoperative	IR greater in control group than placebo, CHO and CHO/glutamine groups	0.04 **
Perrone 2011 [166]	17	Cholecystectomy and inguinal hernia repair	Unknown	POCL with whey: 474 ml (pm) + 237 ml (am)	Placebo (water)	1 hour before anaesthesia and day 1 postoperative	IR significantly lower in POCL-whey group than placebo group.	0.03 **
Mathur 2010 [230]	142	Colorectal and hepatic surgery	General + Epidural	POCL 800 ml (pm) + 400 ml (am)	Placebo	Baseline to days 1, 5, 7 postoperative	IR significantly higher in placebo group	< 0.05 **
Wang 2010 [232]	48	Colorectal surgery	General	POCL 400 ml (am)	Standard fasting Placebo	4 hours before surgery and immediately postoperative	IR increased significantly in all study groups but were significantly lower in the POCL group	< 0.001 **
Tran 2009* [223]	38	Coronary artery bypass and spinal surgery	General	POCL 800 ml (pm) + 400 ml (am)	Standard fasting	Baseline (after 12 hour fast) and immediately postoperative	No significant difference.	0.14
Faria 2009 [138]	21	Laparoscopic cholecystectomy	General	200 ml POCL	Standard fasting	At induction of anaesthesia and 10 hours postoperative	IR is higher in POCL group than fasting group	0.03 **
Rapp-Kesek 2007 [233]	18	Coronary artery bypass	Unknown	POCL 400 ml (pm) + 400 ml (am)	Standard fasting	Day before surgery to days 1, 2 and 6	IR is higher in POCL group than fasting group on day 6.	< 0.05 **

						postoperative		
Quantitative Insulin Sensitivity Check Index								
Kaska 2010 [222]	194	Colorectal surgery	General	POCL: 400 ml (pm) + 400 ml (am)	Standard Fasting 500 ml 10% IV glucose overnight and 2-6 hours preoperative	1 day preoperative to immediate, day 1, 3 and 7 postoperative	IS reduced in fasting group when compared with the other groups	< 0.05 **
Insulin Tolerance Test								
Lidder 2013* [226]	120	Colorectal surgery	General + epidural	POCL + Postop placebo; Preop placebo + Postop ONS; POCL + Postop ONS	Preop placebo + Postop placebo	Before surgery and day 1, 2, 3 postoperative	IS increased in group receiving POCL + Postop ONS	< 0.001 **
Tran 2009 * [223]	38	Coronary artery bypass and spinal surgery	General	POCL 800 ml (pm) + 400 ml (am)	Standard fasting	Baseline (after 12 hour fast) and immediately postoperative	No significant difference.	0.41

* measured insulin resistance by both HOMA-IR and ITT

** Statistical significant result ($p < 0.05$)

n = number of participants; POCL = preoperative oral carbohydrate loading; CHO = carbohydrate; IR = insulin resistance; IS = insulin sensitivity; pm = evening before surgery; am = morning of surgery; ? = information missing; ONS = oral nutritional supplementation

The hypocaloric nutrition and immobilisation that are common during the postoperative period exacerbate the development of insulin resistance. It is known that insulin resistance develops in healthy volunteers after three days of hypocaloric feeding[234] and after 6–7 days of bed rest.[235] Therefore, the results should be interpreted according to the time of postoperative measurement (i.e. immediate postoperative versus 24 hours or more postoperative). Nygren et al compared POCL to standard fasting and placebo with a significant decrease in insulin sensitivity in the standard fasting and placebo groups; unfortunately, there were confounding factors with regards to type of surgery (fasting group received colorectal surgery while the placebo group received hip replacement) since the degree of postoperative insulin resistance is related to the magnitude of surgical trauma, and the time interval of measuring the outcomes (colorectal surgery group within 24 hours and hip replacement group immediately postoperative) since hypocaloric nutrition during the first few days postoperative is associated with increased insulin resistance.[185] In contrast, Ljunggren 2012 et al compared POCL to standard fasting and placebo in patients receiving hip replacement surgery with a significant decrease in insulin sensitivity in the POCL group compared to the fasting group, and no significant difference between the POCL and placebo groups.[228] Ljunggren 2014 et al completed another trial with no significant difference between the POCL and placebo groups.[227] Svanfeldt 2005 et al reported a 50% reduction in insulin sensitivity in the POCL group three hours after the intake of the beverage. Unfortunately, this was a simulated situation with no surgery or anaesthesia.[231] The landmark study by Ljungqvist et al in 1994 showed that the administration of IV glucose had a significant lower reduction in insulin sensitivity when compared with standard fasting.[161]

Trials evaluating insulin resistance by the HOMA-IR method. The trials evaluating insulin resistance by means of HOMA-IR included different carbohydrate beverages i.e. standard POCL,[138,223,230,232] POCL with pea protein hydrolysate,[167] POCL with glutamine,[174] POCL with whey protein,[166] and POCL with postoperative oral nutritional supplementation.[226] Pexe-Machado et al used a carbohydrate drink which contained a pea protein hydrolyse; there was no significant difference between the groups, which can be attributable to the fact that the HOMA-IR measurement only took place on day 2 postoperative when patients were already established on oral or enteral nutrition.[167] Dock-Nascimento et al compared a carbohydrate drink with added glutamine (total of 0.77g of body weight), carbohydrate drink without glutamine, water and standard fasting; there was a significant increase in insulin resistance in the fasting group compared with the other groups.[174] The authors of this trial took the necessary precautions of the effect of nutrition into account and evaluated insulin resistance ten hours postoperative before nutrition intake. There was no significant difference between the two POCL groups (one with glutamine and one without glutamine). Most likely, the minor type of surgery might have influenced these results, and might be different in larger trials with major surgery. Perrone et al. compared POCL with added whey protein to a placebo of water intake; the POCL-whey group had significant lower insulin resistance. It is

difficult to draw a conclusion since there was no POCL group without whey protein or just a whey group to act as control, so theoretically these results may also reflect only the effect of POCL.[166] Lidder et al investigated the effect of combining POCL with postoperative oral nutritional supplementation, and concluded that when POCL are combined with a postoperative oral nutritional supplementation, benefit is seen when compared with no supplements; and with patients adhering to POCL or a postoperative oral nutritional supplementation, an intermediate effect is seen.[226] Rapp-Kesek et al reported severe insulin resistance postoperative in both the POCL and standard fasting groups – only significant difference on day 6 postoperative.[233] The severity of insulin resistance could be attributable to the fact that the study population was elderly and that the participants received POCL as well as glucose infusion. Nevertheless, five trials indicated that the POCL groups (with or without added protein) had significant less insulin resistance in the postoperative period when compared with standard fasting or placebo.[166,174,226,230,232] Two trials had no difference in postoperative insulin resistance between POCL and fasting groups.[167,223] Two trials had significant higher postoperative insulin resistance in the POCL group than compared to fasting.[138,233]

Trials evaluating insulin resistance by the QUICKI method. Kaska et al was the only trial using this method to measure insulin resistance.[222] The trial focused exclusively on POCL as an element of the ERAS protocol. POCL was compared with standard fasting and IV glucose administration. The fasting group had significant higher insulin sensitivity levels immediate postoperative with the POCL group having the best results by preserved insulin sensitivity in the postoperative period. Keep in mind that the QUICKI method only provided a crude estimation of insulin sensitivity (since basal glucose and insulin concentrations were used for its calculation), and could not be compared to the HEC method.

Trials evaluating insulin resistance by the ITT method. The trials by Lidder et al and Tran et al used the HOMA-IR as well as the ITT methods.[223,226] The ITT uses the rate of glucose disposal in response to insulin as a measure of insulin sensitivity (the reciprocal of insulin resistance), and are more reproducible than the HOMA-IR since serum insulin and glucose fluctuate even under strict controlled conditions. Lidder et al had four comparison groups with POCL and/or postoperative ONS: HOMA-IR reported a significant decrease in insulin resistance in the group receiving both POCL and postoperative ONS ($p = 0.011$) confirmed by the ITT method which showed significant increased levels of insulin sensitivity in the group receiving both POCL and postoperative ONS ($p < 0.001$).[226] In contrast, Tran et al reported no significant difference between the POCL or standard fasting groups whether measured by HOMA-IR or ITT ($p > 0.05$).[223]

4.2.2 Protein status

The catabolic state of surgery and fasting is associated with depleted glycogen stores, which increase the demand for protein and in return, causes loss of protein stores.[236] Confounding factors

like bed rest increases protein loss with malnutrition exacerbating the response even further.[164] By reducing insulin resistance, any energy and protein consumed will be utilised in a more anabolic fashion, hyperglycaemia reduced, less lean body mass will be lost and patients will be mobilised quicker.[193] Since muscle function correlates closely with total body protein, a loss of muscle mass results in decreased muscle strength, and decreased muscle strength is associated with loss of physical functionality and negative impact on recovery.[237] Some authors studied POCL and the effect on muscle preservation by attenuating protein catabolism but further studies are needed to prove that POCL is able to significantly preserve muscle mass and function. The varied outcome and methodology measures used could be a contributing factor to the uncertainty. Different methods were employed to measure muscle mass and strength i.e. blood tests, mid-arm circumference, dynamometer and digital tension meter. The question still remained whether the energy provided during POCL can minimise the loss of lean tissue brought about by increased gluconeogenesis during the early postoperative period.

4.2.2.1 Total body protein (Muscle mass)

Muscle mass was expressed as total body protein when derived from measuring total body nitrogen (total body protein = total body nitrogen X 6.25).[230] Data included in this review with regards to protein status was limited with no trial assessing the effect of POCL to standard fasting or IV glucose administration. Mathur et al and Soop 2004 et al compared POCL to a placebo with no significant difference between the groups at any of the stipulated time points with regards to total body protein.[186,230] In contrast, Yuill et all concluded that muscle mass as indicated by mid-arm muscle circumference was significantly more in the placebo group than the POCL group ($p < 0.05$).[188] Worth mentioning is that the influence of gender should be accounted for if it is not the same in the different groups due to gender differences in body composition.[186] Postoperative nitrogen losses are associated with increased peripheral proteolysis while protein synthesis is not that much affected.[238] Furthermore, the attenuation of postoperative endogenous glucose release may be associated with reduced nitrogen losses.[186] Increased levels of insulin-like growth factor type 1 with its insulin-like effects on glucose uptake have been described as an underlying mechanism when POCL increases glycogen synthesis and reduces postoperative catabolism. [186]

4.2.2.2 Muscle strength (muscle function)

Handgrip strength is an indicator of nutritional status as well as functional status with a predictive importance to show morbidity and mortality.[239,240] Impaired handgrip strength is a predictor of increased postoperative complications, increased length of stay and decreased physical status.[237] Mathur et al reported that compared with the baseline, grip strength in both the POCL and placebo groups, when measured with a dynamometer was reduced for the first seven days postoperative ($p < 0.010$), returning to baseline by day 28, with no significant difference between groups.[230] Furthermore, Kaska et al confirmed that there was no significant difference in handgrip (as measured by a digital tension meter) between the POCL, fasting and IV glucose groups on

postoperative days one to seven.[222] In contrast, Noblett et al reported that the fasted group had a significant reduction in grip strength (as measured by the dynamometer) on discharge when compared with baseline ($p < 0.05$), with a mean drop of 11% (compared to the 5% drop of the POCL and 8% of the placebo groups).[236] The exact mechanism underlying the change in handgrip strength is unclear but may be related to a reduction in protein loss. One limitation of handgrip strength is that it is only an indicator of upper limb strength.[237] Nevertheless, it is a simple bedside measurement that provides valuable information on nutritional and/or functional status.

4.2.3 Immune status: C-reactive protein

Surgical stress involves the activation of the sympathetic nervous system, secretion of catabolic hormones and cytokine responses, which cause tissue damage.[130] The stress response has developed as an evolutionary response to allow injured beings to survive without food and still heal their wounds. However, in a highly controlled surgical environment this response is associated with deleterious effects (i.e. immunosuppression and impaired wound healing).[241] Because of wide availability, good reproducibility, and low-cost plasma, CRP concentrations could be an attractive biomarker to evaluate the inflammatory response to surgery.[242] CRP is a positive acute phase protein produced in the liver as a response to a stimulation by interleukin-6 (IL-6).[243] The hepatic synthesis of CRP start six to eight hours after the onset and peaks 36 to 50 hours after the infection has started, whereas IL-6 (proinflammatory cytokines) appear within one hour after the onset of infection.[244] The effect of POCL needs to be evaluated as soon as possible (within 24hours) postoperative to account for the confounding factors that may affect the outcomes when the measurement is delayed (i.e. initiation of enteral nutrition or food intake, effect of medication). Therefore, IL-6 may be a better indicator of inflammation than CRP within the first 24 hours postoperative due to its early appearance. Interestingly, in this review the only significant difference between the groups was reported on day 1 postoperative when the POCL group had a significantly lower CRP than the fasting group ($p = 0.006$). Therefore, the results must be interpreted with caution since there are no comparable IL-6 results available.

4.2.4 Complication status

4.2.4.1 Return of intestinal function

Literature differentiates between return of intestinal function as days from surgery to first flatus/stool or bowel movement. In this review only two trials reported on this outcome: Serclova et al reported a significant fewer days (MD -1.80 days; $p < 0.00001$) for return of intestinal function in the oral CHO group compared to the fasting group;[245] Noblett et al reported no significant difference in return of intestinal function between the oral CHO, fasting and placebo groups (even though there was a trend towards increased return of intestinal function in the oral CHO group).[236] A Cochrane Review concluded that POCL is associated with a small increase in the return of intestinal function when measured as time to first flatus/stool when compared with fasting or

placebo (MD -0.39; (95% CI 0.70 to -0.07 days).[122] The reason for this is that the Cochrane Review included additional trials: An et al reported a significant reduction in time to passage of flatus[246] and Ozdemir et al reported on time to first bowel movement with no evidence of treatment effect.[247] The effect of the other ERAS elements on the return of intestinal function must be taken into account when reporting on these outcomes i.e. the type of surgery (laparoscopic versus open; major versus minor) and type of anaesthesia. An intestinal ischaemia reperfusion animal model showed that POCL preserves the intestinal function (by increased jejunal motility) which results in decreased inflammation and reduced bacterial translocation which consequently promotes early enteral feeding.[248] It is important to remember that it may not always be possible to directly extrapolate results obtained in animal models to the clinical situation in humans. The early return of intestinal function could also be a contributing factor to reduced length of stay since one of the discharge criteria from a hospital is a functional intestinal tract. The question still remains that whether any changes seen were due to the preoperative calories received through the POCL and/or due to the hydration and maintenance of peristalsis by fluid intake.[236] Findings from this review suggest further research on this outcome.

4.2.4.2 Length of stay

Although ten trials were included in this review; only a limited number could be pooled together since statistical results were reported as mean and median, and they were categorised according to ICU length of stay, hospital length of stay and fit for discharge. Jarvela et al was the only trial reporting on the length of ICU stay with no significant difference between the POCL and fasting groups ($p = 0.13$).[224] The majority of trials reported on hospital length of stay but there were significant heterogeneity between trials and results were reported as mean and median. Results for two trials comparing POCL to the inactive control (fasting and placebo) were pooled together with no significant difference in length of stay between the groups ($p = 0.37$).[229,249] The results of Serclova et al could not be pooled due to heterogeneity but reported significant shorter hospital stay in the POCL group compared to the fasting group ($p < 0.05$).[245] Another trial by Soop 2004 et al could not be pooled due to missing data but reported no significant difference between POCL and placebo groups.[186] The other trials on hospital length of stay reported results as median/interquartile range with three trials showing no significant difference between groups[188,222,230] and one trial showing significant shorter hospital stay in favour of the POCL group ($p = 0.008$).[223] Mathur et al was the only trial reporting on length of stay as fit for discharge with no significant difference between the POCL and placebo groups.[230] Unfortunately, none of the trials compared POCL to IV glucose administration. A meta-analysis by Awad et al indicated that POCL had no significant effect on length of stay; however, when a subgroup analysis was performed on the type of surgery the group receiving major abdominal surgery had a significant shorter length of stay (-1.08 days; $p = 0.007$).[121] Evidently, it is important to do subgroup analyses on the type of surgery performed since patients going for minor surgery (i.e. day surgery or minimal invasive

laparoscopic surgery) would have an expected short length of stay and it would be impossible to demonstrate a measurable difference in length of stay between POCL and control groups. The main underlying mechanism in the difference in length of stay between POCL and control groups are thought to be enhanced recovery and/or reduction in complications – both associated with the magnitude of insulin resistance.[121] Insulin resistance is an independent predictor in length of stay.[132] Minor surgery is associated with minimal insulin resistance and complication rates; therefore, an intervention such as POCL would not be expected to improved clinical outcomes (primary outcomes) but rather improved patient well-being (secondary outcomes).[191,192] The Cochrane Review concluded that POCL was associated with a decrease in length of hospital stay when compared with fasting or placebo (by 0.30 days; 95% CI 0.56 to 0.04); however, no significant difference was detected between the POCL and placebo groups (-0.13 days; 95% CI -0.38 to 0.12).[122] The analysis of major surgery when using the fast track ERAS protocol showed a reduction in length of stay by 2.0 to 2.5 days and complications reduced by 30 to 50%.[208]

4.2.4.3 Adverse events

Adverse events can be classified as major (i.e. aspiration, regurgitation, morbidity and mortality) and minor (i.e. thirst, hunger, nausea, vomiting, anxiety, pain, fatigue, weakness, tiredness and malaise). The major adverse events will be discussed in this section while the minor adverse events will be discussed in section 4.3 as secondary outcomes. As expected, the data in relation to major adverse events was limited per specific outcome. However, no incidence of major adverse events was reported in this review (either directly or indirectly). This is in line with other reviews published on the same topic stating no decrease or increase in adverse events.[16,74,122,122] Though some trials did report on regurgitation and aspiration as an outcome most relied on surrogate indicators of risk i.e. participants' gastric volume and pH, and doctor reported incidence. The influence of H2-receptor antagonists should be clearly stated since this will have a direct effect on the gastric volume and pH; however, the routine use of this medication is not recommended for the population group studied in this review. Furthermore, no events involving aspiration pneumonitis due to POCL have been registered in any clinical trial up to now.[183] When reporting on the morbidity of the intervention it is important to distinguish between complications directly related to the intake of the oral CHO beverage (i.e. allergic reaction, intolerability requiring discontinuation of the beverage, or clinical signs of electrolyte abnormalities) and other indirect confounding factors. Few trials specifically reported on mortality as an adverse event; therefore, the data was extrapolated from data provided in the published articles by assuming that there was no mortality if the same number of participants that started with the trial completed the trial (taking into account participants who were lost to follow-up due to not meeting inclusion criteria). From the data published in the literature no definite conclusion can be made with respect to major adverse events due to limited data. However, there is no indication that participants drinking a preoperative oral carbohydrate beverage are at increased risk compared to participants who followed a standard fast

or had a placebo to drink. Therefore, the intake of a carbohydrate drink preoperatively is safe (taking into account timing of the intervention).

4.3 SECONDARY OUTCOMES

POCL affects the well-being of a patient during the perioperative period. However, data on well-being presented in this systematic review are conflicting with variability in terms of type of data, unit of measurement, time of measurement, interventions and comparisons. It is important to differentiate between the intragroup (i.e. measurements from the beginning to the end in the same intervention groups) and intergroup comparisons (i.e. measurements from the beginning to the end in different intervention groups), different scales used to measure the same outcomes, as well the time of measurement (i.e. preoperative and/or postoperative) when reporting on these outcomes.

4.3.1 Thirst and hunger

The majority of data shows that the intake of oral CHO significantly decrease the sense of thirst and hunger during the preoperative period when compared with fasting.[190,191,223,232,250,251,252] Yildiz et al also indicated that the oral CHO group felt significantly less thirsty and hungry two hours postoperative than the fasting group while at 24 hours postoperative there was no significant difference.[251] The results between thirst and hunger in the oral CHO and placebo groups are contradictory, and the question still remains if a CHO drink reduces thirst more than the placebo.[57191,230,232] Trials by Wang et al and Mathur et al comparing oral CHO intake to placebo during the perioperative period indicated no significant difference between the groups with regards to thirst and hunger.[230,232] Nygren et al indicated that patients drinking an oral CHO drink felt less thirsty for 60 minutes compared to the placebo group feeling less thirsty for 40 minutes preoperatively; with regards to hunger the CHO group had no change in the sense of hunger while the placebo group felt significantly less hungry for a short period of 20 minutes.[57] There is little indication that patients given different beverages preoperatively experience different levels of thirst and hunger.[74] The obvious reasoning would be that the intake of fluid would decrease the sense of thirst without considering the type of fluid (i.e. oral CHO versus placebo). The volume of fluid ingested will also have an effect on the intensity of thirst experienced.

Brady et al (Cochrane Review) reported that there was a decrease in thirst in the low volume intake (< 150 ml) and high volume intake (> 150 ml) in the preoperative period; attributable to the fact that given access to an unlimited volume of fluid intake preoperatively it is likely that most patients will exercise a natural restraint in the volume of their intake. [74] In the same review, the fasted group reported increasing hunger while the group given a high volume (> 150 ml) reported feeling less hungry or a experiencing a reduction in the sense of hunger; however, no difference in the hunger rating was reported when unlimited fluid intake was compared with standard fasting. [74] Further, IV CHO administration does not decrease the sense of thirst and hunger as effectively as oral CHO.[253] The effect of hunger in the oral CHO group is probably directly related to the intake of

energy, and may have an indirect positive effect on anxiety by making the patient more at ease.[191] The outcome of receiving additional oral CHO the evening before surgery might influence the thirst and hunger scoring preoperatively and must be investigated.

4.3.2 Nausea and vomiting

Postoperative nausea and vomiting occurs in 20 to 40% of patients despite preventative measures.[254] Nausea and vomiting may cause electrolyte imbalance, infections, dehydration, increase the risk for aspiration and delay recovery and hospital discharge. From the patient's perspective, nausea and vomiting may be even worse than pain after surgery and the effect will definitely delay hospital discharge.[255] Several trials assessed nausea[190-192,224,230,232,245,249,251,252,254,255] and vomiting[224,245,249,254,255,192] as an outcome with conflicting results.

Preoperatively, there was no difference in severity of nausea experienced between the oral CHO and fasting groups.[232,252] However, Hausel 2001 et al reported that the placebo group felt significantly more nauseous during the preoperative period.[191] Postoperatively, Yilmaz et al reported a significant reduction in the severity of nausea on day 1 in the CHO group compared to the fasting group with Zelic et al reporting a non-significant reduction in the severity of nausea on day 2 in the same group.[254,255] However, Bisgaard et al reported no difference in the severity of nausea between oral CHO and placebo groups on day 1 postoperative (worth mentioning is that Bisgaard et al used an ordinal scale and not a VAS like the other trials measuring this outcome).[192] The number of patients experiencing postoperative nausea varied with Hausel et al indicating no difference between groups on day 1,[249] Jarvela et al indicating that significantly more patients felt nauseous in the CHO group compared to the fasting group on day one postoperative,[224] Serclova et al indicating significantly fewer patients felt nauseous in the CHO group compared to the fasting group on day two to four.[245] However, Bisgaard et al reported no significant difference in the number of patients experiencing postoperative nausea in the oral CHO and placebo groups. [A115] The three trials reporting on the severity of nausea experienced during the perioperative period reported no significant difference between the oral CHO, fasting and placebo groups.[230,249,251] These findings are in line with another systematic review indicating no difference in the rates of nausea between oral CHO intake versus standard fasting or placebo.[120]

Vomiting was only assessed in the postoperative period, but it should be noted that carbohydrate loading takes place during the preoperative period. Therefore, factors influencing vomiting should be taken into account, and there should be distinction between vomiting due to illness, type of anaesthesia, type and duration of surgery, and the direct effect of drinking a clear fluid preoperatively.[249] The severity of vomiting was significant less when oral CHO was compared to fasting on day one postoperative;[254] however, there was no difference between the oral CHO and placebo group on day one postoperative.[192] Although the trial by Serclova et al indicated that the number of patients vomiting in the oral CHO group was significant less than the fasting group

during the postoperative period,[245] the other trials failed to show a significant effect even though there was a trend of less vomiting in the oral CHO group.[192,224,249,255]

The majority of trials did not take the immediate postoperative emetic effect of anaesthesia and surgery into account as well as the anti-emetics drugs used. Although anti-emetic drugs are not routinely recommended, they will definitely decrease the incidence and severity of nausea and vomiting and should be taken into consideration when trials are reviewed. A Cochrane review concluded the following regarding nausea and vomiting: it rarely occurred when a shortened fluid fast was compared to a standard fast (timing of intake); there was no difference in nausea and vomiting when water was compared to a standard fast and little indication that participants given different drinks preoperatively experienced different levels of nausea and vomiting (type of intake); no indication that the volume of fluid intake increased the sense of nausea and vomiting (volume of intake).[74] Another Cochrane Review confirmed that the evidence is insufficient to show whether oral CHO beverages increase or decrease postoperative nausea and vomiting.[122]

4.3.3 Anxiety

The majority of trials indicated that preoperative oral CHO intake significantly decreased anxiety in the preoperative period when compared to standard fasting[223,252,254,191] and IV CHO administration.[253] However, the same is not true when oral CHO is compared to a placebo in the preoperative and postoperative period – there was no significant difference between the groups.[191,230,232] A Cochrane Review confirmed that participants given a preoperative oral CHO beverage reported less anxiety than those in the standard fasting group, but emphasised that less anxiety was reported by participants permitted an oral CHO beverage when compared with a placebo or water.[74] It is important to take the external triggers of anxiety into consideration when commenting on these findings, and the timing of measuring the outcomes (i.e. preoperative versus postoperative). The preoperative waiting period itself is a cause of anxiety and the exact preoperative time of the preoperative waiting period should be indicated in trials. Yagmurdur et al indicated that even though anxiety decreased preoperatively after the intake of the oral CHO, it increased intraoperative due to the conscious state of the patient during the surgical procedure without any sedation.[252] Furthermore, perioperative anxiety is associated with postoperative pain, healing and length of hospital stay.[256]

4.3.4 Pain

Even though pain increased from the preoperative to the postoperative period, the majority of trials indicated that the patients experience no significant difference in pain between the different groups.[191,192,230,249,252,253,255] Serclova et al was the only trial indicating that pain was significantly better controlled in the oral CHO group when compared to standard fasting.[245] Note that this trial measured the results in the postoperative period up to day five. Intraoperative pain was assessed in a trial by Yagmurdur et al with no difference between the oral CHO intake and standard fasting

group. It is worthwhile to mention that pain should not differ after spinal anaesthesia (without sedation) between groups, and therefore, the type of anaesthesia should be considered when commenting on the severity of pain experienced.[252] A Cochrane Review confirmed that the duration of fasting, type of fluid ingested or the volume of the fluid ingested had no significant difference on the pain experienced.[74] It is important that the effect of postoperative pain management by an epidural catheter with constant infusion as well as oral medication must be considered when comparing these results.

4.3.5 Fatique/weakness/tiredness/malaise

Due to the direct insult of surgery there is increased discomfort with regards to fatigue, weakness, tiredness and malaise from the preoperative to the postoperative period in all groups. The oral CHO intake group experienced less discomfort in trends of fatigue, weakness, tiredness and malaise during the preoperative period when compared with standard fasting.[190,191,251,252] The fasted group had a notable increase in discomfort during the preoperative period while the placebo group did not differ significantly from the oral CHO group during this period.[230,232] The data for the postoperative period is limited with results for only fatigue and malaise. The trial by Yildiz et al indicated no difference in fatigue between the oral CHO and fasting group while there was significantly less malaise experienced in the oral CHO group compared to the fasting group.[251] Unsurprisingly, there was no difference in the severity of fatigue and malaise experienced between the oral CHO and placebo groups.[192,230] Interestingly, both oral CHO and IV CHO alleviates feelings of discomfort, specifically weakness and tiredness.[253] A systematic review on the outcomes concluded that oral CHO intake led to a vast improvement in discomfort.[16]

4.4 METHODOLOGICAL QUALITY

The methodological quality of trials have been described in detail in Chapter 3. The overall quality of trials focussing on POCL was moderate with most trials having one or more domains of uncertainty or high risk of bias. We considered a trial as having a low risk of bias if all domains were assessed as adequate, and high risk of bias if one or more domains were assessed as unclear or a definite high risk of bias. The risk of bias assessment was performed using the risk of bias tool in The Cochrane Handbook of Systematic Reviews of Interventions. Unfortunately, the small study numbers per outcomes led to the decision that GRADE assessment is beyond the scope of the review at this stage.

The majority of trials included in this review were from developed and emerging countries (and could not be directly compared to a developing country like South Africa). Even though there was a wide range of geographical settings for the trials, the methodological consistency was remarkable to include a total of 24 trials in this review. All trials included in this review had detailed lists of inclusion and exclusion criteria minimising the possibility of bias. All trials also stated adequate methods of generating the randomisation sequence with more than half of the trials confirming

concealment of allocation. Double blinding in preoperative fasting trials is difficult since the patient will know if they were fasted or received a preoperative drink. By definition, only trials in which a carbohydrate drink is compared to a placebo can be adequately blinded. Single blinding will be possible if different personnel give the drink and evaluate the outcomes. Inadequate blinding will not have an effect on the biochemical primary outcomes (i.e. glucose, insulin, insulin resistance, protein status, immune status) evaluated in this review since they are clinical outcomes based on physiological processes, but it will definitely have an impact on the primary outcomes where clinicians will be involved (i.e. return of intestinal function, length of stay) and patient-reported psychosomatic secondary outcomes (i.e. thirst, hunger, nausea, vomiting, anxiety, pain, fatigue, weakness, tiredness, malaise). It was easy to keep all dietary exposures identical for all participants in the included trials since they only received a preoperative drink (i.e. oral carbohydrate drink or a placebo) or were fasted. All participants lost to follow-up were reported, but the majority of the trials had incomplete outcome data increasing the risk of bias since this data had to be excluded from the review and could not form part of the meta-analysis. Protocols for the included trials were not available to compare if all outcomes were addressed in the published articles. Therefore, no clear evidence was available for selective reporting. Funding of trials is a high risk of bias since the majority of preoperative oral carbohydrate drinks used in this review was sponsored by the same company, and one of the authors holds the patent for the drink. Participants were recruited from a very specific surgical population group (i.e. otherwise healthy individuals with no increased risk of regurgitation or aspiration) making the information provided biased to a specific group.

As with all systematic reviews there was a potential for bias at all the different stages of the review process. Publication bias is always a concern since trials with negative results are not always published and may easily be missed during the search process, skewing the overall result of the question posed. We recommend that the results of this review should be interpreted with caution since not all trials included in this review scored a low risk of bias.

4.5 AGREEMENTS AND DISAGREEMENTS WITH OTHER REVIEWS

Initially, when the protocol for this review was submitted the authors could not identify any other systematic review addressing this question. Subsequently there were several reviews (including narrative and systematic) published on the same topic: Pogatschnik 2015, Nygren 2015, Hill 2015, Smith 2014, Bilku 2014, Awad 2013, Li 2012, Jones 2011, Brady 2010 and Shanley 2009.[16,74,119,120,121,122,164,183,257,258]

Pogatschnik et al published a narrative review in 2015 - *Review of preoperative carbohydrate loading.* [164] The following topics were discussed: carbohydrate metabolism (fasting versus fed state), effect of surgery on carbohydrate metabolism (glycaemic control and insulin resistance), traditional fasting and its complications (risk of aspiration and new fasting guidelines), potential

benefits of CHO beverages (insulin resistance and immune response; preservation of muscle mass and function; postoperative well-being; surgical complications and length of stay), and the enhanced recovery after surgery concept. Even though the metabolic effects of lowering insulin resistance cannot be attributable to POCL alone, the authors concluded that POCL is safe and improves patient comfort prior to surgery.

Nygren et al published a narrative review in 2015 - *Preoperative oral carbohydrate therapy*.[183] This review, by three of the renowned authors on the topic, summarises the current evidence and rationale for avoiding preoperative fasting and rather implementing POCL. The use of oral carbohydrate was favoured in light of their role in reducing the response to surgical stress and in improving patient outcomes. The authors concluded that the impact of POCL was most evident in patients receiving major abdominal surgery.

Hill et al published a narrative review in 2015 - *Carbohydrate loading in the preoperative setting.* [257] This short review was the first to be published on local grounds in the *South African Medical Journal.* The review addressed the issues of permitting preoperative clear fluids in lack of associated aspiration risk, and actively promoted POCL due to the associated benefit. The authors concluded that a change in culture is necessary to ensure that practice is based on evidence and not on individual beliefs aroused by fear. They recommended a proactive, multidisciplinary approach to optimise the nutrition support in the surgical population.

Smith et al conducted a Cochrane review in 2014 - *Preoperative carbohydrate treatment for enhancing recovery after elective surgery*. [122] The objectives of this review were to assess the effects of POCL, compared with a placebo or preoperative fasting, on postoperative recovery and insulin resistance in adult patients undergoing elective surgery. Databases were searched from inception up to March 2014 with no language restrictions. Only randomised controlled trials were included in this review. The treatment group needed to receive at least 45 g of carbohydrates within four hours before surgery or anaesthesia start time. A total of 27 trials involving 1976 participants undergoing mainly elective abdominal surgery were included. In 19 trials (1351 participants), preoperative carbohydrate treatment was associated with shortened hospital stay compared with the placebo or fasting groups (by 0.30 days; 95% confidence interval 0.56 to 0.04; very low quality evidence). No significant effect on length of stay was noted when preoperative carbohydrate treatment was compared with the placebo (14 trials including 867 participants; mean difference -0.13 days, 95% confidence interval -0.38 to 0.12). Preoperative carbohydrate treatment was associated with shortened time to passage of flatus when compared with the placebo or fasting groups (2 trials including 86 participants; mean difference 0.39 days; 95% confidence interval 0.70 to 0.07) as well as increased postoperative peripheral insulin sensitivity (3 trials including 41 participants; mean increase in glucose infusion rate measured by hyperinsulinaemic euglycaemic clamp of 0.76 mg/kg/min; 95% confidence interval 0.24 to 1.29; high quality

evidence). In 14 trials (913 participants) preoperative carbohydrate treatment was not associated with an increased or decreased risk of postoperative complications compared with placebo or fasting (risk ration of complications 0.98; 95% confidence interval 0.86 to 1.11; low quality evidence). Aspiration pneumonitis was not reported in any of the treatment groups. Postoperative well-being (4 trials including 310 participants; moderate quality evidence), nausea (2 trials including 292 participants; moderate quality evidence), vomiting (4 trials including 407 participants; risk ration 1.25 confidence interval 0.77 to 2.04; low quality evidence) and fatigue (6 trials including 576 participants; moderate quality evidence) could not be reported on since the confidence intervals included no effects, making the data insufficient to show whether preoperative carbohydrate drinks had an effect on postoperative outcomes.

Bilku et al conducted a systematic review in 2014 – *Role of preoperative carbohydrate loading: a systematic review*.[16] The objectives of this review were to analyse the effect of POCL on insulin resistance, gastric emptying, gastric acidity, patient well-being, immunity and nutrition in adult patients undergoing general surgery. The authors did not elaborate on the systemic process followed during the searches. PubMed was the only electronic database searched (up to September 2011) to obtain articles for inclusion in the review. Reference lists of all articles were cross-checked to include all relevant articles. English language restriction was applied during the searches. A total of 17 trials consisting of 1 445 participants met the inclusion criteria where only randomised controlled trials were included in the review. The treatment group received carbohydrates – the type of beverage, volume consumed and time taken preoperative differed between trials. The control group consisted of standard fasting and/or placebo and/or low oral CHO intake and/or IV glucose administration. Data were too heterogeneous for a meta-analysis due to multiple combinations of outcomes. Seven trials (328 participants) investigated the effect of POCL on insulin sensitivity with various methods used to analyse insulin resistance (i.e. HEC, HOMA-IR, artificial pancreas closed loop system, QUICKI); six trials showed a significant reduction in insulin resistance and one trial showed no effect. Five trials (584 participants) investigated the effect of preoperative carbohydrate treatment on gastric emptying; all trials reported no difference in gastric emptying between groups (after variability was ruled out). Three trials (543 participants) investigated the effect of carbohydrate treatment on gastric acidity; all trials demonstrated that there was no difference between groups (even though the modes of assessing gastric acidity varied between trials). Eight trials examined the effect of carbohydrate treatment on patient well-being (1151 participants) with various measurements including a visual analogue scale (i.e. thirst, hunger, anxiety, depression, pain, tiredness, weakness, inability to concentrate, mouth dryness and nausea), modified Beck questionnaire (assessing the psychosomatic status of the patients) and a combination of the visual analogue scale and objective analysis by nursing staff. POCL led to a significant reduction in thirst, hunger, anxiety and malaise compared with fasting and placebo in two trials; two other trials demonstrated that fasted patients had increased thirst, hunger,

tiredness, anxiety and mouth dryness scores compared to oral and IV carbohydrate administration; both oral and IV carbohydrate administration alleviated tiredness and weakness. IV carbohydrate administration did not decrease thirst and hunger as effectively as oral carbohydrates. One trial concluded that between 12 to 24 hours postoperative there was a significant lower incidence of nausea and vomiting in the oral carbohydrate group than the fasting group while three trials demonstrated no beneficial effect of carbohydrate drinks on general well-being. Two trials examined the effect of carbohydrate treatment on immunity and clinical outcomes: one showed no difference in infection, length of stay and time to intake of oral diet between carbohydrate and placebo groups; while the other trial showed a significant decrease in the length of hospital stay and a trend to earlier return of gut function in the carbohydrate group when compared with the placebo. Five trials examined the effect of preoperative carbohydrate treatment on postoperative nutritional status i.e. anthropometric measurements, triceps skinfold thickness, mid-arm circumference, and handgrip strength. No significant differences between groups were reported. One trial examined the effect in diabetic patients with no delayed gastric emptying reported.

Awad et al conducted a systematic review in 2013 – *A meta-analysis of randomised controlled trials on preoperative oral carbohydrate treatment in elective surgery*.[121] The objectives of this review were to address the effects of preoperative carbohydrate treatment on length of hospital stay, insulin resistance, complications (i.e. vomiting, aspiration or pneumonia), and postoperative nausea and vomiting. The review was conducted according to the standard methods recommended by The Cochrane Collaboration. Multiple electronic databases were searched from January 1980 to April 2012. Additionally, reference lists of published trials were scanned and companies manufacturing preoperative carbohydrate drinks were contacted for unpublished data. Inclusion criteria included randomised controlled trials of adult patients undergoing elective surgery. No language restriction was placed on the searches. Preoperative carbohydrate treatment of at least 50 g was administered two to four hours preoperatively compared with a control (fasting/placebo). This review did not include IV carbohydrate administration as a control. Twenty-one trials (1685 participants) were included in this review. GRADE assessment revealed significant heterogeneity amongst trials with low to moderate quality evidence. Twelve trials (1198 participants) reported on length of stay: preoperative carbohydrate treatment was associated with a reduction in length of stay after major abdominal surgery [mean difference, 95% confidence interval: -1.08 (-1.87 to -0.29); p = 0.007], but that was not the case after minor surgery (expected stay of ≤ 2 days) or orthopaedic surgery. Insulin resistance was measured by three trials using the HEC method (all trials showed significant reduction in postoperative insulin resistance in the POC group when compared with the control), 6 trials using the HOMA-IR method (two trials showed significant reduction in insulin resistance between POC and control) and 1 trial using the QUICKI method (significant reduction in insulin resistance in the POC group). Nine trials (878 participants) reported on the occurrence of drink-related complications in the hospital with no occurrence in any

of the study groups [risk ration, 95% confidence interval: 0.88 (0.50 – 1.53); p = 0.640]. Five trials reported on postoperative nausea and vomiting: three trials reported no difference in occurrence between groups, one trial reported fewer episodes in the POC group and one trial reported more episodes in the POC group.

Li et al conducted a systematic review in 2012 – *Preoperative carbohydrate loading for elective surgery: a systematic review and meta-analysis*.[120] The review consisted of a systematic literature search of multiple electronic databases up to September 2010 on POCL in surgical patients. Reference lists from relevant review articles were also hand-searched. English and Chinese language restriction applied during the searches and only randomised controlled trials were included. The POC loading was compared to fasting, placebo and/or IV glucose administration. The administration time, dose and amount of CHO ingested were not considered, which may have affected the clinical outcomes. Quality of the trials was graded according to the recommendations provided in the *Cochrane Handbook of Systematic Reviews and Interventions* including the GRADE approach with the majority of outcomes having low to very low quality ratings. Multiple reviewers identified the 22 trials (1919 participants) included in this review measuring a variety of outcomes. No statistically significant difference was found in the changes in the glucose levels at the induction of anaesthesia, at the end of surgery or on day one postoperative between the different groups. There was no statistically significant difference in the changes in the insulin levels at the induction of anaesthesia and at the end of surgery between groups; however, there was a significant increase in the insulin levels in the CHO group on the first day after surgery when compared with the fasting and IV groups, but no differences were found between the CHO and placebo groups. A significant difference in the change in insulin sensitivity was seen between the CHO and placebo groups, but no differences were found in the other two comparisons. No significant differences were reported for the changes in postoperative insulin resistance between groups. There was also no statistically significant differences in length of stay (ICU and hospital) between the groups or in the postoperative gastric pH and volume between groups. Also, there were no significant differences in the incidence of postoperative vomiting or any reported aspiration. Results of the preoperative well-being were inconsistent and contradictory. This review also did subgroup analysis of patients undergoing different surgical procedures, including colorectal surgery, laparoscopic cholecystectomy, total hip replacement and cardiac surgery.

Jones et al conducted a systematic review in 2011 – *The role of carbohydrate drinks in pre-operative nutrition for elective colorectal surgery*.[119] The review was based on a systematic literature search of three electronic databases. Limitations of the review included English language restriction, searches conducted over the previous 10 years, only included patient scheduled for colorectal surgery, and it was not restricted for study type. Eleven trials (743 participants) were included in the review. The data was not statistically pooled in a meta-analysis but the authors concluded that preoperative carbohydrate treatment is both safe and effective since it does not

alter gastric pH or volume and there were no increased complications. The results of this review were not comparable due to the lack of methodological quality assessment, lack of statistical analysis and different preoperative carbohydrate regimens.

Brady et al conducted a Cochrane review in 2010 – *Preoperative fasting for adults to prevent perioperative complications.*[74] The objectives were to systematically review the effect of different preoperative fasting regimens (duration, type and volume of permitted intake) on perioperative complications and patient well-being (including aspiration, regurgitation, morbidity, thirst, hunger, pain, nausea, vomiting and anxiety) in different adult populations going for elective surgery. Databases were searched from inception up to August 2003, conference proceedings and reference lists were searched and experts in the field were consulted. Only randomised controlled trials were included in this review. The quality of the trials was graded according to the recommendations provided in the *Cochrane Handbook of Systematic Reviews and Interventions* and were classified as high methodological quality (note that the GRADE approach was not utilised in this review). Preoperative fluids evaluated included water, coffee, fruit juice, sport drinks and other carbohydrate containing drinks. A total of 22 trials (2270 participants) were included. The review concluded that there was no evidence to suggest a shortened fluid fast resulted in increased risk of aspiration, regurgitation or morbidity when compared with a standard fast, and that the volume of fluid permitted during the preoperative period had no effect on the outcomes.

Shanley conducted a systematic review in 2009 – *Preoperative carbohydrate loading: a review of the current evidence*.[258] A structured review was carried out in a systematic manner including randomised controlled trials. The searches were limited to trials published between 1998 and 2008, English language restrictions applied and only four electronic databases were searched. Thirteen randomised controlled trials were included in this review. The study intervention consisted of preoperative carbohydrate loading two to three hours before elective surgery. The review reported that no statistical significant results were reached, and that none of the trials reported any adverse effects with regards to preoperative carbohydrate loading. The review concluded that further research is warranted since small sample sizes lead to trends rather than conclusive evidence, and that a meta-analysis may produce more conclusive results.

To conclude, the findings of the above-mentioned reviews were in line with the findings of this systematic review. All reviews reported that there is a trend to improved clinical outcomes but data is insufficient to draw firm conclusions. Data shows that POCL has no proven adverse effects, which makes it a safe option during the preoperative period. Due to heterogeneity, limited data can be pooled in meta-analyses - indicating the need for larger randomised controlled trials on the topic with standardised interventions.

4.6 STUDY LIMITATIONS

Systematic reviews are only as good as its components i.e. the included trials. The limitations of a systematic review should always be kept in mind when interpreting results. Well conducted systematic reviews still provide the user with the best available evidence through accumulation of scientific data. However, systematic reviews can only contribute but never replace sound clinical judgement. The limitations as discussed below did not directly affect the outcomes of this systematic review since it is standard limitations associated with the POCL concept and systematic reviews. None the less, these limitations should be kept in mind when implementing the concept in practice.

Limitations as a direct result of the study design as it was implemented:

- Methodological quality was assessed according to the details described in the *Cochrane Handbook for Systematic Reviews and Interventions*; however, GRADE assessment was not conducted.
- Numerous studies were excluded based on the volume of the preoperative oral carbohydrate drink consumed (see Chapter 3). The volume of intake in this review was restricted to 400ml 90 – 300 minutes preoperative. However, when participants received 150 to 1000ml the volume did not appear to have an impact on the participants' gastric volume or pH when compared to a standard fast. Therefore, larger volumes can be consumed preoperatively without increased risk.
- Including co-interventions with different macronutrient profiles into the review were not possible since the change in macronutrient profile would increase the osmolality above 300mOsm/kg and immediately exclude the trial from the systematic review since a higher osmolality poses an increased risk for delayed gastric emptying. Now it is known that the type of macronutrient added might increase the osmolality but not necessarily delay gastric emptying.
- The high degree of incomplete outcome data due to poor reporting in the published articles and no response upon request had an impact on the number of trials included per outcomes. As per protocol the authors were contacted twice to obtain missing data.

Other limitations that appeared in the review that was not directly as a result of the design but rather due to the design of the included POCL studies and systematic reviews in general included:

- Majority of the included trials had a small sample size (17 trials < 100 participants).
- Complete blinding of both participant and investigator as to intake of a beverage or fasting is impossible to achieve. They cannot be blinded as to whether or not they consumed something to drink, and the volume of the beverage consumed. This limitation will not affect the primary outcomes but will definitely impact the psychosomatic secondary outcomes.

- POCL is just one of many components linked to the success in the ERAS protocol. Trials evaluating the effect of POCL do not always clearly state all the ERAS components present in the trial. Therefore, the results must be interpreted with caution since the beneficial effect of POCL can be as a result of other ERAS elements implemented in combination. In future it is going to be difficult to evaluate the effect of preoperative oral CHO treatment as the only intervention since the ERAS protocol is implemented in many hospitals.
- Publication bias is always a concern when a systematic review is conducted since trials with negative results are mostly not published causing trials to indirectly be excluded from the review that might cause misleading results. All stages of conducting a systematic review poses potential risk of bias.

4.7 DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- Inclusion of co-interventions with different macronutrient profiles were planned but due to an increase in osmolality, once other macronutrients are added to the carbohydrate beverage, these trials were excluded from the review.
- High-risk anaesthetic patients with an ASA score of III and IV were included in five trials due to the trials not differentiating between ASA scores. The other high risk anaesthetic groups (i.e. obese patients, elderly, pregnant women, patients with abnormal blood glucose levels, emergency cases) were still excluded as planned in the protocol.
- Statistical analyses were planned for all primary outcomes but due to the small number of trials, this could not be performed for all the outcomes.
- Statistical analyses were planned for the secondary outcomes but due to heterogeneity descriptive statistics were used.
- Subgroup and sensitivity analyses were planned for all outcomes but due to the small number of trials per comparison, this could not be performed.
- The aim was to make clear recommendations regarding preoperative oral carbohydrate loading in practice, but due to limited trials included per comparison, the results must be interpreted with caution.

CHAPTER 5: CONCLUSION

5.1 AUTHOR'S CONCLUSION

Even though POCL is considered safe and is recommended by numerous anaesthesia societies, preoperative fasting is still the standard of care in most hospitals around the world, including South Africa. Standard fasting is associated with deleterious effects on the metabolism with consequent negative clinical outcomes of the surgical patient. POCL is considered a safe alternative to standard fasting; therefore, the preoperative focus should be on what to give (dose specific), when to give it (time specific) and to whom to give it too (patient specific) to improve patient outcomes. The 'what to give' focuses on the specific type of clear fluid with emphasis on a beverage containing at least 45 g of CHO (mainly maltodextrin to ensure rapid gastric emptying) that pass the stomach within the recommended time. The 'when to give it' refers to the safety of giving a clear fluid up to two hours before induction of anaesthesia to avoid the risk of aspiration. The 'whom to give it too' refers to the specific population, which include low-risk elective surgery patients. This review confirmed that the concept of POCL is safe and no adverse events were associated with the intake of the beverage. Well-being of patients receiving POCL was also improved or at least maintained in most of the trials included in this review. No evidence of effect for POCL was demonstrated for any other clinical outcomes due to the heterogeneity of trials, small number of included trials per comparison, small sample size and available data. The role of confounding parameters, such as the impact of the magnitude of surgery and the effect of the different elements of the ERAS protocol, must be taken into account. There is, however, not enough evidence in this review to draw conclusions with absolute certainty. Therefore, the potential benefits with respect to clinical outcomes and well-being needs to be balanced against the cost of this intervention as well as participant preference before implementing it into hospitals as an isolated standard of care. At this stage POCL should be seen as a single element of the ERAS protocol, and the combination of these elements might produce more beneficial results than a single element by itself.

5.2 RECOMMENDATIONS FOR PRACTICE

The traditional practice of overnight fasting before surgery has been shown to be unnecessary and numerous anaesthesia societies have changed or are in the process of changing their guidelines to allow clear fluid intake up to two hours before induction of anaesthesia. To further optimise the practice, POCL is recommended to create a more anabolic milieu for enhancement of surgical outcomes. The goal is to achieve a CHO loading typical to a meal but with low osmolality to ensure rapid gastric emptying. POCL forms an integral part of the ERAS® protocol; however, since POCL is only one element of the ERAS protocol the beneficial effects of these elements as a whole should be taken into account. The methodological quality of this review is of concern since it is rated as moderate to low; therefore, caution should be practiced when these results are applied into practice. Emphasis should be on the type of surgery performed since most of the trials in this review were based on otherwise healthy participants receiving abdominal surgery. Furthermore,

there should be a distinction made between minor and major surgery due to the different effects on various outcomes.

Glucose control during the perioperative period is frequently emphasised to improve surgical outcomes. Findings in this review showed that glucose increased after POCL before induction of anaesthesia, but on day 1 postoperative there was no significant difference in glucose levels seen between the groups. Data on insulin levels were conflicting with differences at baseline and no trend to follow in this review. Theoretically, POCL has the metabolic benefit of lowering insulin resistance; unfortunately, it is difficult to prove that POCL is the only parameter in the surgical journey improving outcomes, and due to limited data and methodological differences between trials data in this review could not be pooled. Furthermore, data on insulin resistance must be interpreted with caution due to the different methods measuring different parameters. The magnitude of the surgery (i.e. minor versus major) and postoperative care pathways have an immense impact on the outcomes. Therefore, POCL in combination with these parameters are worth considering to ensure enhanced recovery after surgery.

Trials included in this review did not find a significant difference between the protein status (i.e. muscle mass and strength) of POCL, placebo and IV glucose groups; however, there was a trend for weaker protein status in the standard fasting group. Therefore, the question still remains if muscle preservation is maintained by the attenuation of protein catabolism through the energy provided by the POCL. The effect of confounding factors like bed rest, malnutrition and gender differences in body composition should be taken into account when evaluating this outcome.

The immune status in this review was evaluated by means of the CRP value. The POCL group had a significantly lower CRP level than the standard fasting group on day one postoperative ($p = 0.006$). However, the CRP values should be interpreted with caution within the first 24 hours since it only peaks after 36 to 50 hours of infection. It is recommended that the immune status be evaluated within the first 24 hours postoperatively to exclude confounding factors (like the initiation of enteral or food intake, effect of medication).

There is no indication that patients drinking a preoperative oral carbohydrate beverage are at an increased risk compared to patients who followed a standard fast or had a placebo to drink. The trials evaluating return of intestinal function could not be pooled but there was an increase in the return of intestinal function in the POCL group. The overall trend between trials was that there was no significant difference in length of stay between groups. However, no subgroup analysis on the magnitude of surgery was performed to differentiate between minor versus major surgery. Since minor surgery has an expected shorter length of stay compared to major surgery, it will be difficult to detect change between comparison groups.

The data on well-being presented in this review is conflicting mainly due to different methods used to measure the change, different time intervals and different surgical procedures. The POCL group experienced less thirst and hunger when compared with standard fasting; however, there was no difference in thirst and hunger between the POCL and placebo groups; and IV glucose does not decrease thirst and hunger as effectively as POCL. No evidence of effect could be concluded for nausea and vomiting since the results have shown no trend. The majority of trials indicated that POCL significantly decreases anxiety when compared with standard fasting and IV glucose administration; but there was no difference when POCL was compared with a placebo. The evidence of this review was insufficient to show whether POCL reduces pain, fatigue, weakness, tiredness and malaise significantly more than the other groups. To note, the majority of the trials showed that overall well-being was improved or at least maintained in the POCL group.

Currently in South Africa, there are numerous clear fluids available (preOp®, Fortijuce®, Provide Xtra®, Fresubin Jucy®, Ensure Plus Juce®). When choosing a clear fluid for POCL, the following must be considered: macronutrient profile (i.e. carbohydrate content, added protein), osmolality together with gastric emptying time, palatability, cost and patient preference. Implementing the POCL concept in a developing country like South Africa will be challenging since there is an immense difference in structural and operational procedures between the private versus state sector. Nonetheless, it is challenging to move evidence into practice and implementation of a new concept takes commitment and patience from all parties involved.

5.3 RECOMMENDATIONS FOR FUTURE RESEARCH

A large volume of evidence on the topic is already available but as other authors have indicated, it is recommended that further research be done on this topic since the current recommendations are based on moderate to low quality heterogeneous data. The strength of the evidence to support POCL could be improved by well-designed, double blind placebo controlled trials. It is very difficult to blind participants who received a preoperative beverage from participants who do not receive a beverage. The aim would be to double blind the participants and staff by putting participants who receive or who do not receive a beverage in separate or single rooms, and ensure that the same individual who hands out the beverage to the participant does not measure the outcomes as well. Double blinding in a country like South Africa might be impossible due to constant bed and personnel shortage.

The advantage of including more than one comparison group would be that the different elements of the groups can be compared, and the exact element for clinical benefit can be pointed out. The ideal trial would include the following groups: POCL-protein group, POCL group, IV glucose group, water group (placebo) and a standard fasting group. By including different groups, different effects are measured; for example comparing the standard fasting and placebo groups, the safety of giving a preoperative fluid compared to nothing will be evaluated; by comparing the placebo and

POCL groups, the benefit of giving a carbohydrate load will be evaluated; by comparing POCL and POCL-protein groups, the benefit of giving added protein will be evaluated; by comparing POCL and IV glucose groups, the effect of the route of administration (i.e. per os or intravenous) will be evaluated.

Sample size is of great concern because the majority of trials on this topic used a small sample size, which degrades the quality of the current recommendations. The number of patients included in a trial should be of size to add value to the methodological quality: small enough to be feasible and large enough to detect difference. GRADE assessment should be considered as a standard tool for all meta-analyses to ensure that the outcome of a trial is graded according to the methodological quality. Therefore, attention should be on above mentioned recommendations to improve the overall methodological quality of the trials in future.

At this stage, the researcher is aware of nine ongoing trials and two unpublished trials focusing on various surgical populations, i.e. colorectal, gastric, oral, orthopaedic and cardiac surgery (Appendix 6.7). These trials should be evaluated for inclusion in future systematic reviews to hopefully provide further evidence for POCL. It is also advised that foreign language trials should be considered for inclusion in future if possible. Ten foreign language citations (i.e. Chinese, German, French, Portuguese and Turkish) were identified for possible inclusion but were excluded due to language constraints (Appendix 6.7).

It is important to establish which patient population will be most likely to benefit from POCL. Well-documented trials in different surgical populations could contribute usefully to the literature and future meta-analyses. Focus should be on major open abdominal surgery, minimally invasive laparoscopic surgery, orthopaedic and cardiac surgery. Different medical settings across different countries would also contribute valuable information for future meta-analyses. Since data is limited, further trials on high risk anaesthetic patients (i.e. obese patients, patients with an ASA score > II, patients with diabetes mellitus and patients undergoing emergency surgery) should be employed to investigate the effect on POCL in this population group. Trials could also focus on the beneficial effect of giving POCL in the paediatric population.

The main requirement of POCL is that the beverage must contain at least 45 g of carbohydrates to mimic the intake of breakfast and evoke an insulin release, and it must pass the stomach fast enough to avoid aspiration during induction of anaesthesia. Trials should investigate whether the volume of permitted CHO intake has an effect on outcomes since this review only included trials where the participants received 400 ml two hours before the induction of anaesthesia and/or 800 ml the evening before surgery. The majority of trials gave POCL two hours before the induction of anaesthesia, as well as the evening before surgery. To what extent the evening dose of CHO contributed to clinical outcomes has not been established and should be investigated. The

rationale for giving CHO the evening before surgery is to prevent glycogen depletion. Numerous trials exist on the effect of adding glutamine, whey protein or hydrolysed protein to the POCL beverage. Data should be pooled to investigate whether there is benefit in adding protein to the CHO beverage. Noteworthy for future trials, it is important for investigators to record how much of the POCL beverage was actually consumed by the participants, and report on the actual time of ingestion of the POCL beverage to the induction of anaesthesia and start of surgery.

Future trials should aim to measure as many outcomes as possible by using standardised measurements. Trials using the gold standard of the hyperinsulinaemic euglycaemic clamp method to measure insulin resistance, especially in major abdominal surgery patients, will be of utmost value. The trials measuring length of stay should focus on major abdominal surgery where the expected length of stay is long enough to detect a difference in using POCL or not. Standardised instruments such as the visual analogue scale should be used to evaluate the patients' well-being to limit heterogeneity to ensure that outcomes can be pooled. The main outcome focus to detect clinical benefit such as decreased insulin resistance and length of stay should be in patients receiving major surgery, whereas the main outcome focus in patients receiving minor surgery should be well-being. Trials comparing minor versus major surgery will be able to confirm this speculation.

Since POCL is incorporated into the ERAS® concept, it will be difficult to conduct trials with only one intervention in future. Therefore, trials should clearly indicate all the ERAS® components used to optimise recovery since a combination of elements will have a greater effect than a single component. Confounding factors such as medication used prophylactically and postoperative feeding regimens should be accounted for when reporting on the outcomes. Incomplete outcome data is an important matter that needs to be addressed as well as poor reporting and correspondence.

Industry-sponsored research will always be a limitation in trials on this topic since the POC beverage is patented and usually sponsored. A trial on the effect of different POC beverages is a possibility but it will be extremely difficult to conduct due to confounding factors and industry influence. It is important for all authors to declare their conflict of interest so that the reader can interpret data with caution.

CONFLICT OF INTEREST

The principal author, Janine Kriel, currently works as a clinical nutrition sales consultant for Fresenius Kabi South Africa. The systematic review was conceptualised while she was a clinical dietitian in the surgical field at Tygerberg Academic Hospital. Financial support for the intuition fees of the principal author at Stellenbosch University was granted by Fresenius Kabi South Africa in 2015 and 2016. One of the co-authors, Professor Renèe Blaauw, acts as a key opinion leader for Fresenius Kabi South Africa. The current positions of these two authors at Fresenius Kabi South Africa will have no impact on the outcomes of this review since a systematic approach was followed as stipulated by The Cochrane Collaboration. The other authors have no disclosure.

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227	Ljunggren S, Hahn RG, Nystrom T. Insulin sensitivity and beta-cell function after carbohydrate oral loading in hip replacement surgery: a double-blind, randomised trial. Clinical Nutrition, 2014; 33: 392 – 398.	A3
250	Canby O, Adar S, Karagoz AH, Celebi N, Bilen CY. Effect of preoperative consumption of high carbohydrate drink (Pre-op®) on postoperative metabolic stress reaction in patients undergoing radical prostatectomy. Int Urol Nephrol, 2014; 46: 1329 – 1333.	A6
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228	Ljunggren S, Hahn RG. Oral nutrition or water loading before hip replacement surgery; a randomized clinical trial. Trials, 2012; 13: 97.	A19
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232	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. British Journal of Surgery, 2010; 97: 317 – 327.	A64
230	Mathur S, Plank LD, McCall JL, Shapkov P, McIlroy K, Gillanders LK, et al. Randomized controlled trial of preoperative oral carbohydrate treatment in major abdominal surgery. British Journal of Surgery, 2010; 97: 485 – 494.	A66
222	Kaksa M, Grosmanova T, Havel E, Hyspler R, Petrova Z, Brtko M, et al. The impact and safety of preoperative oral or intravenous carbohydrate administration versus fasting in colorectal surgery – a randomized controlled trial. Wien Klin Wochenschr, 2010; 122: 23 – 30.	A68
253	Helminen H, Viitanen H, Sajanti J. Effect of preoperative intravenous carbohydrate loading on preoperative discomfort in elective surgery	A71

REFERENCING NUMBER	REFERENCING DESCRIPTION	STUDY ID
	patients. European Journal of Anaesthesiology, 2009; 26: 123 – 127.	
223	Tran S. Preoperative carbohydrate loading in patients undergoing coronary artery bypass or spinal surgery. Thesis, 2009.	A74
245	Šerclová P, Z Dytrych, Marvan J, Nova K, Hankeova Z, Ryska O, et al. Fast-track in open intestinal surgery: prospective randomized study (Clinical Trials Gov Identifier no. NCT00123456). Clinical Nutrition, 2009; 28: 618 – 624.	A75
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REFERENCING NUMBER	REFERENCING DESCRIPTION	STUDY ID
191	Hausel J, Nygren J, Lagerkranser M, et al. A carbohydrate-rich drink reduces preoperative discomfort in elective surgery patients. Anesthesia and Analgesia, 2001; 93(5): 1344 – 1350.	A121
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APPENDICES

Appendix 6.1: Eligibility form

STUDY ID: **REVIEWER ID:**

A single failed eligibility criterion is sufficient for a study to be excluded from the review, and the remaining criteria need not be assessed.

LANGUAGE			
Is the study available in English?	**YES**	**UNCLEAR**	**No**
	↓ Go to next question		**Exclude: Foreign Language**
TYPE OF STUDY			
Is the study a randomized controlled trial?	**YES**	**UNCLEAR**	**No**
	↓ Go to next question		**Exclude: Study Type**
TYPES OF PARTICIPANTS			
Are the participants humans?	**YES**	**UNCLEAR**	**No**
	↓ Go to next question		**Exclude: Animal Study**
Are the participants older than 18 years?	**YES**	**UNCLEAR**	**No**
	↓ Go to next question		**Exclude: Age Restriction**
Did the participants undergo elective surgery?	**YES**	**UNCLEAR**	**No**
	↓ Go to next question		**Exclude: Non-Elective Surgery**
Did the participants have normal glucose levels before surgery?	**YES**	**UNCLEAR**	**No**
	↓ Go to next question		**Exclude: Abnormal Glucose Levels**

EXPERIMENTAL INTERVENTION			
Is the beverage for oral consumption?	**YES**	**UNCLEAR**	**No**
	↓ Go to next question		**Exclude: Feeding Route**
Did the beverage contain > 12% carbohydrates with an osmolality of < 300 mOsm/kg?	**YES**	**UNCLEAR**	**No**
	↓ Go to next question		**Exclude: Concentration and/or Osmolality**
Did the participants consume at least 400ml of the beverage 90 – 300 minutes before the induction of anaesthesia?	**YES**	**UNCLEAR**	**No**
	↓ Go to next question		**Exclude: Dosage and/or Timing**
OUTCOMES			
Was at least 1 of the pre-specified outcomes in the protocol addressed?	**YES**	**UNCLEAR**	**No**
	↓ Go to next question		**Exclude: Outcomes**
OTHER			
Any other reason for excluding study?	**NO**		**YES**
	INCLUDE (Subject to clarification of 'unclear' points)		**EXCLUDE (Please Specify)**
FINAL DECISION	**INCLUDE**		**EXCLUDE**

Appendix 6.2: Data extraction form

SOURCE

REVISION DATE		
REVIEW AUTHOR ID	**JANINE KRIEL (8603030236080)**	**LAUREN PIETERSEN (8611160177081)**
STUDY ID (last name of first author and the year of the primary reference; unique identifying number)		
TITLE		
AUTHORS (only the first six)		
CONTACT DETAILS		
CITATION		

ELIGIBILITY *(see Eligibility Form)*

CONFIRM ELIGIBILITY	
REASON FOR EXCLUSION	

METHODS

ETHICS APPROVAL OBTAINED	**YES**	**NO**	**UNCLEAR**	**NOT REPORTED**
STUDY DESIGN				
DATE OF STUDY / STUDY DURATION				
COUNTRY / SETTING				
RISK OF BIAS	***SEE RISK OF BIAS FORM***			

PARTICIPANTS

PLEASE SPECIFY INTERVENTION GROUP (IF APPLICABLE)	**ORAL CHO** (EXPERIMENTAL INTERVENTION)		**STANDARD FASTING** (CONTROL INTERVENTION)		**PLACEBO** (CONTROL INTERVENTION)		**IV CHO** (CONTROL INTERVENTION)	
TOTAL NUMBER								
AGE								
GENDER	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE
BMI / WEIGHT								
DIAGNOSIS								
GLUCOSE VALUE PRIOR TO SURGERY								
TYPE OF SURGERY	**ABDOMINAL**		**OTHER**		**UNCLEAR**			
TYPE OF ANAESTHESIA	**GENERAL**	**SPINAL**	**EPIDURAL**	**COMBINATION**	**UNCLEAR**			
ANAESTHETIC RISK	**HIGH**		**LOW**		**UNCLEAR**			
TIME FROM INGESTION TO INDUCTION OF ANAESTHESIA								
TIME FROM INGESTION TO START OF SURGERY								
ERAS PROTOCOL FOLLOWED	**YES**		**NO**		**UNCLEAR**			

INTERVENTION

TOTAL NUMBER OF INTERVENTION GROUPS	

	ROUTE	PRODUCT	NUTRIENT PROFILE	OSMOLALITY	VOLUME	TIMING	DIET EVENING BEFORE SURGERY
EXPERIMENTAL							
CONTROL							
CONTROL							
CONTROL							

RANDOMIZATION / ALLOCATION

NUMBER OF PARTICIPANTS ALLOCATED TO EACH INTERVENTION GROUP				
	ORAL CHO (EXPERIMENTAL INTERVENTION)	**STANDARD FASTING** (CONTROL INTERVENTION)	**PLACEBO** (CONTROL INTERVENTION)	**IV CHO** (CONTROL INTERVENTION)
NUMBER OF PARTICIPANTS RANDOMIZED				
NUMBER OF PARTICIPANTS MISSING (REASON)				
NUMBER OF PARTICIPANTS FINISHING THE TRIAL				

PRIMARY OUTCOMES (CONTINUOUS DATA)

DESCRIPTION (definition with diagnostic criteria if relevant)		**UNIT OF MEASUREMENT** (for scales give upper and lower limits and state whether high or low score is good)	

RESULTS	**TIMING**	**ORAL CHO**			**STANDARD FASTING**			**PLACEBO**			**IV CHO**		
		MEAN	STANDARD DEVIATION	STANDARD MEAN DIFFERENCE	MEAN	STANDARD DEVIATION	STANDARD MEAN DIFFERENCE	MEAN	STANDARD DEVIATION	STANDARD MEAN DIFFERENCE	MEAN	STANDARD DEVIATION	STANDARD MEAN DIFFERENCE

PRIMARY OUTCOMES (DICHOTOMOUS DATA)

OUTCOMES	ORAL CHO (EXPERIMENTAL INTERVENTION)			STANDARD FASTING (CONTROL INTERVENTION)			PLACEBO (CONTROL INTERVENTION)			IV CHO (CONTROL INTERVENTION)		
	YES (PLEASE INDICATE NUMBER)	**NO**	**NOT INDICATED**	**YES** (PLEASE INDICATE NUMBER)	**NO**	**NOT INDICATED**	**YES** (PLEASE INDICATE NUMBER)	**NO**	**NOT INDICATED**	**YES** (PLEASE INDICATE NUMBER)	**NO**	**NOT INDICATED**
REGURGITATION												
ASPIRATION												
MORBIDITY												
MORTALITY												

SECONDARY OUTCOMES (CONTINUOUS DATA)

DESCRIPTION (definition with diagnostic criteria if relevant)		**UNIT OF MEASUREMENT** (for scales give upper and lower limits and state whether high or low score is good)	

	TIMING	**ORAL CHO**			**STANDARD FASTING**			**PLACEBO**			**IV CHO**		
		MEAN	STANDARD DEVIATION	STANDARD MEAN DIFFERENCE	MEAN	STANDARD DEVIATION	STANDARD MEAN DIFFERENCE	MEAN	STANDARD DEVIATION	STANDARD MEAN DIFFERENCE	MEAN	STANDARD DEVIATION	STANDARD MEAN DIFFERENCE
CONTINUOUS RESULTS													

SECONDARY OUTCOMES (DICHOTOMOUS DATA)

DESCRIPTION (definition with diagnostic criteria if relevant)		**UNIT OF MEASUREMENT** (for scales give upper and lower limits and state whether high or low score is good)	

DICHOTOMOUS RESULTS	**TIMING**	**ORAL CHO**			**STANDARD FASTING**			**PLACEBO**			**IV CHO**		
		YES (PLEASE INDICATE NUMBER)	**NO**	**NOT INDICATED**	**YES** (PLEASE INDICATE NUMBER)	**NO**	**NOT INDICATED**	**YES** (PLEASE INDICATE NUMBER)	**NO**	**NOT INDICATED**	**YES** (PLEASE INDICATE NUMBER)	**NO**	**NOT INDICATED**
	PREOPERATIVE												
	POSTOPERATIVE												

SECONDARY OUTCOMES (DESCRIPTIVE)

TIMING	MAIN FINDINGS / CONCLUSION	SIMPLIFIED OUTCOMES

MISCELLANEOUS

FUNDING SOURCE	**NAME**			
	SOURCE OF BIAS	**YES**	**UNCLEAR**	**NO**
KEY CONCLUSION OF STUDY AUTHORS				
MISCELLANEOUS COMMENTS FROM STUDY AUTHORS				

<table>
<tr><td>REFERENCES TO OTHER RELEVANT STUDIES</td><td colspan="2"></td></tr>
<tr><td rowspan="2">CORRESPONDENCE REQUIRED</td><td>YES
(please indicate what should be asked)</td><td></td></tr>
<tr><td colspan="2">NO</td></tr>
</table>

END OF DATA EXTRACTION

Appendix 6.3: Assessment of risk of bias form

DOMAIN	JUDGEMENT	DESCRIPTION
RANDOM SEQUENCE GENERATION		
Adequate Sequence Generation	LOW RISK	
	HIGH RISK	
	UNCLEAR	
ALLOCATION CONCEALMENT		
Allocation Concealment	LOW RISK	
	HIGH RISK	
	UNCLEAR	
BLINDING		
Blinding of Participants	LOW RISK	
	HIGH RISK	
	UNCLEAR	
Blinding of Personnel	LOW RISK	
	HIGH RISK	
	UNCLEAR	
Blinding of Primary Outcomes	LOW RISK	
	HIGH RISK	
	UNCLEAR	
Blinding of Secondary Outcomes	LOW RISK	
	HIGH RISK	
	UNCLEAR	
INCOMPLETE OUTCOME DATA		
Primary Outcomes	LOW RISK	
	HIGH RISK	
	UNCLEAR	
Secondary Outcomes	LOW RISK	
	HIGH RISK	
	UNCLEAR	
SELECTIVE REPORTING		
Selective Reporting	LOW RISK	
	HIGH RISK	
	UNCLEAR	

OTHER BIAS		
Was Intention-To-Treat Analysis of Data Conducted?	LOW RISK	
	HIGH RISK	
	UNCLEAR	
Baseline Comparability	LOW RISK	
	HIGH RISK	
	UNCLEAR	
≥ 80% Participants Followed Up?	LOW RISK	
	HIGH RISK	
	UNCLEAR	
Ethics Approval	LOW RISK	
	HIGH RISK	
	UNCLEAR	
Funding	LOW RISK	
	HIGH RISK	
	UNCLEAR	
Other	LOW RISK	

Appendix 6.4: Ethics approval

UNIVERSITEIT·STELLENBOSCH·UNIVERSITY
jou kennisvennoot · your knowledge partner

Ethics Letter

14-Jun-2012

Ethics Reference #: S12/06/152
Clinical Trial Reference #:
Title: Preoperative oral carbohydrate treatment to prevent perioperative complications in adults: A systematic review of the evidence

Dear Miss Janine KRIEL,

Thank you for your application. The application is for a systematic review using only information that is available in the public domain therefore the Health Research Ethics Committee has considered this proposal to be exempt from ethical review.

This letter confirms that this project is now registered and you can proceed with the work.

If you have any queries or need further help, please contact the REC Office 0219389657.

Sincerely,

REC Coordinator
Franklin Weber
Health Research Ethics Committee 1

Appendix 6.5: Prospero Registration

Dear Miss Kriel

Thank you for submitting details of your systematic review *Preoperative oral carbohydrate treatment to prevent perioperative complications in adults: a systematic review of the evidence* to the PROSPERO register. We are pleased to confirm that the record has been published on the database.

Your registration number is: CRD42012002313

You are free to update the record at any time; all submitted changes will be displayed as the latest version with previous versions available to public view. Please also give brief details of the key changes in the Revision notes facility. You can log in to PROSPERO and access your records at http://www.crd.york.ac.uk/PROSPERO.

An email reminder will be sent to you on the anticipated completion date, prompting you to update the record. Comments and feedback on your experience of registering with PROSPERO are welcome at crd-register@york.ac.uk.

Best wishes for the successful completion of your review.

Yours sincerely

Jimmy Christie

PROSPERO Administrator
Centre for Reviews and Dissemination
University of York
York YO10 5DD
t: +44 (0) 1904 321040
f: +44 (0) 1904 321041
e: CRD-register@york.ac.uk
www.york.ac.uk/inst/crd

CRD is part of the National Institute for Health Research and is a department of the University of York.

Appendix 6.6: Included studies (phase 1)

STUDY ID	AUTHOR AND YEAR (TRIAL IDENTIFIER)	TITLE
A1	Carli 2015	Physiological Considerations of Enhanced Recovery After Surgery (ERAS)
A2	Singh 2015	Evaluation of effects of a Preoperative 2-hour Fast with Glutamine and Carbohydrate Rich Drink on Insulin Resistance in Maxillofacial Surgery
A3	Ljunggren 2014	Insulin Sensitivity and Beta-cell Function after Carbohydrate Oral Loading in Hip Replacement Surgery: A Double-blind, Randomised Controlled Clinical Trial
A4	Webster 2014	Does Preoperative Oral Carbohydrate reduce Hospital Stay? A Randomized Trail
A5	Wijk 2014	Implementing a Structured Enhanced Recovery after Surgery (ERAS) Protocol reduces Length of Stay after Abdominal Hysterectomy
A6	Canby 2014	Effects of Preoperative Consumption of High Carbohdyrate Drink (Pre-Op®) on Postoperative Metabolic Stress Reaction in Patients undergoing Radical Prostatectomy
A7	Zhao 2014	Fast-Track Surgery Improves Postoperative Clinical Recovery and Reduces Postoperative Insulin Resistance after Esophagectomy for Esophageal Cancer
A8	De Anguilar – Nascimento 2014	Preoperative Education in Cholecystectomy in the Context of a Multimodal Protocol of Perioperative Care: A Randomized, Controlled Trial
A9	Li 2014	Fast-Tract Improves Post-operative Nutrition and Outcomes of Colorectal Surgery: A Single-Centre Prospective Trial in China
A10	Jones 2013	Randomized Clinical Trial on Enhanced Recovery versus Standard Care following Open Liver Resection
A11	Pexe-Machado 2013	Shrinking Preoperative Fast Time with Maltodextrin and Protein Hydrolysate in Gastrointestinal Resections due to Cancer
A12	Suliman 2013	Pre-Operative Oral Carbohydrate Loading is Safe and Improves Patients Satisfaction with Elective Ambulatory Surgery and Anesthesia: It's Time for Change
A13	Zareba 2013	Parenteral Nutrition and PreOp Preoperation in Prevention of Post-operative Insulin Resistance in Gastrointestinal Carcinoma
A14	Yilmaz 2013	Preoperative Carbohydrate Nutrition Reduces Postoperative Nausea and Vomiting Compared to Preoperative Fasting
A15	Zelic 2013	Preoperative Oral Feeding Reduces Stress Response after Laparoscopic Cholecystectomy

STUDY ID	AUTHOR AND YEAR (TRIAL IDENTIFIER)	TITLE
A16	Yildiz 2013	Oral Carbohydrate Supplementation reduces Preoperative Discomfort in Laparoscopic Cholecystectomy
A17	Miller 2013	An Evidence-Based Approach to Perioperative Nutrition Support in the Elective Surgery Patient
A18	Braga, 2012	Oral Preoperative Antioxidants in Pancreatic Surgery: A Double-blind, Randomized, Clinical Trial
A19	Ljunggren, 2012	Oral Nutrition or Water Loading before Hip Replacement Surgery: A Randomized Clinical Trial
A20	Viganò 2012	Effects of Preoperative Oral Carbohydrate Supplementation on Postoperative Metabolic Stress Response of Patients Undergoing Elective Abdominal Surgery
A21	Dock-Nascimento 2012	Evaluation of the effects of a preoperative 2-hour fast with maltodextrine and glutamine on insulin resistance, Acute-phase response, nitrogen balance, and serum glutathione after laparoscopic cholecystectomy: A controlled randomized trial
A22	Verheijen 2012	Feasibility of enhanced recovery programme in various patient groups
A23	Awad 2012	Metabolic conditioning to attenuate the adverse effects of perioperative fasting and improve patient outcomes
A24	Power 2012	Reducing preoperative fasting in elective adult surgical patients: a case-control study
A25	Itou 2012	Safety and efficacy of oral rehydration therapy until 2 h before surgery: a multicenter randomized controlled trial
A26	Wang 2012	Immunologic Response after Laparoscopic Colon Cancer Operation within an Enhanced Recovery Programme
A27	Yang 2012	Fast-Track Surgery Improves Postoperative Clinical Recovery and Immunity after Elective Surgery for Colorectal Carcinoma: Randomized Controlled Clinical Trial
A28	Huibers 2012	The Effect of the Introduction of the ERAS Protocol in Laparoscopic Total Mesorectal Excision for Rectal Cancer
A29	Kennedy 2012	EnROL: A Multicentre Randomised Trial of Conventional versus Laparoscopic Surgery for Colorectal Cancer within an Enhanced Recovery Programme
A30	Aarts 2012	Adoption of Enhanced Recovery After Surgery (ERAS) Strategies for Colorectal Surgery at Academic Teaching Hospitals and Impact on Total Length of Hospital Stay
A31	Ren 2012	Enhanced Recovery After Surgery (ERAS) Program Attenuates Stress and Accelerates Recovery in Patients after Radical Resection for Colorectal Cancer: A Prospective Randomized Controlled Trial

STUDY ID	AUTHOR AND YEAR (TRIAL IDENTIFIER)	TITLE
A32	Pawa 2012	Enhanced Recovery Program following Colorectal Resection in the Elderly Patient
A33	Bopp 2011	A liberal preoperative fasting regimen improves patient comfort and satisfaction with anesthesia care in day-stay minor surgery
A34	Awad 2011	A randomized crossover study of the effects of glutamine and lipid on the gastric emptying time of a preoperative carbohydrate drink
A35	Awad 2011	A randomized cross-over study of the metabolic and hormonal responses following two preoperative conditioning drinks
A36	Gustafsson 2011	Adherence to the Enhanced Recovery after Surgery Protocol and Outcomes After Colorectal Cancer Surgery
A37	Burden 2011	An unblinded randomised controlled trial of preoperative oral supplements in colorectal cancer patients
A38	Goichon 2011	Effects of an enteral glucose supply on protein synthesis, proteolytic pathways, and proteome in human duodenal mucosa
A39	Perrone 2011	Effects of preoperative feeding with a whey protein plus carbohydrate drink on the acute phase response and insulin resistance. A randomized trial
A40	Martelli 2011	Pre-Operative Oral Nutrition Supplementation of Carbohydrates in Aortic Surgery: A Randomized Trial of 40 Patients
A41	Ramirez 2011	Enhanced Recovery in colorectal surgery: a multicentre study
A42	Vermeulen 2011	Gastric emptying, glucose metabolism and gut hormones: Evaluation of a common preoperative carbohydrate beverage
A43	Okabayashi 2011	Oral supplementation with carbohydrate- and branched-chain amino acid-enriched nutrients improves postoperative quality of life in patients undergoing hepatic resection
A44	Gustafsson 2011	Perioperative nutritional management in digestive tract surgery
A45	Manchikanti 2011	Preoperative fasting before interventional techniques: Is it necessary or evidence-based?
A46	Crenshaw 2011	Preoperative Fasting: Will the evidence ever be put into practice?
A47	Donatelli 2011	Preoperative insulin resistance and the impact of feeding on postoperative protein balance: A stable isotope study

STUDY ID	AUTHOR AND YEAR (TRIAL IDENTIFIER)	TITLE
A48	Kratzing 2011	Pre-operative nutrition and carbohydrate loading
A49	Gianotti 2011	Revising concepts of artificial nutrition in contemporary surgery: from energy and nitrogen to immune-metabolic support
A50	Christensen 2011	Short hospital stay and low complication rate are possible with a fully implemented fast-track model after elective colonic surgery
A51	Ozdemir 2011	The Effect of Preoperative Oral Carbohydrate Loading on Stress Response in Patients Undergoing Major or Minor Surgery
A52	Yagmurdur 2011	The effects of carbohydrate-rich drink on perioperative discomfort, insulin response and arterial pressure in spinal aesthesia
A53	Jones 2011	The role of carbohydrate drinks in pre-operative nutrition for elective colorectal surgery
A54	Awad 2010	Cellular mechanisms underlying the protective effects of preoperative feeding: A randomized study investigating muscle and liver glycogen content, mitochondrial function, gene and protein expression
A55	De Aguilar-Nascimento 2010	Clinical benefits after the implementation of a multimodal perioperative protocol in elderly patients
A56	Ahmed 2010	Compliance with enhanced recovery programmes in elective colorectal surgery
A57	Proctic 2010	Effect of preoperative feeding on gastric emptying following spinal anaesthesia: a randomized controlled trial
A58	Teeuwen 2010	Enhanced Recovery After Surgery (ERAS) versus conventional postoperative care in colorectal surgery
A59	Liu 2010	Multimodal optimization of surgical care shows beneficial outcome in gastrectomy surgery
A60	Senesse 2010	Perioperative nutrition care protocols / Nutrition périopératoire: protocols de soins
A61	Coti-Bertrand 2010	Preoperative Nutritional Support
A62	Okabayashi 2010	Preoperative oral supplementation with carbohydrate and branched-chain amino acid-enriched nutrient improves insulin resistance in patients undergoing a hepatectomy: a randomized clinical trial using an artificial pancreas
A63	Hendry 2010	Randomized clinical trial of laxatives and oral nutritional supplements within an enhanced recovery after surgery protocol following liver resection

STUDY ID	AUTHOR AND YEAR (TRIAL IDENTIFIER)	TITLE
A64	Wang 2010	Randomized clinical trial to compare the effects of preoperative oral carbohydrate versus placebo on insulin resistance after colorectal surgery
A65	Lassen 2010	Randomized controlled trial of preoperative oral carbohydrate treatment in major abdominal surgery
A66	Mathur 2010	Randomized controlled trial of preoperative oral carbohydrate treatment in major abdominal surgery
A67	Awad 2010	The effects of fasting and refeeding with a 'metabolic preconditioning' drink on substrate reserves and mononuclear cell mitochondrial function
A68	Kaška 2010	The impact and safety of preoperative oral or intravenous carbohydrate administration versus fasting in colorectal surgery-a randomized controlled trial
A69	Aronsson 2009	A carbohydrate rich drink shortly before surgery affected IGF-I bioavailability after a total hip replacement: A double-blind placebo controlled study on 29 patients
A70	De Oliveira 2009	Does abbreviation of preoperative fasting to two hours with carbohydrates increase the anesthetic risk? [A abreviação do jejum pré-operatório para duas horas com carboidratos aumenta o risco anestésico?]
A71	Helminen 2009	Effect of preoperative intravenous carbohydrate loading on preoperative discomfort in elective surgery patients
A72	Yang 2009	Effects of drinking fluid hours before anesthesia on gastric fluid volume and pH in patients with colorectal cancer
A73	Lauwick 2009	Effects of oral preoperative carbohydrate on early postoperative outcome after thyroidectomy
A74	Tran 2009	Preoperative Carbohydrae Loading in Patients undergoing Coronary Artery Bypass or Spinal Surgery
A75	Šerclová 2009	Fast-track in open intestinal surgery: prospective randomized study (Clinical Trials Gov Identifier no. NCT00123456)
A76	Sutanto 2009	Gastric emptying of oral nutritional supplements assessed by ultrasound
A77	Lobo 2009	Gastric emptying of three liquid oral preoperative metabolic preconditioning regimens measured by magnetic resonance imaging in healthy adult volunteers: A randomised double-blind, crossover study
A78	Ljungqvist 2009	Modulating postoperative insulin resistance by preoperative carbohydrate loading

STUDY ID	AUTHOR AND YEAR (TRIAL IDENTIFIER)	TITLE
A79	Roig 2009	Perioperative care in colorectal surgery: Current practice patterns and opinions
A80	Can 2009	Preoperative administration of oral carbohydrate-rich solutions: comparison of glucometabolic responses and tolerability between patients with and without insulin resistance
A81	Faria 2009	Preoperative fasting of 2 hours minimizes insulin resistance and organic response to trauma after video-cholecystectomy: A randomized, controlled, clinical trial
A82	Taniguchi 2009	Preoperative fluid and electrolyte management with oral rehydration therapy
A83	Awad 2009	Short-term starvation and mitochondrial dysfunction–A possible mechanism leading to postoperative insulin resistance
A84	Yagci 2008	Effects of preoperative carbohydrate loading on glucose metabolism and gastric contents in patients undergoing moderate surgery: a randomized, controlled trial
A85	An 2008	Effects of preoperative carbohydrate loading on the changes in serum tumor necrosis factor receptors 1 and 2 and insulin resistance in patients of colon carcinoma
A86	Meisner 2008	Liberalisation of preoperative fasting guidelines: Effects on patient comfort and clinical practicability during elective laparoscopic surgery of the lower abdomen [Liberalisierte Präoperative Flüssigkeitskarenz: Patientenbefinden und Klinische Praktikabilität bei Elektiven Laparoskopischen Eingriffen im Unterbauch]
A87	Gustafsson 2008	Pre-operative carbohydrate loading may be used in type 2 diabetes patients
A88	Hendry 2008	Preoperative conditioning with oral carbohydrate loading and oral nutritional supplements can be combined with mechanical bowel preparation prior to elective colorectal resection
A89	Tully 2008	Pre-operative modification of dietary glycemic index improves pre but not post-operative indices of insulin resistance in patients undergoing coronary artery bypass graft surgery
A90	Järvelä 2008	Pre-operative oral carbohydrate treatment before coronary artery bypass surgery
A91	Deniz 2007	Oral carbohydrate solution ameliorates endotoxemia-induced splanchnic ischemia
A92	Svanfeldt 2007	Randomized clinical trial of the effect of preoperative oral carbohydrate treatment on postoperative whole-body protein and glucose kinetics
A93	Soop 2007	Stress-induced insulin resistance: recent developments

STUDY ID	AUTHOR AND YEAR (TRIAL IDENTIFIER)	TITLE
A94	Melis 2006	A carbohydrate-rich beverage prior to surgery prevents surgery-induced immunodepression: A randomized, controlled, clinical trial
A95	Soreide 2006	Modern preoperative fasting guidelines: a summary of the present recommendations and remaining questions
A96	Breuer 2006	New preoperative fasting guidelines: potential for metabolic conditioning. / Reduktion der präoperativen Nahrungskarenz: Potenzial zur metabolischen Konditionierung
A97	Soop 2006	Optimizing perioperative management of patients undergoing colorectal surgery: what is new?
A98	Waitzberg 2006	Postsurgical Infections are Reduced with Specialized Nutrition Support
A99	Furrer 2006	Preoperative fasting times. Patients' perspective [Präoperative nüchternzeiten. Sicht der patienten]
A100	Breuer 2006	Preoperative oral carbohydrate administration to ASA III-IV patients undergoing elective cardiac surgery
A101	Noblett 2006	Pre-operative oral carbohydrate loading in colorectal surgery: a randomized controlled trial
A102	Pu 2005	Effect of preoperative carbohydrate supplementation on insulin resistance in patients after scarectomy
A103	Svanfeldt 2005	Effect of "preoperative" oral carbohydrate treatment on insulin action--a randomised cross-over unblinded study in healthy subjects
A104	Diks 2005	Preoperative fasting: an outdated concept?
A105	Hausel 2005	Randomized clinical trial of the effects of oral preoperative carbohydrates on postoperative nausea and vomiting after laparoscopic cholecystectomy
A106	Yuill 2005	The administration of an oral carbohydrate-containing fluid prior to major elective upper-gastrointestinal surgery preserves skeletal muscle mass postoperatively--a randomised clinical trial
A107	Scheepers 2004	Carbohydrate solution intake during labour just before the start of the second stage: A double-blind study on metabolic effects and clinical outcome
A108	Tjandra 2004	Carboydrate-electrolyte (E-Lyte) solution enhances bowel preparation with oral fleet phospsho-soda
A109	Noblett 2004	Pre-operative oral carbohydrate loading in colorectal surgery: a randomized controlled trial

STUDY ID	AUTHOR AND YEAR (TRIAL IDENTIFIER)	TITLE
A110	Soop 2004	Preoperative oral carbohydrate treatment attenuates endogenous glucose release 3 days after surgery
A111	Smedley 2004	Randomized clinical trial of the effects of preoperative and postoperative oral nutritional supplements on clinical course and cost of care
A112	Ljungqvist 2004	To fast or not to fast? Metabolic preparation for elective surgery
A113	Ali 2003	Effect of supplemental pre-operative fluid on postoperative nausea and vomiting
A114	Henriksen 2003	Effects of preoperative oral carbohydrates and peptides on postoperative endocrine response, mobilization, nutrition and muscle function in abdominal surgery
A115	Bisgaard 2003	Randomized clinical trial comparing an oral carbohydrate beverage with placebo before laparoscopic cholecystectomy
A116	Anderson 2003	Randomized clinical trial of multimodal optimization and standard perioperative surgical care
A117	Ljungqvist 2003	Preoperative fasting
A118	Fearon 2003	The nutritional management of surgical patients: enhanced recovery after surgery
A119	Scheepers 2002	A double-blind, randomised, placebo controlled study on the influence of carbohydrate solution intake during labour
A120	Erdem 2002	The effects of perioperative oral enteral support with glutamine-added elemental formulas in patients with gastrointestinal cancers. A prospective, randomized, clinical study
A121	Hausel 2001	A carbohydrate-rich drink reduces preoperative discomfort in elective surgery patients
A122	Naguib 2001	Metabolic, hormonal and gastric fluid and pH changes after different preoperative feeding regimens
A123	Ljungqvist 2001	Preoperative nutrition—elective surgery in the fed or the overnight fasted state
A124	Nygren 2001	Preoperative oral carbohydrate nutrition: an update
A125	Soop 2001	Preoperative oral carbohydrate treatment attenuates immediate postoperative insulin resistance

STUDY ID	AUTHOR AND YEAR (TRIAL IDENTIFIER)	TITLE
A126	Nygren 1999	Preoperative oral carbohydrates and postoperative insulin resistance
A127	Hausel 1999	Preoperative oral carbohydrates improve well-being after elective colorectal surgery
A128	Nygren 1998	Preoperative oral carbohydrate administration reduces postoperative insulin resistance
A129	Soop 1997	Preoperative oral carbohydrate intake attenuates metabolic changes immediately after hip replacement
A130	Nygren 1996	Safety and patient well-being after preoperative oral intake of carbohydrate rich beverage
A131	Nygren 1995	Preoperative gastric emptying. Effects of anxiety and oral carbohydrate administration
A132	NCT02330263	Effect of Preoperative Oral Carbohydrates on Postoperative Insulin Resistance in Patients Undergoing OPCAB (Off-Pump Coronary Artery Bypass Surgery)
A133	NCT01844375	A Trial of Preoperative CHO Drinks on Postoperative Walking Capacity in Colorectal Surgery
A134	NCT02062788	Evaluation of Preoperative Oral Rehydration Solution in Colectomy
A135	NCT02537262	Effect of Preoperative Oral Carbohydrates on Quality of Recovery in Laparoscopic Colorectal Surgery Patients
A136	NCT01167387	Preoperative Oral Carbohydrate Loading: Effects on The Glucose Metabolism and Postoperative Infections
A137	ISRCTN91109766	Feasibility and Metabolic Effects of Carbohydrate Loading in Patients with Fragile Hip Fracture – A Randomised Doulble Blind Pilot Study
A138	TRC-10001517	Study of preoperative oral carbohydrate-rich solusion ameliorating insulin resistance in postoperative patients of radical gastrectomy
A139	KCT0000108	The safety and the effectiveness of the Fast-track recovery system in gastric cancer patients who undergo laparoscopy assisted distal gastrectomy
A140	CTRI/2009/091/000070	The Effect of Preoperative Carbohydrate Loading in Major Colorectal Resections: A Randomized Controlled Trial
A141	NCT00868400	Clinical Value of Preoperative Oral Carbohydrate Loading in Colorectal Surgery.

STUDY ID	AUTHOR AND YEAR (TRIAL IDENTIFIER)	TITLE
A142	JPRN-UMIN000010742	Effects of Oral Carbohydrate Beverage on Glucose Metabolism and Preoperative Discomforts in Oral Surgery: A Randomized Controlled Trial.
A143	NCT00538954	Optimised recovery with accelerated nutrition and GI enhancement (a randomised controlled trial optimised surgical recovery: the potential synergy between enhanced gastrointestinal motility and oral nutritional/metabolic support)
A144		Randomised controlled study into pre-operative oral carbohydrate loading before resectional colorectal surgery
A145		The effect of the preoperative oral carbohydrate attenuating immediate postoperative insulin resistance on PI3K dependent signalling pathway

Appendix 6.7: Excluded studies + reason for exclusion (phase 2)

STUDY ID	AUTHOR AND YEAR	TITLE	REASON FOR EXCLUSION
A1	Carli 2015	Physiological Considerations of Enhanced Recovery After Surgery (ERAS)	Review
A9	Li 2014	Fast-Tract Improves Post-operative Nutrition and Outcomes of Colorectal Surgery: A Single-Centre Prospective Trial in China	Foreign Language: Chinese
A12	Suliman 2013	Pre-Operative Oral Carbohydrate Loading is Safe and Improves Patients Satisfaction with Elective Ambulatory Surgery and Anesthesia: It's Time for Change	Abstract
A17	Miller 2013	An Evidence-Based Approach to Perioperative Nutrition Support in the Elective Surgery Patient	Comments / Letter / Editorial Comments
A23	Awad 2012	Metabolic conditioning to attenuate the adverse effects of perioperative fasting and improve patient outcomes	Review
A32	Pawa 2012	Enhanced Recovery Program following Colorectal Resection in the Elderly Patient	Review
A36	Gustafsson 2011	Adherence to the Enhanced Recovery after Surgery Protocol and Outcomes After Colorectal Cancer Surgery	Abstract
A40	Martelli 2011	Pre-Operative Oral Nutrition Supplementation of Carbohydrates in Aortic Surgery: A Randomized Trial of 40 Patients	Comments / Letter / Editorial Comments
A44	Gustafsson 2011	Perioperative nutritional management in digestive tract surgery	Review
A46	Crenshaw 2011	Preoperative Fasting: Will the evidence ever be put into practice?	Comments / Letter / Editorial Comments
A48	Kratzing 2011	Pre-operative nutrition and carbohydrate loading	Review
A49	Gianotti 2011	Revising concepts of artificial nutrition in contemporary surgery: from energy and nitrogen to immune-metabolic support	Review
A51	Ozdemir 2011	The Effect of Preoperative Oral Carbohydrate Loading on Stress Response in Patients Undergoing Major or Minor Surgery	Foreign Language: Turkish
A53	Jones 2011	The role of carbohydrate drinks in pre-operative nutrition for elective colorectal surgery	Review
A60	Senesse 2010	Perioperative nutrition care protocols / Nutrition périopératoire: protocols de soins	Foreign Language: French

STUDY ID	AUTHOR AND YEAR	TITLE	REASON FOR EXCLUSION
A61	Coti-Bertrand 2010	Preoperative Nutritional Support	Review
A65	Lassen 2010	Randomized controlled trial of preoperative oral carbohydrate treatment in major abdominal surgery	Comments / Letter / Editorial Comments
A70	De Oliveira 2009	Does abbreviation of preoperative fasting to two hours with carbohydrates increase the anesthetic risk? [A abreviação do jejum pré-operatório para duas horas com carboidratos aumenta o risco anestésico?]	Foreign Language: Portuguese
A72	Yang 2009	Effects of drinking fluid hours before anesthesia on gastric fluid volume and pH in patients with colorectal cancer	Foreign Language: Chinese
A76	Sutanto 2009	Gastric emptying of oral nutritional supplements assessed by ultrasound	Abstract
A78	Ljungqvist 2009	Modulating postoperative insulin resistance by preoperative carbohydrate loading	Comments / Letter / Editorial Comments
A83	Awad 2009	Short-term starvation and mitochondrial dysfunction–A possible mechanism leading to postoperative insulin resistance	Review
A85	An 2008	Effects of preoperative carbohydrate loading on the changes in serum tumor necrosis factor receptors 1 and 2 and insulin resistance in patients of colon carcinoma	Foreign Language: Chinese
A86	Meisner 2008	Liberalisation of preoperative fasting guidelines: Effects on patient comfort and clinical practicability during elective laparoscopic surgery of the lower abdomen [Liberalisierte Präoperative Flüssigkeitskarenz: Patientenbefinden und Klinische Praktikabilität bei Elektiven Laparoskopischen Eingriffen im Unterbauch]	Foreign Language: German
A89	Tully 2008	Pre-operative modification of dietary glycemic index improves pre but not post-operative indices of insulin resistance in patients undergoing coronary artery bypass graft surgery	Abstract
A91	Deniz 2007	Oral carbohydrate solution ameliorates endotoxemia-induced splanchnic ischemia	Animal Study
A93	Soop 2007	Stress-induced insulin resistance: recent developments	Review
A95	Soreide 2006	Modern preoperative fasting guidelines: a summary of the present recommendations and remaining questions	Practice Guidelines
A96	Breuer 2006	New preoperative fasting guidelines: potential for metabolic conditioning. / Reduktion der präoperativen Nahrungskarenz: Potenzial zur metabolischen Konditionierung	Foreign Language: German

STUDY ID	AUTHOR AND YEAR	TITLE	REASON FOR EXCLUSION
A97	Soop 2006	Optimizing perioperative management of patients undergoing colorectal surgery: what is new?	Review
A98	Waitzberg 2006	Postsurgical Infections are Reduced with Specialized Nutrition Support	Review
A99	Furrer 2006	Preoperative fasting times. Patients' perspective [Präoperative nüchternzeiten. Sicht der patienten]	Foreign Language: German
A102	Pu 2005	Effect of preoperative carbohydrate supplementation on insulin resistance in patients after scarectomy	Foreign Language: Chinese
A104	Diks 2005	Preoperative fasting: an outdated concept?	Comments / Letter / Editorial Comments
A108	Tjandra 2004	Carboydrate-electrolyte (E-Lyte) solution enhances bowel preparation with oral fleet phospsho-soda	Abstract
A109	Noblett 2004	Pre-operative oral carbohydrate loading in colorectal surgery: a randomized controlled trial	Multiple Publication
A112	Ljungqvist 2004	To fast or not to fast? Metabolic preparation for elective surgery	Comments / Letter / Editorial Comments
A117	Ljungqvist 2003	Preoperative fasting	Review
A118	Fearon 2003	The nutritional management of surgical patients: enhanced recovery after surgery	Review
A123	Ljungqvist 2001	Preoperative nutrition—elective surgery in the fed or the overnight fasted state	Comments / Letter / Editorial Comments
A124	Nygren 2001	Preoperative oral carbohydrate nutrition: an update	Review
A126	Nygren 1999	Preoperative oral carbohydrates and postoperative insulin resistance	Review
A127	Hausel 1999	Preoperative oral carbohydrates improve well-being after elective colorectal surgery	Abstract
A129	Soop 1997	Preoperative oral carbohydrate intake attenuates metabolic changes immediately after hip replacement	Abstract
A130	Nygren 1996	Safety and patient well-being after preoperative oral intake of carbohydrate rich beverage	Abstract

STUDY ID	AUTHOR AND YEAR	TITLE	REASON FOR EXCLUSION
A132	NCT02330263	Effect of Preoperative Oral Carbohydrates on Postoperative Insulin Resistance in Patients Undergoing OPCAB (Off-Pump Coronary Artery Bypass Surgery)	Ongoing Trial
A133	NCT01844375	A Trial of Preoperative CHO Drinks on Postoperative Walking Capacity in Colorectal Surgery	Ongoing Trial
A134	NCT02062788	Evaluation of Preoperative Oral Rehydration Solution in Colectomy	Ongoing Trial
A135	NCT02537262	Effect of Preoperative Oral Carbohydrates on Quality of Recovery in Laparoscopic Colorectal Surgery Patients	Ongoing Trial
A136	NCT01167387	Preoperative Oral Carbohydrate Loading: Effects on The Glucose Metabolism and Postoperative Infections	Ongoing Trial
A137	ISRCTN91109766	Feasibility and Metabolic Effects of Carbohydrate Loading in Patients with Fragile Hip Fracture – A Randomised Double Blind Pilot Study	Ongoing Trial
A138	TRC-10001517	Study of preoperative oral carbohydrate-rich solution ameliorating insulin resistance in postoperative patients of radical gastrectomy	Ongoing Trial
A139	KCT0000108	The safety and the effectiveness of the Fast-track recovery system in gastric cancer patients who undergo laparoscopy assisted distal gastrectomy	Ongoing Trial
A140	CTRI/2009/091/000070	The Effect of Preoperative Carbohydrate Loading in Major Colorectal Resections: A Randomized Controlled Trial	Ongoing Trial
A141	NCT00868400	Clinical Value of Preoperative Oral Carbohydrate Loading in Colorectal Surgery.	Unpublished Trial
A142	JPRN-UMIN000010742	Effects of Oral Carbohydrate Beverage on Glucose Metabolism and Preoperative Discomforts in Oral Surgery: A Randomized Controlled Trial.	Unpublished Trial
A143		Optimised recovery with accelerated nutrition and GI enhancement (a randomised controlled trial optimised surgical recovery: the potential synergy between enhanced gastrointestinal motility and oral nutritional/metabolic support)	Multiple Publication
A144		Randomised controlled study into pre-operative oral carbohydrate loading before resectional colorectal surgery	Multiple Publication
A145		The effect of the preoperative oral carbohydrate attenuating immediate postoperative insulin resistance on PI3K dependent signalling pathway	Multiple Publication

Appendix 6.8: Study eligibility phase 3

Study ID	STUDY ELIGIBILITY A tick in EVERY column is necessary for study INCLUSION													INCLUDED OR EXCLUDED
	English Language	Randomized Controlled Trial (not crossover)	Humans	Adults	Elective and Emergency Surgery	Normal Glucose Values	Administration: Oral Consumption	Concentration: > 12% CHO	Osmolality: < 300mOsm	Dosage: > 400ml	Timing: 90 – 300 min	≥ 1 outcomes addressed	Other	
A2	✓	✓	✓	✓	✓	✓	✓	x	✓	x	✓	✓		x
A3	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
A4	✓	✓	✓	✓	✓	✓	✓	✓	✓	x	✓	✓		x
A5	✓	x	✓	✓	✓	?	?	?	?	?	?	✓		x
A6	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
A7	✓	✓	✓	✓	✓	✓	✓	x	?	?	✓	✓		x
A8	✓	✓	✓	✓	✓	✓	✓	✓	✓	x	✓	✓		x
A10	✓	✓	✓	✓	✓	x	✓	✓	✓	✓	✓	✓		x
A11	✓	✓	✓	✓	✓	✓	✓	✓	✓	x	✓	✓		x
A13	✓	?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	x	x
A14	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
A15	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
A16	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
A18	✓	✓	✓	✓	✓	x	✓	?	?	?	✓	✓		x
A19	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
A20	✓	x	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		x
A21	✓	✓	✓	✓	✓	✓	✓	✓	✓	x	✓	✓		x
A22	✓	x	✓	✓	✓	?	✓	?	?	?	?	✓		x
A24	✓	x	✓	✓	✓	?	✓	x	?	?	✓	✓		x
A25	✓	✓	✓	✓	✓	?	✓	x	✓	x	✓	✓		x
A26	✓	✓	✓	✓	✓	?	✓	✓	✓	✓	✓	✓	x	x
A27	✓	✓	✓	✓	✓	✓	✓	x	?	x	✓	✓		x
A28	✓	x	✓	✓	✓	?	✓	?	?	?	✓	✓		x
A29	✓	?	✓	✓	✓	?	✓	✓	✓	x	✓	✓		x
A30	✓	x	✓	✓	✓	?	✓	?	?	?	✓	✓		x
A31	✓	✓	✓	✓	✓	✓	✓	✓	✓	x	✓	✓		x

Study ID	STUDY ELIGIBILITY A tick in EVERY column is necessary for study INCLUSION													INCLUDED OR EXCLUDED
	English Language	Randomized Controlled Trial (not crossover)	Humans	Adults	Elective and Emergency Surgery	Normal Glucose Values	Administration: Oral Consumption	Concentration: > 12% CHO	Osmolality: < 300mOsm	Dosage: > 400ml	Timing: 90 – 300 min	≥ 1 outcomes addressed	Other	
A33	✓	✓	✓	✓	✓	?	✓	✓	✓	x	✓	✓		x
A34	✓	x	✓	✓	x	?	✓	✓	✓	✓	✓	✓		x
A35	✓	x	✓	✓	x	✓	✓	✓	✓	✓	✓	✓		x
A37	✓	✓	✓	✓	✓	?	✓	✓	?	✓	x	✓		x
A38	✓	✓	✓	✓	x	?	x	?	?	✓	x	✓		x
A39	✓	✓	✓	✓	✓	✓	✓	✓	?	x	✓	✓		x
A41	✓	x	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		x
A41	✓	x	✓	✓	x	✓	✓	✓	✓	✓	✓	✓		x
A43	✓	✓	✓	✓	✓	x	✓	x	?	?	x	✓		x
A45	✓	x	✓	✓	✓	?	✓	?	x	x	x	✓		x
A47	✓	x	✓	✓	✓	X	✓	?	?	?	x	✓		x
A50	✓	x	✓	✓	✓	?	?	?	?	?	?	x		x
A52	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
A54	✓	✓	✓	✓	✓	✓	✓	✓	?	x	✓	✓		x
A55	✓	x	✓	✓	✓	?	✓	✓	?	x	✓	✓		x
A56	✓	x	✓	✓	✓	?	✓	?	?	?	✓	✓		x
A57	✓	✓	✓	✓	✓	?	✓	✓	?	x	✓	✓		x
A58	✓	x	✓	✓	✓	?	✓	?	?	✓	✓	✓		x
A59	✓	?	✓	✓	✓	?	x	x	?	?	✓	✓		x
A62	✓	✓	✓	✓	✓	x	✓	x	?	?	x	✓		x
A63	✓	✓	✓	✓	✓	x	✓	✓	✓	✓	✓	✓		x
A64	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
A66	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
A67	✓	x	✓	✓	x	?	✓	✓	?	?	✓	✓		x
A68	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
A69	✓	✓	✓	✓	✓	✓	✓	✓	✓	x	✓	✓		x
A71	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
A73	✓	✓	✓	✓	✓	✓	✓	✓	x	✓	✓	✓		x

Study ID	STUDY ELIGIBILITY A tick in EVERY column is necessary for study INCLUSION													INCLUDED OR EXCLUDED
	English Language	Randomized Controlled Trial (not crossover)	Humans	Adults	Elective and Emergency Surgery	Normal Glucose Values	Administration: Oral Consumption	Concentration: > 12% CHO	Osmolality: < 300mOsm	Dosage: > 400ml	Timing: 90 – 300 min	≥ 1 outcomes addressed	Other	
A74	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
A75	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
A77	✓	x	✓	✓	x	?	✓	✓	✓	✓	✓	✓		x
A79	✓	x	✓	✓	✓	?	?	?	?	?	?	?		x
A80	✓	?	✓	✓	✓	x	✓	✓	✓	✓	✓	✓		x
A81	✓	✓	✓	✓	✓	?	✓	✓	✓	x	✓	✓		x
A82	✓	✓	✓	✓	✓	✓	✓	x	✓	✓	?	✓		x
A84	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
A87	✓	?	✓	✓	x	x	✓	✓	✓	✓	✓	✓		x
A88	✓	x	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		x
A90	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
A92	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	x	x
A94	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
A100	✓	✓	✓	✓	✓	x	✓	✓	✓	✓	✓	✓		x
A101	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
A103	✓	x	✓	✓	x	✓	✓	✓	✓	✓	✓	✓		x
A105	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
A106	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
A107	✓	✓	✓	✓	x	✓	✓	✓	?	?	x	✓		x
A110	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
A111	✓	✓	✓	✓	✓	?	✓	x	?	?	x	✓		x
A113	✓	✓	✓	✓	✓	?	x	?	?	x	x	✓		x
A114	✓	✓	✓	✓	✓	✓	✓	✓	?	✓	x	✓		x
A115	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
A116	✓	✓	✓	✓	✓	✓	✓	✓	x	✓	✓	✓		x
A119	✓	✓	✓	✓	x	✓	✓	✓	✓	?	x	✓		x
A120	✓	✓	✓	✓	✓	?	x	✓	x	x	x	✓		x
A121	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓

Study ID	STUDY ELIGIBILITY A tick in EVERY column is necessary for study INCLUSION													INCLUDED OR EXCLUDED
	English Language	Randomized Controlled Trial (not crossover)	Humans	Adults	Elective and Emergency Surgery	Normal Glucose Values	Administration: Oral Consumption	Concentration: > 12% CHO	Osmolality: < 300mOsm	Dosage: > 400ml	Timing: 90 – 300 min	≥ 1 outcomes addressed	Other	
A122	✓	✓	✓	✓	✓	✓	✓	x	?	?	✓	✓		x
A125	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
A128	✓	x	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		x
A131	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓

Appendix 6.9: Excluded studies + resson for exclusion (phase 3)

STUDY ID	AUTHOR AND YEAR	TITLE	REASON FOR EXCLUSION
A2	Singh 2015	Evaluation of effects of a Preoperative 2-hour Fast with Glutamine and Carbohydrate Rich Drink on Insulin Resistance in Maxillofacial Surgery	Concentration: <12% CHO
A4	Webster 2014	Does Preoperative Oral Carbohydrate reduce Hospital Stay? A Randomized Trail	Dosage: 200ml
A5	Wijk 2014	Implementing a Structured Enhanced Recovery after Surgery (ERAS) Protocol reduces Length of Stay after Abdominal Hysterectomy	Study Design: Observational
A7	Zhao 2014	Fast-Track Surgery Improves Postoperative Clinical Recovery and Reduces Postoperative Insulin Resistance after Esophagectomy for Esophageal Cancer	Concentration: <12% CHO
A8	De Anguilar – Nascimento 2014	Preoperative Education in Cholecystectomy in the Context of a Multimodal Protocol of Perioperative Care: A Randomized, Controlled Trial	Dosage: 200ml
A10	Jones 2013	Randomized Clinical Trial on Enhanced Recovery versus Standard Care following Open Liver Resection	Abnormal Glucose Value
A11	Pexe-Machado 2013	Shrinking Preoperative Fast Time with Maltodextrin and Protein Hydrolysate in Gastrointestinal Resections due to Cancer	Dosage: 200ml
A13	Zareba 2013	Parenteral Nutrition and PreOp Preoperation in Prevention of Post-operative Insulin Resistance in Gastrointestinal Carcinoma	>1 Active Control
A18	Braga, 2012	Oral Preoperative Antioxidants in Pancreatic Surgery: A Double-blind, Randomized, Clinical Trial	Abnormal Glucose Value
A20	Viganò 2012	Effects of Preoperative Oral Carbohydrate Supplementation on Postoperative Metabolic Stress Response of Patients Undergoing Elective Abdominal Surgery	Study Design: Cohort Study
A21	Dock-Nascimento 2012	Evaluation of the effects of a preoperative 2-hour fast with maltodextrine and glutamine on insulin resistance, Acute-phase response, nitrogen balance, and serum glutathione after laparoscopic cholecystectomy: A controlled randomized trial	Dosage: 200ml
A22	Verheijen 2012	Feasibility of enhanced recovery programme in various patient groups	Study Design: Cohort Study
A24	Power 2012	Reducing preoperative fasting in elective adult surgical patients: a case-control study	Study Design: Non-Randomized
A25	Itou 2012	Safety and efficacy of oral rehydration therapy until 2 h before surgery: a multicenter randomized controlled trial	Concentration: < 12% CHO

STUDY ID	AUTHOR AND YEAR	TITLE	REASON FOR EXCLUSION
A26	Wang 2012	Immunologic Response after Laparoscopic Colon Cancer Operation within an Enhanced Recovery Programme	>1 Active Control
A27	Yang 2012	Fast-Track Surgery Improves Postoperative Clinical Recovery and Immunity after Elective Surgery for Colorectal Carcinoma: Randomized Controlled Clinical Trial	Concentration: <12% CHO
A28	Huibers 2012	The Effect of the Introduction of the ERAS Protocol in Laparoscopic Total Mesorectal Excision for Rectal Cancer	Study Design: Cohort Study
A29	Kennedy 2012	EnROL: A Multicentre Randomised Trial of Conventional versus Laparoscopic Surgery for Colorectal Cancer within an Enhanced Recovery Programme	Dosage: 200ml
A30	Aarts 2012	Adoption of Enhanced Recovery After Surgery (ERAS) Strategies for Colorectal Surgery at Academic Teaching Hospitals and Impact on Total Length of Hospital Stay	Study Design: Cohort Study
A31	Ren 2012	Enhanced Recovery After Surgery (ERAS) Program Attenuates Stress and Accelerates Recovery in Patients after Radical Resection for Colorectal Cancer: A Prospective Randomized Controlled Trial	Dosage: 200ml
A33	Bopp 2011	A liberal preoperative fasting regimen improves patient comfort and satisfaction with anesthesia care in day-stay minor surgery	Dosage: 200ml
A34	Awad 2011	A randomized crossover study of the effects of glutamine and lipid on the gastric emptying time of a preoperative carbohydrate drink	Study Design: Cross-over Study
A35	Awad 2011	A randomized cross-over study of the metabolic and hormonal responses following two preoperative conditioning drinks	Study Design: Cross-over Study
A37	Burden 2011	An unblinded randomised controlled trial of preoperative oral supplements in colorectal cancer patients	Timing: > 300min preoperative
A38	Goichon 2011	Effects of an enteral glucose supply on protein synthesis, proteolytic pathways, and proteome in human duodenal mucosa	No Surgery
A39	Perrone 2011	Effects of preoperative feeding with a whey protein plus carbohydrate drink on the acute phase response and insulin resistance. A randomized trial	Dosage: < 400ml
A41	Ramirez 2011	Enhanced Recovery in colorectal surgery: a multicentre study	Study Design: Observational Study
A42	Vermeulen 2011	Gastric emptying, glucose metabolism and gut hormones: Evaluation of a common preoperative carbohydrate beverage	Study Design: Cross-over Study
A43	Okabayashi 2011	Oral supplementation with carbohydrate- and branched-chain amino acid-enriched nutrients improves postoperative quality of life in patients undergoing hepatic resection	Abnormal Glucose Values

STUDY ID	AUTHOR AND YEAR	TITLE	REASON FOR EXCLUSION
A45	Manchikanti 2011	Preoperative fasting before interventional techniques: Is it necessary or evidence-based?	Study Design: Observational Study
A47	Donatelli 2011	Preoperative insulin resistance and the impact of feeding on postoperative protein balance: A stable isotope study	Study Design: Observational Study
A50	Christensen 2011	Short hospital stay and low complication rate are possible with a fully implemented fast-track model after elective colonic surgery	Study Design: Observational Study
A54	Awad 2010	Cellular mechanisms underlying the protective effects of preoperative feeding: A randomized study investigating muscle and liver glycogen content, mitochondrial function, gene and protein expression	Dosage: < 400ml
A55	De Aguilar-Nascimento 2010	Clinical benefits after the implementation of a multimodal perioperative protocol in elderly patients	Study Design: Cohort Study
A56	Ahmed 2010	Compliance with enhanced recovery programmes in elective colorectal surgery	Study Design: Case Note Review
A57	Proctic 2010	Effect of preoperative feeding on gastric emptying following spinal anaesthesia: a randomized controlled trial	Dosage: < 400ml
A58	Teeuwen 2010	Enhanced Recovery After Surgery (ERAS) versus conventional postoperative care in colorectal surgery	Study Design: Cohort Study
A59	Liu 2010	Multimodal optimization of surgical care shows beneficial outcome in gastrectomy surgery	Administration: IV
A62	Okabayashi 2010	Preoperative oral supplementation with carbohydrate and branched-chain amino acid-enriched nutrient improves insulin resistance in patients undergoing a hepatectomy: a randomized clinical trial using an artificial pancreas	Abnormal Glucose Values
A63	Hendry 2010	Randomized clinical trial of laxatives and oral nutritional supplements within an enhanced recovery after surgery protocol following liver resection	Abnormal Glucose Values
A67	Awad 2010	The effects of fasting and refeeding with a 'metabolic preconditioning' drink on substrate reserves and mononuclear cell mitochondrial function	Study Design: Observational Study
A69	Aronsson 2009	A carbohydrate rich drink shortly before surgery affected IGF-I bioavailability after a total hip replacement: A double-blind placebo controlled study on 29 patients	Dosage: < 400ml
A73	Lauwick 2009	Effects of oral preoperative carbohydrate on early postoperative outcome after thyroidectomy	Osmolality: > 300mOsm
A77	Lobo 2009	Gastric emptying of three liquid oral preoperative metabolic preconditioning regimens measured by magnetic resonance imaging in healthy adult volunteers: a randomised double-blind crossover study	Study Design: Cross-over Study

STUDY ID	AUTHOR AND YEAR	TITLE	REASON FOR EXCLUSION
A79	Roig 2009	Perioperative care in colorectal surgery: Current practice patterns and opinions	Study Design: Cross-over Study
A80	Can 2009	Preoperative administration of oral carbohydrate-rich solutions: comparison of glucometabolic responses and tolerability between patients with and without insulin resistance	Abnormal Glucose Values
A81	Faria 2009	Preoperative fasting of 2 hours minimizes insulin resistance and organic response to trauma after video-cholecystectomy: A randomized, controlled, clinical trial	Dosage: < 400ml
A82	Taniguchi 2009	Preoperative fluid and electrolyte management with oral rehydration therapy	Concentration: < 12% CHO
A87	Gustafsson 2008	Pre-operative carbohydrate loading may be used in type 2 diabetes patients	No Surgery
A88	Hendry 2008	Preoperative conditioning with oral carbohydrate loading and oral nutritional supplements can be combined with mechanical bowel preparation prior to elective colorectal resection	Study Design: Non-Randomized
A92	Svanfeldt 2007	Randomized clinical trial of the effect of preoperative oral carbohydrate treatment on postoperative whole-body protein and glucose kinetics	Other: > 1 Active Control
A100	Breuer 2006	Preoperative oral carbohydrate administration to ASA III-IV patients undergoing elective cardiac surgery	Abnormal Glucose Values
A103	Svanfeldt 2005	Effect of "preoperative" oral carbohydrate treatment on insulin action--a randomised cross-over unblinded study in healthy subjects	Study Design: Cross-over Study
A107	Scheepers 2004	Carbohydrate solution intake during labour just before the start of the second stage: A double-blind study on metabolic effects and clinical outcome	No Surgery
A111	Smedley 2004	Randomized clinical trial of the effects of preoperative and postoperative oral nutritional supplements on clinical course and cost of care	Concentration: < 12% CHO
A113	Ali 2003	Effect of supplemental pre-operative fluid on postoperative nausea and vomiting	Administration: IV
A114	Henriksen 2003	Effects of preoperative oral carbohydrates and peptides on postoperative endocrine response, mobilization, nutrition and muscle function in abdominal surgery	Timing: > 300min preoperative
A116	Anderson 2003	Randomized clinical trial of multimodal optimization and standard perioperative surgical care	Osmolality: > 300mOsm
A119	Scheepers 2002	A double-blind, randomised, placebo controlled study on the influence of carbohydrate solution intake during labour	No Surgery

STUDY ID	AUTHOR AND YEAR	TITLE	REASON FOR EXCLUSION
A120	Erdem 2002	The effects of perioperative oral enteral support with glutamine-added elemental formulas in patients with gastrointestinal cancers. A prospective, randomized, clinical study	Administration: Enteral
A122	Naguib 2001	Metabolic, hormonal and gastric fluid and pH changes after different preoperative feeding regimens	Concentration: < 12% CHO (unknown)
A128	Nygren 1998	Preoperative oral carbohydrate administration reduces postoperative insulin resistance	Study Design: Non-Randomized

Appendix 6.10: Information of included studies

NAME	STUDY ID	AUTHOR, YEAR	TITLE
1	A3	Ljunggren, 2014	Insulin sensitivity and beta-cell function after carbohydrate oral loading in hip replacement surgery: a double-blind, randomised trial
2	A6	Canby, 2014	Effect of preoperative consumption of high carbohydrate drink (Pre-op®) on postoperative metabolic stress reaction in patients undergoing radical prostatectomy
3	A14	Yilmaz, 2013	Preoperative carbohydrate nutrition reduces postoperative nausea and vomiting compared to preoperative fasting
4	A15	Zelic, 2013	Preoperative oral feeding reduces stress response after laparoscopic cholecystectomy
5	A16	Yildiz, 2013	Oral carbohydrate supplementation reduces preoperative discomfort in laparoscopic cholecystectomy
6	A19	Ljunggren, 2012	Oral nutrition or water loading before hip replacement surgery; a randomized clinical trial
7	A52	Yagmurdur, 2011	The effects of carbohydrate-rich drink on perioperative discomfort, insulin response and arterial pressure in spinal aesthesia
8	A64	Wang, 2010	Randomized clinical trial to compare the effects of preoperative oral carbohydrate versus placebo on insulin resistance after colorectal surgery
9	A66	Mathur, 2010	Randomized controlled trial of preoperative oral carbohydrate treatment in major abdominal surgery
10	A68	Kaska, 2010	The impact and safety of preoperative oral or intravenous carbohydrate administration versus fasting in colorectal surgery – a randomized controlled trial
11	A71	Helminen, 2009	Effect of preoperative intravenous carbohydrate loading on preoperative discomfort in elective surgery patients
12	A74	Tran, 2009	Preoperative carbohydrate loading in patients undergoing coronary artery bypass or spinal surgery
13	A75	Šerclová, 2009	Fast-track in open intestinal surgery: prospective randomized study (Clinical Trials Gov Identifier no. NCT00123456)
14	A84	Yagci, 2008	Effects of preoperative carbohydrate loading on glucose metabolism and gastric contents in patients undergoing moderate surgery: a randomized, controlled trial

NAME	STUDY ID	AUTHOR, YEAR	TITLE
15	A90	Järvelä, 2008	Pre-operative oral carbohydrate treatment before coronary artery bypass surgery
16	A94	Melis, 2006	A carbohydrate-rich beverage prior to surgery prevents surgery induced immunodepression: a randomized, controlled, clinical trial
17	A101	Noblett, 2006	Pre-operative oral carbohydrate loading in colorectal surgery: a randomized controlled trial
18	A105	Hausel, 2005	Randomized clinical trial of the effects of oral preoperative carbohydrates on postoperative nausea and vomiting after laparoscopic cholecystectomy
19	A106	Yuill, 2005	The administration of an oral carbohydrate-containing fluid prior to major elective upper-gastrointestinal surgery preserves skeletal muscle mass postoperatively – a randomised clinical trial
20	A110	Soop, 2004	Preoperative oral carbohydrate treatment attenuates endogenous glucose release 3 days after surgery
21	A115	Bisgaard, 2003	Randomized clinical trial comparing an oral carbohydrate beverage with placebo before laparoscopic cholecystectomy
22	A121	Hausel, 2001	A carbohydrate-rich drink reduces preoperative discomfort in elective surgery patients
23	A125	Soop, 2001	Preoperative oral carbohydrate treatment attenuates immediate postoperative insulin resistance
24	A131	Nygren, 1995	Preoperative gastric emptying (effects of anxiety and oral carbohydrate administration)

Appendix 6.11: Characteristics of included studies (part A)

STUDY	COUNTRY	COMPARISON	SAMPLE SIZE	SEX (MALE: FEMALE)	AGE (YEARS)	BMI (kg/m^2)	ASA SCORE
Ljunggren, 2014 (A3)	Sweden	Oral CHO Placebo	10 / 12	3:7 / 4:8	66 (57 – 75) / 68 (57 – 76)	27.1 ± 3.3 / 27.8 ± 4.4	I – III
Canby, 2014 (A6)	Turkey	Oral CHO Standard Fasting	25 / 25	unknown	60.00 ± 10.37 / 58.36 ± 11.19	unknown	I – II
Yilmaz, 2013 (A14)	Turkey	Oral CHO Standard Fasting	20 / 20	unknown	42.57 ± 14.42 / 45.73 ± 10.39	unknown	I – II
Zelic, 2013 (A15)	Croatia	Oral CHO Standard Fasting	35 / 35	15:20 / 16:19	48.2 / 52.1	unknown	I – II
Yildiz, 2013 (A16)	Turkey	Oral CHO Standard Fasting	30 / 30	5:25 / 8:22	47.63 ± 8.83 / 43.56 ± 9.82	unknown	I – II
Ljunggren, 2012 (A19)	Sweden	Oral CHO Standard Fasting	19 / 20	unknown	65.2 ± 8 / 68.5 ± 9.6	unknown	I – III
Yagmurdur, 2011 (A52)	Turkey	Oral CHO Standard Fasting	22 / 22	12:10 / 14:8	45 ± 7 / 43 ± 8	25 ± 2 / 24 ± 3	I – II
Wang, 2010 (A64)	China	Oral CHO Standard Fasting Placebo	16 / 16 / 16	11:5 / 9:7 / 8:8	66 (48 – 74) / 63 (37 – 74) / 62 (48 – 74)	21 (19 – 24) / 23 (20 – 25) / 23 (18 – 26)	I – II
Mathur, 2010 (A66)	New Zealand	Oral CHO Placebo	69 / 73	29:40 / 44:29	60 (27 – 80) / 65 (22 – 81)	26 (19 – 45) / 25 (17 – 37)	I – III
Kaska, 2010 (A68)	Czech Republic	Oral CHO Standard Fasting IV CHO	63 / 66 / 65	unknown	excluded: age < 35 years and >75 years	excluded: BMI < 20 kg/m^2 and >30 kg/m^2	I - II
Helminen, 2009 (A71)	Finland	Oral CHO Standard Fasting IV CHO	70 / 73 / 67	26:44 / 22:51 / 25:42	60 ± 15 / 58 ± 4 / 61 ± 16	27 ± 5 / 27 ± 5 / 26 ± 4	I - III

STUDY	COUNTRY	COMPARISON	SAMPLE SIZE	SEX (MALE: FEMALE)	AGE (YEARS)	BMI (kg/m^2)	ASA SCORE
Tran, 2009 (A74)	Canada	Oral CHO Standard Fasting	19 / 19	15:4 / 9:10	59 (50;67) / 59 (52; 64)	26.9 (24.4; 30.1) / 25.6 (23.5;29.3)	III – IV
Šerclová, 2009 (A75)	Czech Republic	Oral CHO Standard Fasting	53 / 52	20:33 / 32:20	35.1 ± 11 / 37.6 ± 12.5	23.5 ± 4.7 / 23.3 ± 4.4	I – II
Yagci, 2008 (A84)	Turkey	Oral CHO Standard Fasting	34 / 36	14:20 / 15:21	49.59 ± 15.2 / 43.00 ± 11.0	26.82 ± 4.77 / 25.54 ± 4.4	I – II
Järvelä, 2008 (A90)	Finland	Oral CHO Standard Fasting	50 / 51	39:11 / 45:6	64 ± 8.6 / 66.8 ± 11.4	27.6 ± 4.2 / 27.1 ± 3.5	III - IV
Melis, 2006 (A94)	Netherlands	Oral CHO Standard Fasting	10 / 9	6:4 / 2:7	59 ± 9 / 56 ± 13	24 ± 1 / 25 ± 1.5	unknown
Noblett, 2006 (A101)	United Kingdom	Oral CHO Standard Fasting Placebo	12 / 12 / 11	unknown	58 (30 – 77) / 55 (21 – 79) / 59 (32 – 71)	unknown	I – II
Hausel, 2005 (A105)	Sweden	Oral CHO Standard Fasting Placebo	55 / 58 / 59	14:41 / 13:45 / 18: 41	48.3 ± 14.6 / 48.0 ± 14.9 / 46.8 ± 14.9	24.2 ± 3 / 25.2 ± 2.8 / 23.8 ± 2.9	I – II
Yuill, 2005 (A106)	United Kingdom	Oral CHO Placebo	31 / 34	20:11 / 19:15	52.8 ± 2.5 / 52.1 ± 2.4	25.2 ± 1.2 / 25.1 ± 1.7	unknown
Soop, 2004 (A110)	Sweden	Oral CHO Placebo	8 / 6	3:5 / 6:0	59 ± 3 / 66 ± 2	26 ± 1 / 26 ± 0	I – II
Bisgaard, 2003 (A115)	Denmark	Oral CHO Placebo	43 / 43	6:37 / 9:34	42 (24 – 69) / 44 (18 – 65)	27 (19 – 42) / 26 (19 – 39)	I – II

STUDY	COUNTRY	COMPARISON	SAMPLE SIZE	SEX (MALE: FEMALE)	AGE (YEARS)	BMI (kg/m^2)	ASA SCORE
Hausel, 2001 (A121)	Sweden	Oral CHO Standard Fasting Placebo	80 / 86 / 86	24:56 / 26:60 / 34:52	Chole: 49 (36 – 58) / 48 (37 – 59) / 52 (34 – 58) Colorectal: 56 (50 – 67) / 52 (34 – 66) / 56 (46 – 69)	Chole: 24 (22 – 26) / 25 (23 – 26) / 24 (22 – 26) Colorectal: 25 (21 – 27) / 25 (23 – 27) / 24 (21 – 26)	I – II
Soop, 2001 (A125)	Sweden	Oral CHO Placebo	8 / 7	1:7 / 3:4	66 ± 3 / 58 ± 3	25 ± 1 / 25 ± 1	unknown
Nygren, 1995 (A131)	Sweden	Oral CHO Placebo	6 / 6	3:3 / 4: 2	46 ± 3 / 47 ± 7	25.8 ± 1.6 / 27.1 ± 1.7	I – II

Appendix 6.12: Characteristics of included studies (part B)

STUDY	ADMINISTERED DOSE AND PLANNED TIME OF TREATMENT	ACTUAL TIME FROM INGESTION TO INDUCTION OF ANAESTESIA (minutes)	ACTUAL TIME FROM INGESTION TO START OF SURGERY (minutes)	TYPE OF SURGERY	DURATION OF SURGERY (minutes)	TYPE OF ANAESTHESIA	ERAS PROTOCOL FOLLOWED
Ljunggren, 2014 (A3)	800ml CHO evening before + 400ml CHO 2 hours before anaesthesia / 800ml Placebo evening before + 400ml Placebo 2 hour before anaesthesia / No food from 00:00 evening before surgery	Unknown	Unknown	Other (Hip Replacement)	100 ± 21 / 102 ± 15	Combination (General + Spinal)	No
Canby, 2014 (A6)	800ml CHO evening before + 400ml CHO 2 hours before anaesthesia / Standard Fasting / No food after 00:00 evening before surgery	Unknown	Unknown	Other (Radical Prostatectomy)	Unknown	Unknown	No
Yilmaz, 2013 (A14)	800ml CHO evening before + 400ml CHO 2 hours before anaesthesia / Standard Fasting (fasted for 8 hours)	Unknown	Unknown	Abdominal (Cholecystectomy)	Unknown	General	No
Zelic, 2013 (A15)	800ml CHO evening before + 400ml CHO 2 hours before anaesthesia / Standard Fasting (no oral intake after 17:00 evening before surgery)	Unknown	Unknown	Abdominal (Cholecystectomy)	Unknown	Unknown	No

STUDY	ADMINISTERED DOSE AND PLANNED TIME OF TREATMENT	ACTUAL TIME FROM INGESTION TO INDUCTION OF ANAESTESIA (minutes)	ACTUAL TIME FROM INGESTION TO START OF SURGERY (minutes)	TYPE OF SURGERY	DURATION OF SURGERY (minutes)	TYPE OF ANAESTHESIA	ERAS PROTOCOL FOLLOWED
Yildiz, 2013 (A16)	800ml CHO evening before + 400ml CHO 2 hours before anaesthesia / Standard Fasting (fasted for 8 hours)	Unknown	Unknown	Abdominal (Cholecystectomy)	Unknown	General	No
Ljunggren, 2012 (A19)	800ml CHO evening before + 400ml CHO at least 90minutes before anaesthesia / Standard Fasting	Unknown	Unknown	Other (Hip Replacement)	99 ± 21 / 115 ± 27	Spinal	No
Yagmurdur, 2011 (A52)	800ml CHO evening before + 400ml CHO at least 90minutes before anaesthesia / Standard Fasting	Unknown	Unknown	Abdominal	75 (12) / 72 (18)	Spinal	No
Wang, 2010 (A64)	Low Residue Diet evening before + 400ml CHO 3 hours before anaesthesia / Standard Fasting / Low Residue Diet evening before + Placebo 3 hours before anaesthesia	Unknown	Unknown	Abdominal (Open Major Colorectal Surgery)	98 (70 – 190) / 115 (75 – 180) / 103 (65 – 160)	General	No

STUDY	ADMINISTERED DOSE AND PLANNED TIME OF TREATMENT	ACTUAL TIME FROM INGESTION TO INDUCTION OF ANAESTESIA (minutes)	ACTUAL TIME FROM INGESTION TO START OF SURGERY (minutes)	TYPE OF SURGERY	DURATION OF SURGERY (minutes)	TYPE OF ANAESTHESIA	ERAS PROTOCOL FOLLOWED
Mathur, 2010 (A66)	800ml CHO evening before + 400ml CHO 2 hours before anaesthesia / 800ml evening before + 400ml Placebo 2 hours before anaesthesia	154 (87 – 566) / 144 (85 – 202)	213 (125 – 618) / 201(136 – 251)	Abdominal (Open Major Colorectal and Hepatic Surgery)	154 (43 – 409) / 144 (52 – 420)	Combination (General + Epidural)	No
Kaska, 2010 (A68)	400ml CHO evening before + 400ml CHO 2 hours before anaesthesia / Standard Fasting / NPO + IV CHO	Unknown	Unknown	Abdominal (Open Major Colorectal Surgery)	150 (30)	General	No
Helminen, 2009 (A71)	No restrictions evening before + 400ml CHO 2 hours before anaesthesia / Standard Fasting / NPO + IV CHO	3.8 ± 1.7 / 4.3 ± 1.8 / 4.1 ± 1.9	Unknown	Abdominal/ Other (Abdominal and General Surgery)	100 / 90 / 110	General	No
Tran, 2009 (A74)	800ml CHO evening before + 400ml CHO 2 hours before anaesthesia / Standard Fasting (no intake after 20:00 evening before surgery)	Unknown	Unknown	Other (Coronary Artery Bypass and Spinal Surgery)	Unknown	Combination	No

STUDY	ADMINISTERED DOSE AND PLANNED TIME OF TREATMENT	ACTUAL TIME FROM INGESTION TO INDUCTION OF ANAESTESIA (minutes)	ACTUAL TIME FROM INGESTION TO START OF SURGERY (minutes)	TYPE OF SURGERY	DURATION OF SURGERY (minutes)	TYPE OF ANAESTHESIA	ERAS PROTOCOL FOLLOWED
Šerclová, 2009 (A75)	Light dinner evening before + 400-800ml CHO 2-4 hours before surgery / Standard Fasting	3.6 (±1.7) / > 8.5 hours	Unknown	Abdominal (Open Major Abdominal Surgery)	148.4 (47.6) / 167.5 (51.6)	Combination (General + Epidural)	Yes
Yagci, 2008 (A84)	800ml CHO evening before + 400ml CHO 2 hours before anaesthesia / Standard Fasting	Unknown	Unknown	Abdominal/ Other (laparoscopic cholecystectomy and thyroid surgery)	Unknown	General	No
Järvelä, 2008 (A90)	No restrictions evening before + 400ml CHO 2 hours before anaesthesia / Standard Fasting	Unknown	Unknown	Other (Cardiac Surgery)	279 (97) / 258 (51)	General	No
Melis, 2006 (A94)	Light diet evening before + 400ml CHO 4 hours before anaesthesia / Standard Fasting	Unknown	Unknown	Other (Orthopaedic Surgery)	124 (45) / 155 (74)	Combination (General n = 18; Spinal n = 8; Epidural n = 7)	No

STUDY	ADMINISTERED DOSE AND PLANNED TIME OF TREATMENT	ACTUAL TIME FROM INGESTION TO INDUCTION OF ANAESTESIA (minutes)	ACTUAL TIME FROM INGESTION TO START OF SURGERY (minutes)	TYPE OF SURGERY	DURATION OF SURGERY (minutes)	TYPE OF ANAESTHESIA	ERAS PROTOCOL FOLLOWED
Noblett, 2006 (A101)	800ml CHO evening before + 400ml CHO 3 hours before anaesthesia / Standard Fasting / 800ml Placebo evening before + 400ml Placebo 3 hour before anaesthesia	Unknown	Unknown	Abdominal (Open Major Colorectal Surgery)	Unknown	General	No
Hausel, 2005 (A105)	800ml CHO evening before + 400ml CHO 2 hours before anaesthesia / Standard Fasting / 800ml Placebo evening before + 400ml Placebo 2 hours before anaesthesia	Unknown	Unknown	Abdominal (Laparoscopic Cholecystectomy)	69 (36) / 75 (41) / 67 (33)	General	No
Yuill, 2005 (A106)	800ml CHO evening before + 400ml CHO 2-3 hours before anaesthesia / 800ml Placebo evening before + 400ml Placebo 2-3 hours before anaesthesia	Unknown	Unknown	Abdominal (Major Open Abdominal Surgery)	Unknown	General	No
Soop, 2004 (A110)	800ml CHO evening before + 400ml 2.5 hours before surgery / 800ml Placebo evening before + 400ml Placebo 2.5 hours before surgery	Unknown	190 (10) / 190 (?)	Other (Total Hip Replacement)	84 (9) / 86 (5)	Epidural	No

STUDY	ADMINISTERED DOSE AND PLANNED TIME OF TREATMENT	ACTUAL TIME FROM INGESTION TO INDUCTION OF ANAESTESIA (minutes)	ACTUAL TIME FROM INGESTION TO START OF SURGERY (minutes)	TYPE OF SURGERY	DURATION OF SURGERY (minutes)	TYPE OF ANAESTHESIA	ERAS PROTOCOL FOLLOWED
Bisgaard, 2003 (A115)	800ml CHO evening before + 400ml CHO 2 hours before anaesthesia / 800ml Placebo evening before + 400ml Placebo 2 hours before anaesthesia	145 (110 – 200) / 145 (90 – 245)	162 (100 – 260) / 160 (120 – 215)	Abdominal (Laparoscopic Cholecystectomy)	56 (25 – 130) / 56 (24 – 93)	Combination (General + Epidural)	No
Hausel, 2001 (A121)	800ml CHO evening before + 400ml CHO 2 hours before anaesthesia / Standard Fasting / 800ml Placebo evening before + 400ml Placebo 2 hours before anaesthesia	218 (69) / 215 (75)	Unknown	Abdominal (Laparoscopic Cholecystectomy and Open Major Colorectal Surgery)	Unknown	Combination (General + Epidural)	No
Soop, 2001 (A125)	800ml CHO evening before + 400ml CHO 2 hours before anaesthesia / 800ml Placebo evening before + 400ml Placebo 2 hours before anaesthesia	Unknown	Unknown	Other (Total Hip Replacement)	107 (9) / 123 (23)	Epidural	No
Nygren, 1995 (A131)	400ml CHO 4 hours before anaesthesia / 400ml Placebo 4 hours before anaesthesia	Unknown	Unknown	Abdominal/Other (laparoscopic cholecystectomy and thyroid surgery)	Unknown	Combination	No

Appendix 6.13: Assessment of risk of bias according to the Cochrane tool

STUDY	SEQUENCE GENERATION	ALLOCATION CONCEALMENT	BLINDING OF PARTICIPANTS	BLINDING OF PERSONNEL	BLINDING OF OUTCOMES	INCOMPLETE OUTCOME DATA	SELECTIVE REPORTING	ELIGIBILITY CRITERIA	BASELINE COMPARABILITY	≥ 80% PARTICIPANTS FOLLOWED-UP OR LOSS TO FOLLOWED-UP DESCRIBED	FUNDING	OTHER
Ljunggren, 2014 (A3)	LOW	LOW	LOW	LOW	LOW	HIGH	LOW	LOW	LOW	LOW	UNCLEAR	UNCLEAR
Canby, 2014 (A6)	LOW	LOW	UNCLEAR	UNCLEAR	UNCLEAR	HIGH	UNCLEAR	LOW	LOW	LOW; LOW	UNCLEAR	UNCLEAR
Yilmaz, 2013 (A14)	LOW	LOW	HIGH	LOW	UNCLEAR	HIGH	LOW	LOW	LOW	LOW; LOW	UNCLEAR	UNCLEAR
Zelic, 2013 (A15)	LOW	LOW	LOW	LOW	UNCLEAR	UNCLEAR	UNCLEAR	LOW	LOW	LOW; LOW	UNCLEAR	UNCLEAR
Yildiz, 2013 (A16)	LOW	LOW	HIGH	UNCLEAR	UNCLEAR	HIGH	LOW	LOW	LOW	LOW; LOW	UNCLEAR	UNCLEAR
Ljunggren, 2012 (A19)	LOW	LOW	LOW	LOW	UNCLEAR	UNCLEAR	UNCLEAR	LOW	LOW	LOW; LOW	UNCLEAR	UNCLEAR
Yagmurdur, 2011 (A52)	LOW	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW	UNCLEAR; HIGH	UNCLEAR	UNCLEAR
Wang, 2010 (A64)	LOW	UNCLEAR	LOW	LOW	LOW	HIGH	UNCLEAR	LOW	LOW	LOW; LOW	UNCLEAR	UNCLEAR
Mathur, 2010 (A66)	LOW	LOW	LOW	LOW	LOW	HIGH	UNCLEAR	LOW	HIGH	LOW; LOW	HIGH	UNCLEAR
Kaska, 2010 (A68)	LOW	LOW	UNCLEAR	UNCLEAR	UNCLEAR	HIGH	UNCLEAR	LOW	HIGH	UNCLEAR; UNCLEAR	LOW	HIGH
Helminen, 2009 (A71)	LOW	LOW	UNCLEAR	LOW	LOW	HIGH	UNCLEAR	LOW	LOW	LOW; UNCLEAR	UNCLEAR	UNCLEAR

STUDY	SEQUENCE GENERATION	ALLOCATION CONCEALMENT	BLINDING OF PARTICIPANTS	BLINDING OF PERSONNEL	BLINDING OF OUTCOMES	INCOMPLETE OUTCOME DATA	SELECTIVE REPORTING	ELIGIBILITY CRITERIA	BASELINE COMPARABILITY	≥ 80% PARTICIPANTS FOLLOWED-UP OR LOSS TO FOLLOWED-UP DESCRIBED	FUNDING	OTHER
Tran, 2009 (A74)	UNCLEAR	UNCLEAR	HIGH	LOW	UNCLEAR	HIGH	UNCLEAR	LOW	LOW	LOW; UNCLEAR	UNCLEAR	UNCLEAR
Šerclová, 2009 (A75)	LOW	LOW	HIGH	HIGH	HIGH	HIGH	UNCLEAR	LOW	HIGH	LOW; UNCLEAR	LOW	UNCLEAR
Yagci, 2008 (A84)	LOW	UNCLEAR	HIGH	LOW	HIGH	UNCLEAR	UNCLEAR	LOW	LOW	LOW; UNCLEAR	LOW	UNCLEAR
Järvelä, 2008 (A90)	LOW	LOW	HIGH	LOW	UNCLEAR	HIGH	UNCLEAR	LOW	LOW	LOW; UNCLEAR	LOW	UNCLEAR
Melis, 2006 (A94)	LOW	LOW	HIGH	LOW	UNCLEAR	HIGH	UNCLEAR	LOW	HIGH	LOW; UNCLEAR	UNCLEAR	UNCLEAR
Noblett, 2006 (A101)	LOW	LOW	HIGH	LOW	HIGH	HIGH	UNCLEAR	LOW	LOW	LOW; LOW	UNCLEAR	UNCLEAR
Hausel, 2005 (A105)	LOW	UNCLEAR	LOW	LOW	UNCLEAR	HIGH	UNCLEAR	HIGH	UNCLEAR	LOW; LOW	HIGH	HIGH
Yuill, 2005 (A106)	LOW	UNCLEAR	LOW	LOW	UNCLEAR	UNCLEAR	UNCLEAR	LOW	LOW	LOW; LOW	HIGH	UNCLEAR
Soop, 2004 (A110)	LOW	LOW	LOW	LOW	UNCLEAR	HIGH	UNCLEAR	LOW	HIGH	LOW; LOW	HIGH	UNCLEAR
Bisgaard, 2003 (A115)	LOW	LOW	LOW	LOW	UNCLEAR	UNCLEAR	UNCLEAR	LOW	LOW	LOW; LOW	HIGH	UNCLEAR
Hausel, 2001 (A121)	LOW	UNCLEAR	LOW	LOW	UNCLEAR	HIGH	HIGH	LOW	LOW	LOW; UNCLEAR	HIGH	HIGH
Soop, 2001 (A125)	LOW	LOW	LOW	LOW	UNCLEAR	UNCLEAR	UNCLEAR	LOW	LOW	LOW; LOW	HIGH	UNCLEAR

STUDY	SEQUENCE GENERATION	ALLOCATION CONCEALMENT	BLINDING OF PARTICIPANTS	BLINDING OF PERSONNEL	BLINDING OF OUTCOMES	INCOMPLETE OUTCOME DATA	SELECTIVE REPORTING	ELIGIBILITY CRITERIA	BASELINE COMPARABILITY	≥ 80% PARTICIPANTS FOLLOWED-UP OR LOSS TO FOLLOWED-UP DESCRIBED	FUNDING	OTHER
Nygren, 1995 (A131)	LOW	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	HIGH	UNCLEAR	LOW	LOW	LOW; UNCLEAR	HIGH	UNCLEAR

Appendix 6.14: Detail of the methodological quality

STUDY	SEQUENCE GENERATION	ALLOCATION CONCEALMENT	BLINDING OF PARTICIPANTS	BLINDING OF PERSONNEL	BLINDING OF OUTCOMES	INCOMPLETE OUTCOME DATA	SELECTIVE REPORTING	ELIGIBILITY CRITERIA	BASELINE COMPARABILITY	≥ 80% PARTICIPANTS FOLLOWED-UP or dropouts and withdrawals described	FUNDING	OTHER
Ljunggren, 2014 (A3)	Mentioned; details not stated	Sealed envelope	Blinded	Blinded	Blinded	Yes	No	Yes	Yes	Yes	Unclear	Unclear
Canby, 2014 (A6)	Mentioned; details not stated	Sealed envelope	Unclear	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Unclear	Unclear
Yilmaz, 2013 (A14)	Computer generated randomisation	Not stated	No	Yes	Unclear	Yes	No	Yes	Yes	Yes	Unclear	Unclear
Zelic, 2013 (A15)	Mentioned; details not stated	Sealed envelope	Blinded	Blinded	Unclear	Unclear	Unclear	Yes	Yes	Yes	Unclear	Unclear
Yildiz, 2013 (A16)	Table of random numbers	Sealed envelope	No	Unclear	Unclear	Yes	No	Yes	Yes	Yes	Unclear	Unclear
Ljunggren, 2012 (A19)	Mentioned; details not stated	Sealed envelope	Blinded	Blinded	Unclear	Unclear	Unclear	Yes	Yes	Yes	Unclear	Unclear
Yagmurdur, 2011 (A52)	Mentioned; details not stated	Not stated	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Unclear; No	Unclear	Unclear
Wang, 2010 (A64)	Mentioned; details not stated	Not stated	Blinded	Blinded	Blinded	Yes	Unclear	Yes	Yes	Yes; Yes	Unclear	Unclear
Mathur, 2010 (A66)	Block randomisation	Sealed envelope	Blinded	Blinded	Unclear	Yes	Unclear	Yes	No	Yes; Yes	Nutricia	Unclear
Kaska, 2010 (A68)	Mentioned; details not stated	Sealed envelope	Unclear	Unclear	Unclear	Yes	Unclear	Yes	No	No; Unclear	No Risk	Yes
Helminen, 2009 (A71)	Mentioned; details not stated	Sealed envelope	Unclear	Blinded	Blinded	Yes	Unclear	Yes	Yes	Yes; Unclear	Unclear	Unclear

STUDY	SEQUENCE GENERATION	ALLOCATION CONCEALMENT	BLINDING OF PARTICIPANTS	BLINDING OF PERSONNEL	BLINDING OF OUTCOMES	INCOMPLETE OUTCOME DATA	SELECTIVE REPORTING	ELIGIBILITY CRITERIA	BASELINE COMPARABILITY	≥ 80% PARTICIPANTS FOLLOWED-UP or dropouts and withdrawals described	FUNDING	OTHER
Tran, 2009 (A74)	Mentioned; details not stated	Not stated	No	Blinded	Unclear	Yes	Unclear	Yes	Yes	Yes; Unclear	Unclear	Unclear
Šerclová, 2009 (A75)	Sequence advanced by a statistician	Sealed envelope	No	No	No	Yes	Unclear	Yes	No	Yes; Unclear	No Risk	Unclear
Yagci, 2008 (A84)	Mentioned; details not stated	Not stated	No	Blinded	No	Unclear	Unclear	Yes	Yes	Yes; Unclear	No Risk	Unclear
Järvelä, 2008 (A90)	Mentioned; details not stated	Sealed envelope	No	Blinded	Unclear	Yes	Unclear	Yes	Yes	Yes; Unclear	No Risk	Unclear
Melis, 2006 (A94)	Mentioned; details not stated	Sealed envelope	No	Blinded	Unclear	Yes	Unclear	Yes	No	Yes; Unclear	Unclear	Unclear
Noblett, 2006 (A101)	Random number allocation	Sealed envelope	No	Blinded	No	Yes	Unclear	yes	Yes	Yes; Yes	Unclear	Unclear
Hausel, 2005 (A105)	Computer generated randomisation	Not stated	Blinded	Blinded	Unclear	Yes	Unclear	No	Unclear	Yes; Yes	Numico	Yes
Yuill, 2005 (A106)	Mentioned; details not stated	Not stated	Blinded	Blinded	Unclear	Unclear	Unclear	Yes	Yes	Yes; Yes	Numico	Unclear
Soop, 2004 (A110)	Drinks in random coded lots and given in consecutive order	Manufacturer coding	Blinded	Blinded	Unclear	Yes	Unclear	Yes	No	Yes; Yes	Numico	Unclear
Bisgaard, 2003 (A115)	Block randomisation	Manufacturer coding	Blinded	Blinded	Unclear	Unclear	Unclear	Yes	Yes	Yes; Yes	Nutricia	Unclear
Hausel, 2001 (A121)	Mentioned; details not stated	Not stated	Blinded	Blinded	Unclear	Yes	Yes	Yes	Yes	Yes; Not stated	Numico	Yes

STUDY	SEQUENCE GENERATION	ALLOCATION CONCEALMENT	BLINDING OF PARTICIPANTS	BLINDING OF PERSONNEL	BLINDING OF OUTCOMES	INCOMPLETE OUTCOME DATA	SELECTIVE REPORTING	ELIGIBILITY CRITERIA	BASELINE COMPARABILITY	≥ 80% PARTICIPANTS FOLLOWED-UP or dropouts and withdrawals described	FUNDING	OTHER
Soop, 2001 (A125)	Drinks in random coded lots and given to consecutively enrolled	Manufacturer coding	Blinded	Blinded	Unclear	Unclear	Unclear	Yes	Yes	Yes; Yes	Numico	Unclear
Nygren, 1995 (A131)	Mentioned; details not stated	Not stated	Unclear	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes; Unclear	Nutricia	Unclear

Appendix 6.15: Measured outcomes per trial

Study	Primary Outcomes									Secondary Outcomes									
	Glucose	Insulin	Insulin Resistance	Total Body Protein	Muscle Strength	C-Reactive Protein	Return of Intestinal Function	Length of Stay	Adverse Events	Thirst	Hunger	Nausea	Vomiting	Anxiety	Pain	Fatigue	Weakness	Tiredness	Malaise
n	915	620	270	45	142	406	140	885	1891	932	862	1139	574	902	1081	288	589	573	584
A3	✓*	✓*	✓						✓										
A6									✓	✓	✓			✓					
A14									✓			✓	✓	✓					
A15						✓			✓	✓		✓	✓		✓				
A16									✓	✓	✓	✓		✓		✓	✓		✓
A19			✓					✓	✓										
A52	✓	✓							✓	✓	✓	✓		✓	✓			✓	✓
A64									✓	✓	✓	✓		✓			✓	✓	
A66	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓		✓	✓	✓			✓
A68	✓					✓		✓	✓										
A71	✓	✓							✓	✓	✓			✓	✓		✓	✓	
A74	✓	✓	✓					✓	✓	✓	✓			✓					
A75							✓	✓	✓			✓	✓		✓				
A84	✓	✓							✓										
A90	✓							✓	✓			✓	✓						
A94									✓	✓	✓	✓		✓			✓	✓	
A101							✓		✓										
A105								✓	✓			✓	✓		✓				
A106	✓	✓						✓	✓										
A110	✓*	✓*	✓	✓				✓	✓										
A115									✓			✓	✓		✓	✓			✓
A121									✓	✓	✓	✓		✓	✓		✓	✓	✓
A125	✓*	✓*	✓					✓	✓										
A131										✓	✓			✓					

**glucose and insulin as indicated during a hyperinsulinaemic euglycaemic state when measuring insulin resistance with the hyperinsulinaemic-euglycaemic clamp method*

Appendix 6.16: Results versus discussion representation

The results of the primary outcomes will be presented per comparison in Chapter 3 but will be discussed per time interval in Chapter 4.

Primary Outcomes: Results (Chapter 3) versus Discussion (Chapter 4) [e.g. glucose]

Chapter 3: Results	Chapter 4: Discussion
Comparison 1: Oral CHO versus Inactive Control • Baseline • Before anaesthesia • Day 0 post-surgery • Day 1 post-surgery Comparison 2: Oral CHO versus Fasting • Baseline • Before anaesthesia • Day 0 post-surgery • Day 1 post-surgery Comparison 3: Oral CHO versus Placebo • Baseline • Before anaesthesia • Day 0 post-surgery • Day 1 post-surgery Comparison 4: Oral CHO versus Active Control • Baseline • Before anaesthesia • Day 0 post-surgery • Day 1 post-surgery	Baseline • Oral CHO versus Inactive Control • Oral CHO versus Fasting • Oral CHO versus Placebo • Oral CHO versus Active Control Before Anaesthesia • Oral CHO versus Inactive Control • Oral CHO versus Fasting • Oral CHO versus Placebo • Oral CHO versus Active Control Day 0 Post-Surgery • Oral CHO versus Inactive Control • Oral CHO versus Fasting • Oral CHO versus Placebo • Oral CHO versus Active Control Day 1 Post-Surgery • Oral CHO versus Inactive Control • Oral CHO versus Fasting • Oral CHO versus Placebo • Oral CHO versus Active Control

Appendix 6.17: Median (interquartile range) for some characteristics

Outcome	Trial	Median (Interquartile Range)			
		Oral CHO	Fasting	Placebo	IV CHO
Glucose at Baseline (mmol/l)	Kaska 2010	5.1 (4.7-5.6)	5.4 (4.95-5.85)		5.4 (4.98-6.0)
	Tran 2009 [3]	5.2 (4.9;5.5)	5.0 (4.7;5.2)		
Glucose at Day 0 post-op (mmol/l)	Kaska 2010	7.2 (6.1-8.52)	6.4 (5.47-7.43)[1]		6.8 (6.33-7.88)
	Tran 2009 [3]	6.1 (5.4;6.9)	6.6 (6.0;8.1)		
Glucose at Day 1 post-op (mmol/l)	Kaska 2010	6.4 (5.4-7.5)	6.65 (5.63-7.8)		6.5 (5.7-7.7)
Insulin at Baseline (mU/l)	Mathur 2010	9 (6-14)		8 (6-11)	
	Tran 2009[3]	10 (6;12)	9 (4;19)		
Insulin before Anaesthesia (mU/l)	Mathur 2010	7 (3-16)		5 (3-9)	
Insulin at Day 0 post-op (mU/l)	Tran 2009[3]	7 (6;9)	6 (4;10)		
Insulin at Day 1 post-op (mU/l)	Mathur 2010	11 (7-19)		12 (6-20)	
Insulin Resistance at Baseline (HOMA-IR)	Tran 2009[3]	2.2 (1.5;2.9)	1.7 (1.2;2.0)		
Insulin Resistance at Day 0 post-op (HOMA-IR)	Tran 2009[3]	2.5 (1.1;5.9)	1.8 (1.2;3.1)		
C-Reactive Protein at Baseline (mg/dl)	Kaska 2010	4 (2-11.5)	5 (2.23-12.3)		2.4 (1.15-8.5)
	Mathur 2010	3 (3-4)		3 (3-5)	
C-Reactive Protein before Anaesthesia (mg/dl)	Kaska 2010	4.5 (2-16)	6 (3.25-19.7)		2 (1.53-8)
	Mathur 2010	3 (1-7)		3 (2-8)	
C-Reactive Protein at Day 1 post-op (mg/dl)	Mathur 2010	73 (36-98)		73 (37-117)	
C-Reactive Protein at Day 3 post-op (mg/dl)	Kaska 2010	101 (74.8-150)	125 (76.8-147)		108 (82-157)
	Mathur 2010	99 (46-192)		93 (56-155)	

Outcome	Trial	Median (Interquartile Range)			
		Oral CHO	Fasting	Placebo	IV CHO
C-Reactive Protein at Day 7 post-op (mg/dl)	Kaska 2010	21.5 (14.5-59)	24 (12.5-41.5)		29 (16-55)
	Mathur 2010	56 (36-112)		42 (27-104)	
Return of Stool (days)[2]	Noblett 2006	2	3	3	
Return of Bowel movement (days)[2]	Noblett 2006	2	3.5	5	
Length of Hospital Stay (days)	Mathur 2010	7 (2-35)		8 (2-92)	
	Kaska 2010	11 (9-12)	11(9-13)		10 (9-12)
	Yuill 2005[3]	8 (4)		10 (6)	
	Tran 2009[3]	4.0 (4.0;5.0)	5.0 (5.0;8.0)[1]		
Fit for Discharge (days)	Mathur 2010	6 (2-35)		7 (2-92)	

1 = $p < 0.05$ compared with oral CHO; 2 = only medians given; 3 = median (75^{th}-25^{th})

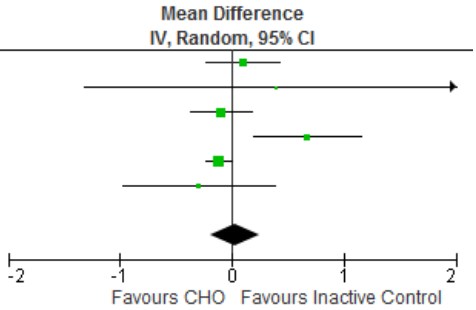
Appendix 6.18: Glucose analyses per comparison

COMPARISON 1: ORAL CHO VERSUS INACTIVE CONTROL (FASTING + PLACEBO)

Analysis 1.1: Glucose (HOMA-IR + QUICKI) at Baseline

	Oral CHO			Inactive Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Helminen 2009	5.6	0.9	70	5.5	1.1	73	20.3%	0.10 [-0.23, 0.43]
Järvelä 2008	5.8	1.7	50	5.4	6	51	1.6%	0.40 [-1.31, 2.11]
Mathur 2010	5	0.83	69	5.1	0.85	73	23.3%	-0.10 [-0.38, 0.18]
Yagci 2008	4.78	0.6	34	4.11	1.34	36	13.5%	0.67 [0.19, 1.15]
Yagmurdur 2011	4.88	0.17	22	5	0.22	22	32.9%	-0.12 [-0.24, -0.00]
Yuill 2005	5.7	1.4	31	6	1.4	34	8.3%	-0.30 [-0.98, 0.38]
Total (95% CI)			**276**			**289**	**100.0%**	**0.03 [-0.19, 0.25]**

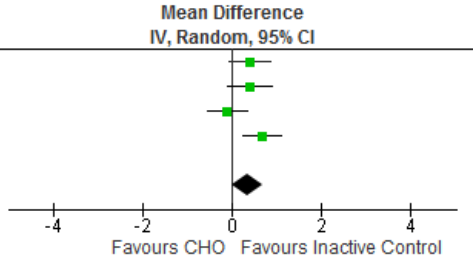
Heterogeneity: Tau² = 0.04; Chi² = 11.56, df = 5 (P = 0.04); I² = 57%
Test for overall effect: Z = 0.26 (P = 0.80)



Analysis 1.2: Glucose (HOMA-IR + QUICKI) before Anaesthesia

	Oral CHO			Inactive Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Helminen 2009	5.3	1.6	70	4.9	1.2	73	24.6%	0.40 [-0.07, 0.87]
Järvelä 2008	5.8	1.7	50	5.4	0.6	51	23.0%	0.40 [-0.10, 0.90]
Mathur 2010	5.3	1.66	69	5.4	0.85	73	26.1%	-0.10 [-0.54, 0.34]
Yagci 2008	4.61	0.46	34	3.93	1.24	36	26.3%	0.68 [0.25, 1.11]
Total (95% CI)			**223**			**233**	**100.0%**	**0.34 [0.01, 0.68]**

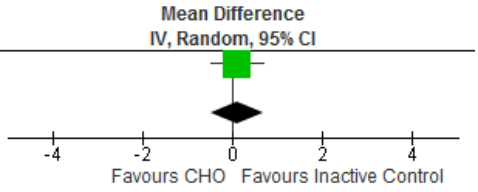
Heterogeneity: Tau² = 0.06; Chi² = 6.37, df = 3 (P = 0.10); I² = 53%
Test for overall effect: Z = 2.02 (P = 0.04)



Analysis 1.3: Glucose (HOMA-IR + QUICKI) at Day 0 Postoperative

	Oral CHO			Inactive Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Järvelä 2008	6.4	1	50	6.3	1.9	51	100.0%	0.10 [-0.49, 0.69]
Total (95% CI)			**50**			**51**	**100.0%**	**0.10 [-0.49, 0.69]**

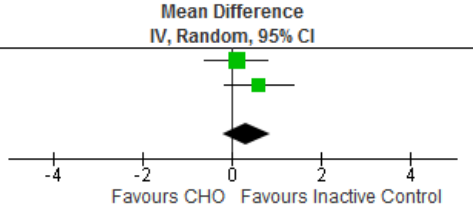
Heterogeneity: Not applicable
Test for overall effect: Z = 0.33 (P = 0.74)



Analysis 1.4: Glucose (HOMA-IR + QUICKI) at Day 1 Postoperative

	Oral CHO			Inactive Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Mathur 2010	6.6	2.49	69	6.5	1.71	73	55.1%	0.10 [-0.61, 0.81]
Yuill 2005	6.8	1.7	31	6.2	1.5	34	44.9%	0.60 [-0.18, 1.38]
Total (95% CI)			**100**			**107**	**100.0%**	**0.32 [-0.20, 0.85]**

Heterogeneity: Tau² = 0.00; Chi² = 0.86, df = 1 (P = 0.35); I² = 0%
Test for overall effect: Z = 1.21 (P = 0.23)

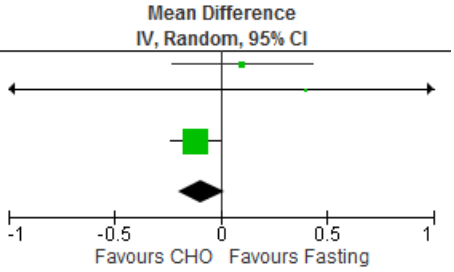


COMPARISON 2: ORAL CHO VERSUS FASTING

Analysis 2.1: Glucose (HOMA-IR + QUICKI) at Baseline

Study or Subgroup	Oral CHO Mean	SD	Total	Fasting Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Helminen 2009	5.6	0.9	70	5.5	1.1	73	11.1%	0.10 [-0.23, 0.43]
Järvelä 2008	5.8	1.7	50	5.4	6	50	0.4%	0.40 [-1.33, 2.13]
Yagci 2008	4.78	0.6	34	4.11	1.34	36		Not estimable
Yagmurdur 2011	4.88	0.17	22	5	0.22	22	88.5%	-0.12 [-0.24, -0.00]
Total (95% CI)			**142**			**145**	**100.0%**	**-0.09 [-0.20, 0.02]**

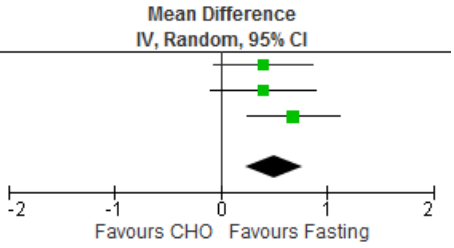
Heterogeneity: Tau² = 0.00; Chi² = 1.84, df = 2 (P = 0.40); I² = 0%
Test for overall effect: Z = 1.68 (P = 0.09)



Analysis 2.2: Glucose (HOMA-IR + QUICKI) before Anaesthesia

Study or Subgroup	Oral CHO Mean	SD	Total	Fasting Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Helminen 2009	5.3	1.6	70	4.9	1.2	73	33.1%	0.40 [-0.07, 0.87]
Järvelä 2008	5.8	1.7	50	5.4	0.6	51	28.8%	0.40 [-0.10, 0.90]
Yagci 2008	4.61	0.46	34	3.93	1.24	36	38.1%	0.68 [0.25, 1.11]
Total (95% CI)			**154**			**160**	**100.0%**	**0.51 [0.24, 0.77]**

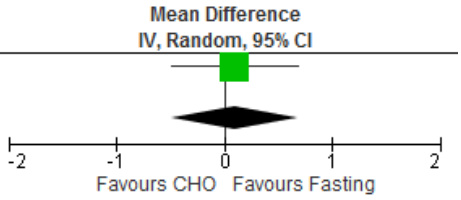
Heterogeneity: Tau² = 0.00; Chi² = 0.99, df = 2 (P = 0.61); I² = 0%
Test for overall effect: Z = 3.71 (P = 0.0002)



Analysis 2.3: Glucose (HOMA-IR + QUICKI) at Day 0 Postoperative

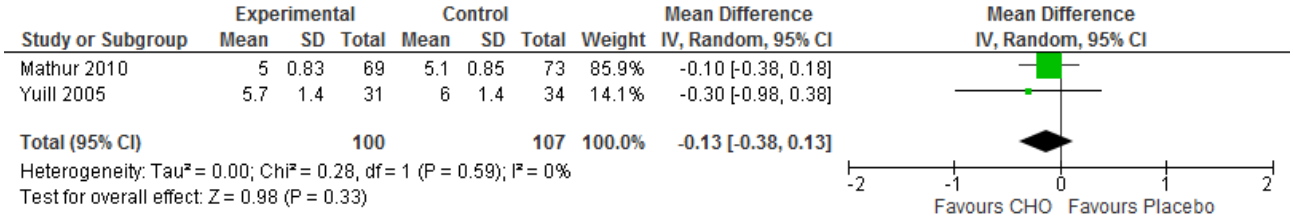
Study or Subgroup	Oral CHO Mean	SD	Total	Fasting Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Järvelä 2008	6.4	1	50	6.3	1.9	51	100.0%	0.10 [-0.49, 0.69]
Total (95% CI)			**50**			**51**	**100.0%**	**0.10 [-0.49, 0.69]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.33 (P = 0.74)

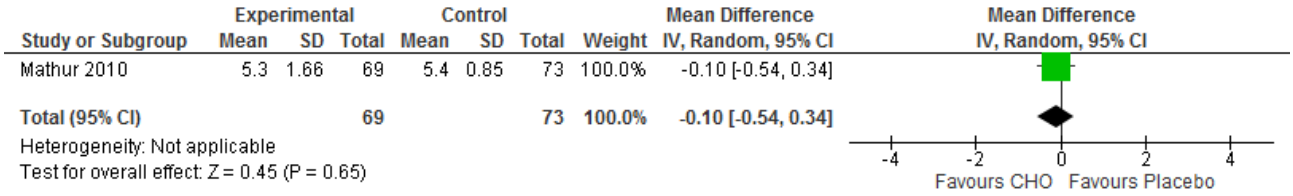


COMPARISON 3: ORAL CHO VERSUS PLACEBO

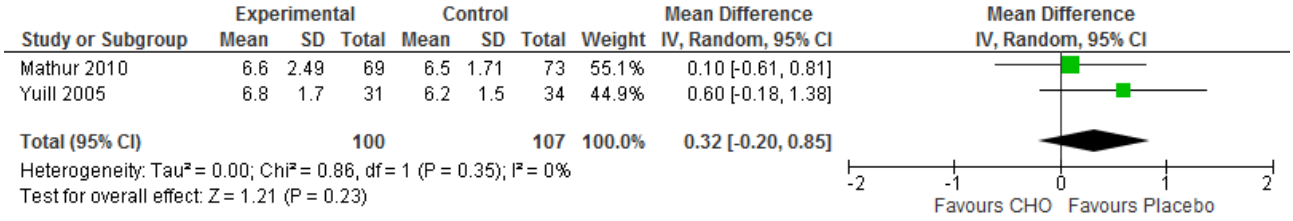
Analysis 3.1: Glucose (HOMA-IR + QUICKI) at Baseline



Analysis 3.2: Glucose (HOMA-IR + QUICKI) before Anaesthesia

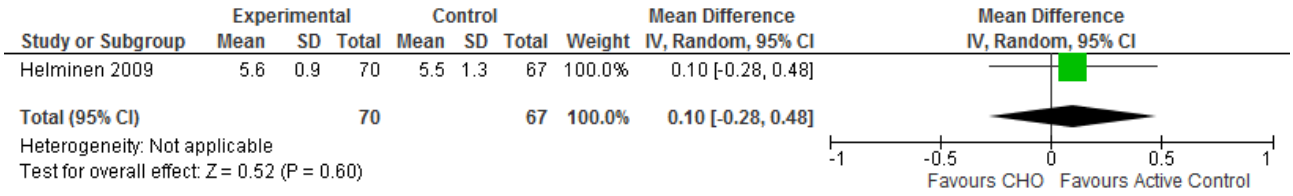


Analysis 3.3: Glucose (HOMA-IR + QUICKI) at Day 1 Postoperative

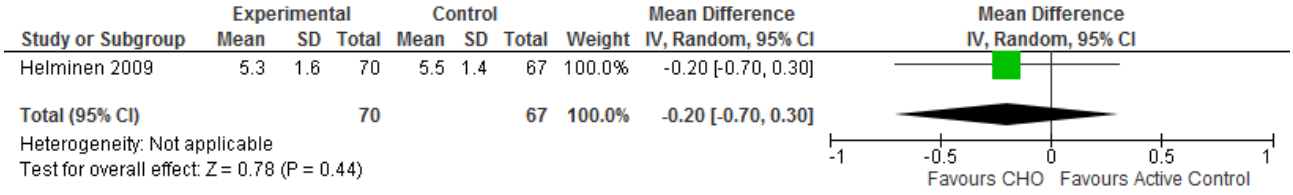


COMPARISON 4: ORAL CHO VERSUS ACTIVE CONTROL (IV CHO)

Analysis 4.1: Glucose (HOMA-IR + QUICKI) at Baseline



Analysis 4.2: Glucose (HOMA-IR + QUICKI) before Anaesthesia



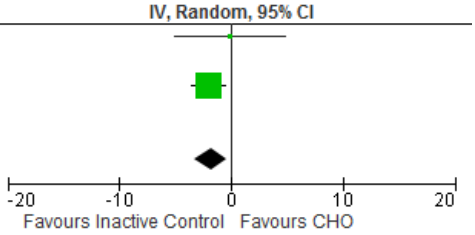
Appendix 6.19: Insulin analyses per comparison

COMPARISON 1: ORAL CHO VERSUS INACTIVE CONTROL (FASTING + PLACEBO)

Analysis 1.1: Insulin (HOMA-IR + QUICKI) at Baseline

Study or Subgroup	Oral CHO Mean	SD	Total	Inactive Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Helminen 2009	10.3	7.2	22	10.4	9.7	23	8.4%	-0.10 [-5.08, 4.88]
Yagci 2008	17.08	5.23	34	3.3	4.78	36	0.0%	13.78 [11.43, 16.13]
Yagmurdur 2011	6	2	22	8	3	22	91.6%	-2.00 [-3.51, -0.49]
Yuill 2005	24.6	6.2	31	20.7	4.9	34	0.0%	3.90 [1.17, 6.63]
Total (95% CI)			**44**			**45**	**100.0%**	**-1.84 [-3.28, -0.40]**

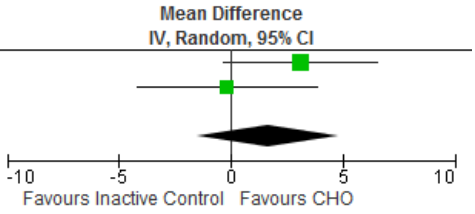
Heterogeneity: Tau² = 0.00; Chi² = 0.51, df = 1 (P = 0.47); I² = 0%
Test for overall effect: Z = 2.50 (P = 0.01)



Analysis 1.2: Insulin (HOMA-IR + QUICKI) before Anaesthesia

Study or Subgroup	Oral CHO Mean	SD	Total	Inactive Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Helminen 2009	8.6	7.5	22	5.5	3.3	23	55.4%	3.10 [-0.31, 6.51]
Yagci 2008	17.66	6.99	34	17.82	9.92	36	44.6%	-0.16 [-4.16, 3.84]
Total (95% CI)			**56**			**59**	**100.0%**	**1.64 [-1.53, 4.82]**

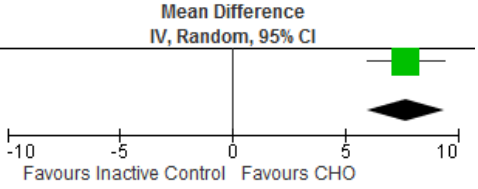
Heterogeneity: Tau² = 1.71; Chi² = 1.48, df = 1 (P = 0.22); I² = 32%
Test for overall effect: Z = 1.01 (P = 0.31)



Analysis 1.3: Insulin (HOMA-IR + QUICKI) at Day 1 Postoperative

Study or Subgroup	Oral CHO Mean	SD	Total	Inactive Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Yuill 2005	17.4	4.4	31	9.7	2.3	34	100.0%	7.70 [5.97, 9.43]
Total (95% CI)			**31**			**34**	**100.0%**	**7.70 [5.97, 9.43]**

Heterogeneity: Not applicable
Test for overall effect: Z = 8.72 (P < 0.00001)

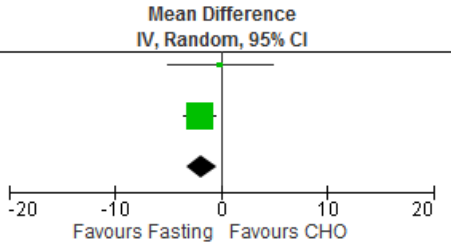


COMPARISON 2: ORAL CHO VERSUS FASTING

Analysis 2.1: Insulin (HOMA-IR + QUICKI) at Baseline

Study or Subgroup	Oral CHO Mean	SD	Total	Fasting Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Helminen 2009	10.3	7.2	22	10.4	9.7	23	8.4%	-0.10 [-5.08, 4.88]
Yagci 2008	17.08	5.23	34	3.3	4.78	36	0.0%	13.78 [11.43, 16.13]
Yagmurdur 2011	6	2	22	8	3	22	91.6%	-2.00 [-3.51, -0.49]
Total (95% CI)			**44**			**45**	**100.0%**	**-1.84 [-3.28, -0.40]**

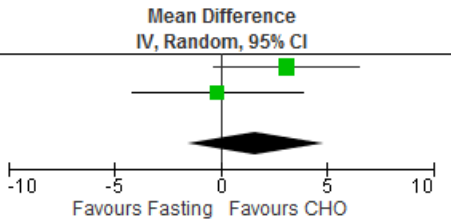
Heterogeneity: Tau² = 0.00; Chi² = 0.51, df = 1 (P = 0.47); I² = 0%
Test for overall effect: Z = 2.50 (P = 0.01)



Analysis 2.2: Insulin (HOMA-IR + QUICKI) before Anaesthesia

Study or Subgroup	Oral CHO Mean	SD	Total	Fasting Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Helminen 2009	8.6	7.5	22	5.5	3.3	23	55.4%	3.10 [-0.31, 6.51]
Yagci 2008	17.66	6.99	34	17.82	9.92	36	44.6%	-0.16 [-4.16, 3.84]
Total (95% CI)			**56**			**59**	**100.0%**	**1.64 [-1.53, 4.82]**

Heterogeneity: Tau² = 1.71; Chi² = 1.48, df = 1 (P = 0.22); I² = 32%
Test for overall effect: Z = 1.01 (P = 0.31)

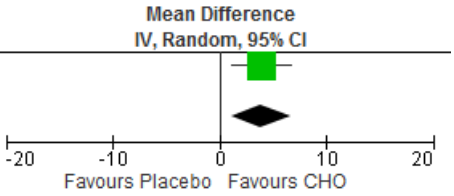


COMPARISON 3: ORAL CHO VERSUS PLACEBO

Analysis 3.1: Insulin (HOMA-IR + QUICKI) at Baseline

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Yuill 2005	24.6	6.2	31	20.7	4.9	34	100.0%	3.90 [1.17, 6.63]
Total (95% CI)			**31**			**34**	**100.0%**	**3.90 [1.17, 6.63]**

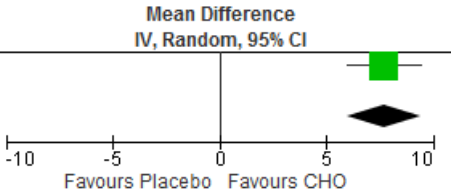
Heterogeneity: Not applicable
Test for overall effect: Z = 2.80 (P = 0.005)



Analysis 3.2: Insulin (HOMA-IR + QUICKI) at Day 1 Postoperative

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Yuill 2005	17.4	4.4	31	9.7	2.3	34	100.0%	7.70 [5.97, 9.43]
Total (95% CI)			**31**			**34**	**100.0%**	**7.70 [5.97, 9.43]**

Heterogeneity: Not applicable
Test for overall effect: Z = 8.72 (P < 0.00001)

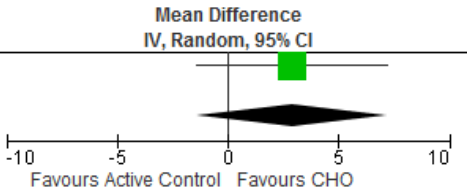


COMPARISON 4: ORAL CHO VERSUS ACTIVE CONTROL (IV CHO)

Analysis 4.1: Insulin (HOMA-IR + QUICKI) at Baseline

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Helminen 2009	10.3	7.2	22	7.4	6.8	19	100.0%	2.90 [-1.39, 7.19]
Total (95% CI)			**22**			**19**	**100.0%**	**2.90 [-1.39, 7.19]**

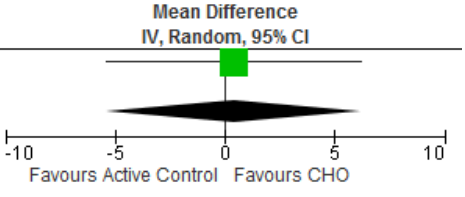
Heterogeneity: Not applicable
Test for overall effect: Z = 1.33 (P = 0.19)



Analysis 4.2: Insulin (HOMA-IR + QUICKI) before Anaesthesia

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Helminen 2009	8.6	7.5	22	8.2	10.8	19	100.0%	0.40 [-5.38, 6.18]
Total (95% CI)			**22**			**19**	**100.0%**	**0.40 [-5.38, 6.18]**

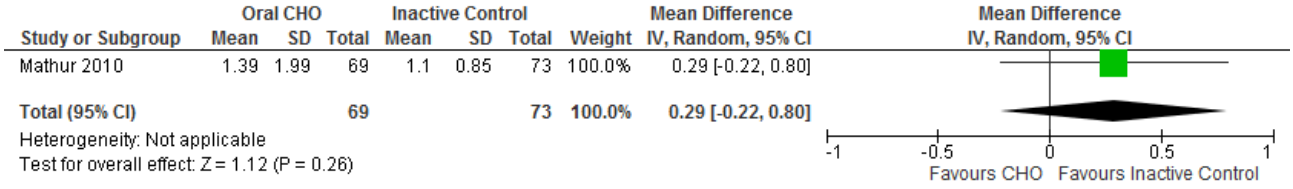
Heterogeneity: Not applicable
Test for overall effect: Z = 0.14 (P = 0.89)



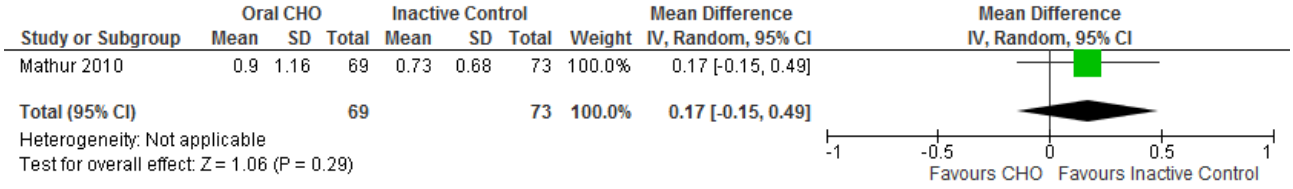
Appendix 6.20: Insulin resistance analyses per comparison

COMPARISON 1: ORAL CHO VERSUS INACTIVE CONTROL (FASTING + PLACEBO)

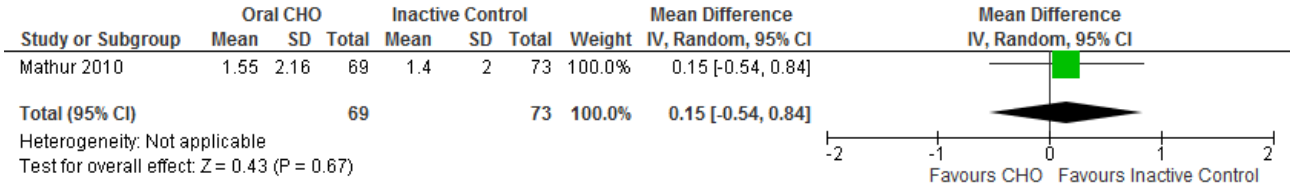
Analysis 1.1: Insulin Resistance (HOMA-IR) at Baseline



Analysis 1.2: Insulin Resistance (HOMA-IR) before Anaesthesia



Analysis 1.3: Insulin Resistance (HOMA-IR) at Day 1 Postoperative

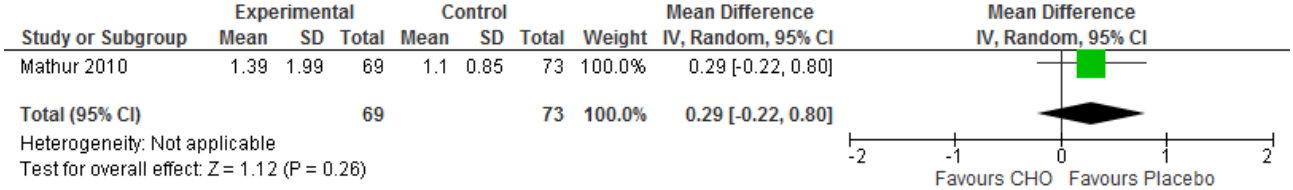


COMPARISON 2: ORAL CHO VERSUS FASTING

No analyses for this comparison.

COMPARISON 3: ORAL CHO VERSUS PLACEBO

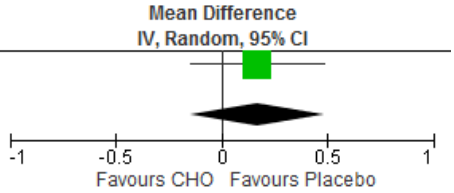
Analysis 3.1: Insulin Resistance (HOMA-IR) at Baseline



Analysis 3.2: Insulin Resistance (HOMA-IR) before Anaesthesia

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Mathur 2010	0.9	1.16	69	0.73	0.68	73	100.0%	0.17 [-0.15, 0.49]
Total (95% CI)			**69**			**73**	**100.0%**	**0.17 [-0.15, 0.49]**

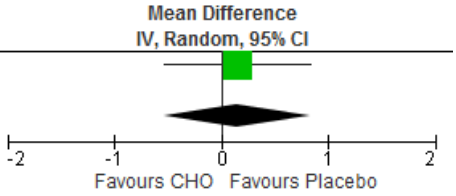
Heterogeneity: Not applicable
Test for overall effect: Z = 1.06 (P = 0.29)



Analysis 3.3: Insulin Resistance (HOMA-IR) at Day 1 Postoperative

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Mathur 2010	1.55	2.16	69	1.4	2	73	100.0%	0.15 [-0.54, 0.84]
Total (95% CI)			**69**			**73**	**100.0%**	**0.15 [-0.54, 0.84]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.43 (P = 0.67)



COMPARISON 4: ORAL CHO VERSUS ACTIVE CONTROL (IV CHO)

No analyses for this comparison.

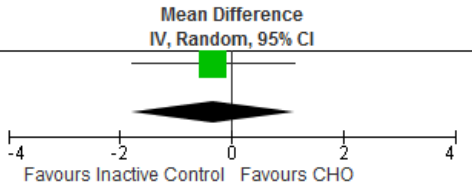
Appendix 6.21: Total body protein analyses per comparison

COMPARISON 1: ORAL CHO VERSUS INACTIVE CONTROL (FASTING + PLACEBO)

Analysis 1.1: Total Body Protein at Baseline

Study or Subgroup	Oral CHO Mean	SD	Total	Inactive Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Mathur 2010	9.5	1.91	14	9.83	2.19	17	100.0%	-0.33 [-1.77, 1.11]
Total (95% CI)			**14**			**17**	**100.0%**	**-0.33 [-1.77, 1.11]**

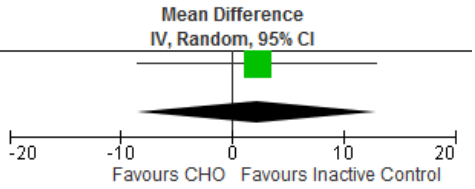
Heterogeneity: Not applicable
Test for overall effect: Z = 0.45 (P = 0.65)



Analysis 1.2: Total Body Protein at Day 3 Postoperative

Study or Subgroup	Oral CHO Mean	SD	Total	Inactive Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Soop 2004	0.96	8.15	8	-1.28	11.37	6	100.0%	2.24 [-8.47, 12.95]
Total (95% CI)			**8**			**6**	**100.0%**	**2.24 [-8.47, 12.95]**

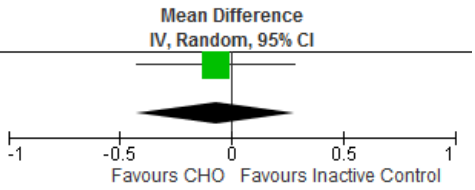
Heterogeneity: Not applicable
Test for overall effect: Z = 0.41 (P = 0.68)



Analysis 1.3: Total Body Protein at Day 7 Postoperative

Study or Subgroup	Oral CHO Mean	SD	Total	Inactive Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Mathur 2010	-0.67	0.37	14	-0.6	0.62	17	100.0%	-0.07 [-0.42, 0.28]
Total (95% CI)			**14**			**17**	**100.0%**	**-0.07 [-0.42, 0.28]**

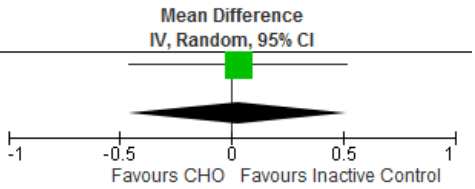
Heterogeneity: Not applicable
Test for overall effect: Z = 0.39 (P = 0.70)



Analysis 1.4: Total Body Protein at Day 28 Postoperative

Study or Subgroup	Oral CHO Mean	SD	Total	Inactive Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Mathur 2010	-0.49	0.56	14	-0.52	0.82	17	100.0%	0.03 [-0.46, 0.52]
Total (95% CI)			**14**			**17**	**100.0%**	**0.03 [-0.46, 0.52]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.12 (P = 0.90)

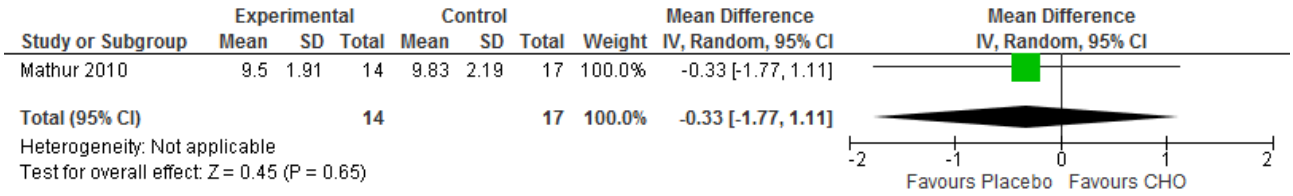


COMPARISON 2: ORAL CHO VERSUS FASTING

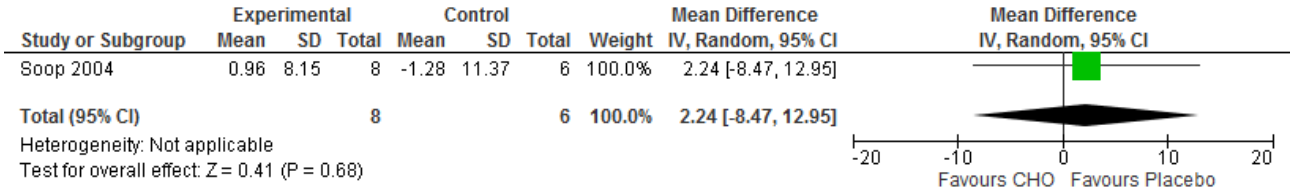
No analyses for this comparison.

COMPARISON 3: ORAL CHO VERSUS PLACEBO

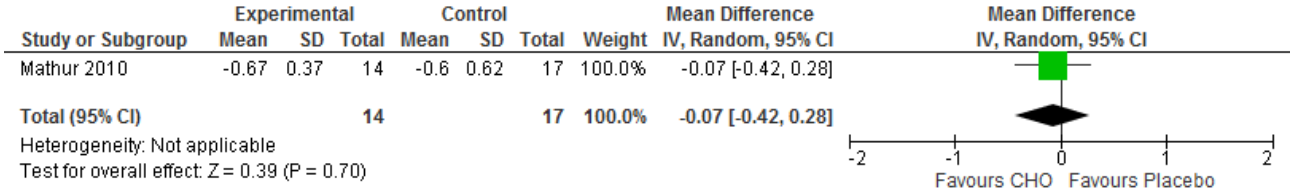
Analysis 3.1: Total Body Protein at Baseline



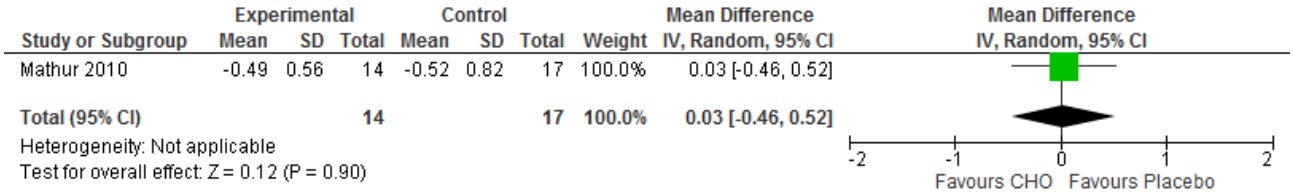
Analysis 3.2: Total Body Protein at Day 3 Postoperative



Analysis 3.3: Total Body Protein at Day 7 Postoperative



Analysis 3.4: Total Body Protein at Day 28 Postoperative



COMPARISON 4: ORAL CHO VERSUS ACTIVE CONTROL (IV CHO)

No analyses for this comparison.

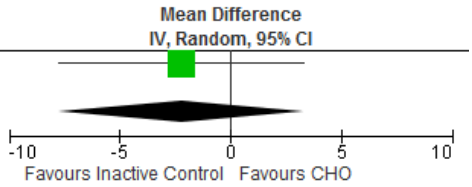
Appendix 6.22: Muscle strength analyses per comparison

COMPARISON 1: ORAL CHO VERSUS INACTIVE CONTROL (FASTING + PLACEBO)

Analysis 1.1: Muscle Strength at Day 1

Study or Subgroup	Oral CHO Mean	SD	Total	Inactive Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Mathur 2010	88.05	19.02	69	90.27	14.1	73	100.0%	-2.22 [-7.75, 3.31]
Total (95% CI)			**69**			**73**	**100.0%**	**-2.22 [-7.75, 3.31]**

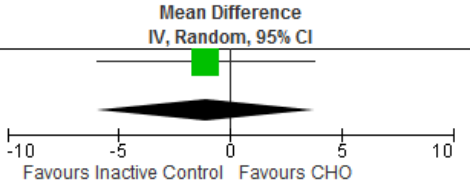
Heterogeneity: Not applicable
Test for overall effect: Z = 0.79 (P = 0.43)



Analysis 1.2: Muscle Strength at Day 3

Study or Subgroup	Oral CHO Mean	SD	Total	Inactive Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Mathur 2010	90.18	14.7	69	91.29	14.86	73	100.0%	-1.11 [-5.97, 3.75]
Total (95% CI)			**69**			**73**	**100.0%**	**-1.11 [-5.97, 3.75]**

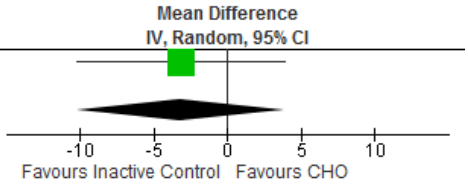
Heterogeneity: Not applicable
Test for overall effect: Z = 0.45 (P = 0.65)



Analysis 1.3: Muscle Strength at Day 7

Study or Subgroup	Oral CHO Mean	SD	Total	Inactive Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Mathur 2010	92.41	23.67	69	95.57	18.88	73	100.0%	-3.16 [-10.23, 3.91]
Total (95% CI)			**69**			**73**	**100.0%**	**-3.16 [-10.23, 3.91]**

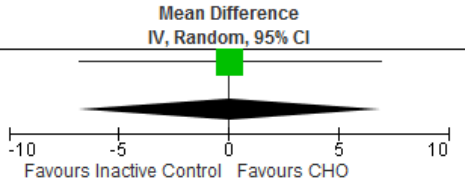
Heterogeneity: Not applicable
Test for overall effect: Z = 0.88 (P = 0.38)



Analysis 1.4: Muscle Strength at Day 28

Study or Subgroup	Oral CHO Mean	SD	Total	Inactive Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Mathur 2010	101.27	20.19	69	101.2	21.7	73	100.0%	0.07 [-6.82, 6.96]
Total (95% CI)			**69**			**73**	**100.0%**	**0.07 [-6.82, 6.96]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.02 (P = 0.98)



COMPARISON 2: ORAL CHO VERSUS FASTING

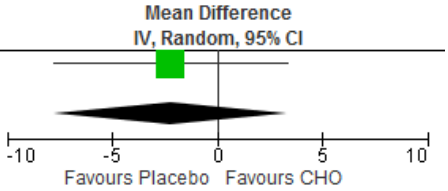
No analyses for this comparison.

COMPARISON 3: ORAL CHO VERSUS PLACEBO

Analysis 3.1: Muscle Strength at Day 1

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Mathur 2010	88.05	19.02	69	90.27	14.1	73	100.0%	-2.22 [-7.75, 3.31]
Total (95% CI)			**69**			**73**	**100.0%**	**-2.22 [-7.75, 3.31]**

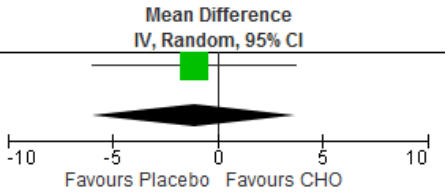
Heterogeneity: Not applicable
Test for overall effect: Z = 0.79 (P = 0.43)



Analysis 3.2: Muscle Strength at Day 3

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Mathur 2010	90.18	14.7	69	91.29	14.86	73	100.0%	-1.11 [-5.97, 3.75]
Total (95% CI)			**69**			**73**	**100.0%**	**-1.11 [-5.97, 3.75]**

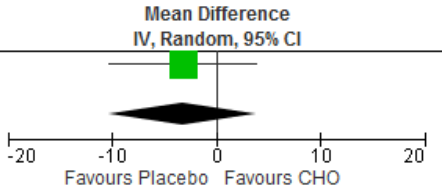
Heterogeneity: Not applicable
Test for overall effect: Z = 0.45 (P = 0.65)



Analysis 3.3: Muscle Strength at Day 7

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Mathur 2010	92.41	23.67	69	95.57	18.88	73	100.0%	-3.16 [-10.23, 3.91]
Total (95% CI)			**69**			**73**	**100.0%**	**-3.16 [-10.23, 3.91]**

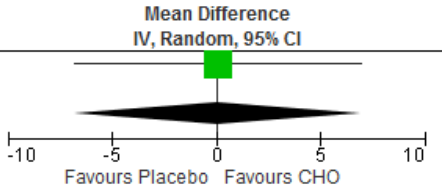
Heterogeneity: Not applicable
Test for overall effect: Z = 0.88 (P = 0.38)



Analysis 3.4: Muscle Strength at Day 28

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Mathur 2010	101.27	20.19	69	101.2	21.7	73	100.0%	0.07 [-6.82, 6.96]
Total (95% CI)			**69**			**73**	**100.0%**	**0.07 [-6.82, 6.96]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.02 (P = 0.98)



COMPARISON 4: ORAL CHO VERSUS ACTIVE CONTROL (IV CHO)

No analyses for this comparison.

Appendix 6.23: CRP analyses per comparison

COMPARISON 1: ORAL CHO VERSUS INACTIVE CONTROL (FASTING + PLACEBO)

Analysis 1.1: CRP at Baseline

No analysis for this time interval.

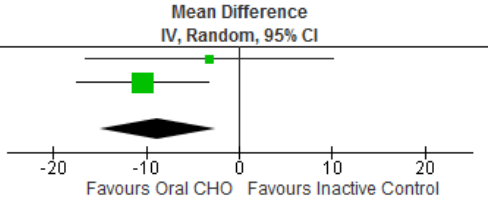
Analysis 1.2: CRP before Anaesthesia

No analysis for this time interval.

Analysis 1.3: CRP at Day 1

Study or Subgroup	Oral CHO Mean	SD	Total	Inactive Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Kaska 2010	86.7	40.4	74	89.9	42.6	75	22.1%	-3.20 [-16.53, 10.13]
Zelic 2013	17.44	12.72	35	27.8	17.28	35	77.9%	-10.36 [-17.47, -3.25]
Total (95% CI)			**109**			**110**	**100.0%**	**-8.77 [-15.05, -2.50]**

Heterogeneity: Tau² = 0.00; Chi² = 0.86, df = 1 (P = 0.35); I² = 0%
Test for overall effect: Z = 2.74 (P = 0.006)



Analysis 1.4: CRP at Day 3

No analysis for this time interval.

Analysis 1.5: CRP at Day 7

No analysis for this time interval.

COMPARISON 2: ORAL CHO VERSUS FASTING

Analysis 2.1: CRP at Baseline

No analysis for this time interval.

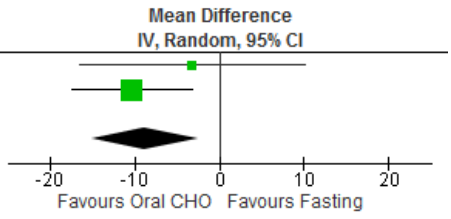
Analysis 2.2: CRP before Anaesthesia

No analysis for this time interval.

Analysis 2.3: CRP at Day 1

Study or Subgroup	Oral CHO Mean	SD	Total	Fasting Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Kaska 2010	86.7	40.4	74	89.9	42.6	75	22.1%	-3.20 [-16.53, 10.13]
Zelic 2013	17.44	12.72	35	27.8	17.28	35	77.9%	-10.36 [-17.47, -3.25]
Total (95% CI)			**109**			**110**	**100.0%**	**-8.77 [-15.05, -2.50]**

Heterogeneity: Tau² = 0.00; Chi² = 0.86, df = 1 (P = 0.35); I² = 0%
Test for overall effect: Z = 2.74 (P = 0.006)



Analysis 2.4: CRP at Day 3

No analysis for this time interval.

Analysis 2.5: CRP at Day 7

No analysis for this time interval.

COMPARISON 3: ORAL CHO VERSUS PLACEBO

No analyses for this comparison.

COMPARISON 4: ORAL CHO VERSUS ACTIVE CONTROL (IV CHO)

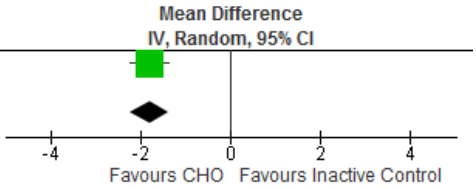
No analyses for this comparison.

Appendix 6.24: Stool/flatus analysis per comparison

COMPARISON 1: ORAL CHO VERSUS INACTIVE CONTROL (FASTING + PLACEBO)

Study or Subgroup	Oral CHO Mean	SD	Total	Inactive Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Šerclová 2009	2.1	1.1	51	3.9	1.1	52	100.0%	-1.80 [-2.22, -1.38]
Total (95% CI)			**51**			**52**	**100.0%**	**-1.80 [-2.22, -1.38]**

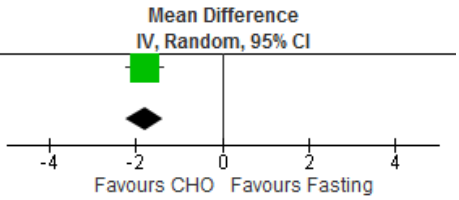
Heterogeneity: Not applicable
Test for overall effect: Z = 8.30 (P < 0.00001)



COMPARISON 2: ORAL CHO VERSUS FASTING

Study or Subgroup	Oral CHO Mean	SD	Total	Fasting Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Šerclová 2009	2.1	1.1	51	3.9	1.1	52	100.0%	-1.80 [-2.22, -1.38]
Total (95% CI)			**51**			**52**	**100.0%**	**-1.80 [-2.22, -1.38]**

Heterogeneity: Not applicable
Test for overall effect: Z = 8.30 (P < 0.00001)



COMPARISON 3: ORAL CHO VERSUS PLACEBO

No analyses for this comparison.

COMPARISON 4: ORAL CHO VERSUS ACTIVE CONTROL (IV CHO)

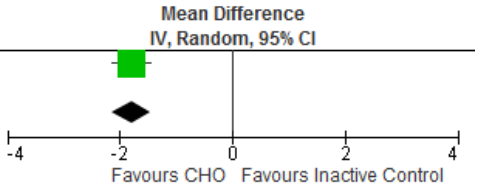
No analyses for this comparison.

Appendix 6.25: Bowel movement analyses per comparison

COMPARISON 1: ORAL CHO VERSUS INACTIVE CONTROL (FASTING + PLACEBO)

Study or Subgroup	Oral CHO Mean	SD	Total	Inactive Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Šerclová 2009	1.3	0.8	51	3.1	1	52	100.0%	-1.80 [-2.15, -1.45]
Total (95% CI)			**51**			**52**	**100.0%**	**-1.80 [-2.15, -1.45]**

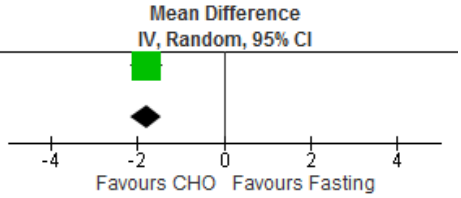
Heterogeneity: Not applicable
Test for overall effect: Z = 10.10 (P < 0.00001)



COMPARISON 2: ORAL CHO VERSUS FASTING

Study or Subgroup	Oral CHO Mean	SD	Total	Fasting Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Šerclová 2009	1.3	0.8	51	3.1	1	52	100.0%	-1.80 [-2.15, -1.45]
Total (95% CI)			**51**			**52**	**100.0%**	**-1.80 [-2.15, -1.45]**

Heterogeneity: Not applicable
Test for overall effect: Z = 10.10 (P < 0.00001)



COMPARISON 3: ORAL CHO VERSUS PLACEBO

No analyses for this comparison.

COMPARISON 4: ORAL CHO VERSUS ACTIVE CONTROL (IV CHO)

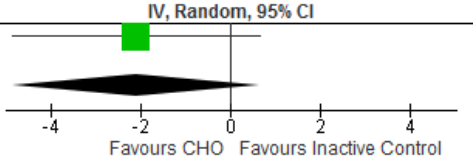
No analyses for this comparison.

Appendix 6.26: Length of ICU stay analyses per comparison

COMPARISON 1: ORAL CHO VERSUS INACTIVE CONTROL (FASTING + PLACEBO)

	Oral CHO			Inactive Control				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Järvelä 2008	22.2	3.6	50	24.3	9.3	51	100.0%	-2.10 [-4.84, 0.64]	
Total (95% CI)			**50**			**51**	**100.0%**	**-2.10 [-4.84, 0.64]**	

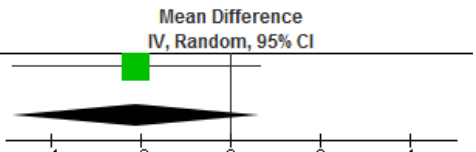
Heterogeneity: Not applicable
Test for overall effect: Z = 1.50 (P = 0.13)



COMPARISON 2: ORAL CHO VERSUS FASTING

	Oral CHO			Inactive Control				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Järvelä 2008	22.2	3.6	50	24.3	9.3	51	100.0%	-2.10 [-4.84, 0.64]	
Total (95% CI)			**50**			**51**	**100.0%**	**-2.10 [-4.84, 0.64]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 1.50 (P = 0.13)



COMPARISON 3: ORAL CHO VERSUS PLACEBO

No analyses for this comparison.

COMPARISON 4: ORAL CHO VERSUS ACTIVE CONTROL (IV CHO)

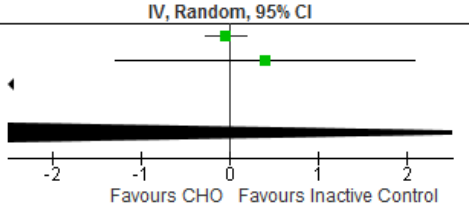
No analyses for this comparison.

Appendix 6.27: Length of hospital stay analyses per comparison

COMPARISON 1: ORAL CHO VERSUS INACTIVE CONTROL (FASTING + PLACEBO)

Study or Subgroup	Oral CHO Mean	SD	Total	Inactive Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Hausel 2005	1.2	0.7	55	1.25	0.76	117	33.6%	-0.05 [-0.28, 0.18]
Soop 2001	5.5	1.41	8	5.1	1.85	7	33.0%	0.40 [-1.28, 2.08]
Šerclová 2009	0	1.3	51	10.4	3.1	52	33.4%	-10.40 [-11.32, -9.48]
Total (95% CI)			**114**			**176**	**100.0%**	**-3.36 [-10.67, 3.95]**

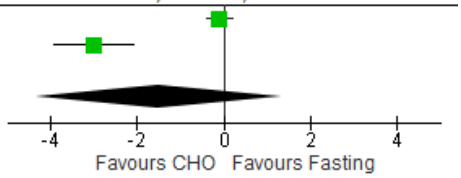
Heterogeneity: Tau² = 41.43; Chi² = 463.67, df = 2 (P < 0.00001); I² = 100%
Test for overall effect: Z = 0.90 (P = 0.37)



COMPARISON 2: ORAL CHO VERSUS FASTING

Study or Subgroup	Oral CHO Mean	SD	Total	Fasting Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Hausel 2005	1.2	0.7	55	1.3	0.9	58	51.2%	-0.10 [-0.40, 0.20]
Šerclová 2009	7.4	1.3	51	10.4	3.1	52	48.8%	-3.00 [-3.92, -2.08]
Total (95% CI)			**106**			**110**	**100.0%**	**-1.52 [-4.36, 1.32]**

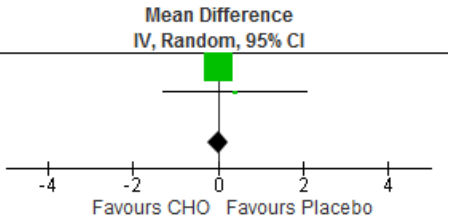
Heterogeneity: Tau² = 4.08; Chi² = 34.92, df = 1 (P < 0.00001); I² = 97%
Test for overall effect: Z = 1.05 (P = 0.30)



COMPARISON 3: ORAL CHO VERSUS PLACEBO

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Hausel 2005	1.2	0.7	55	1.2	0.6	59	98.0%	0.00 [-0.24, 0.24]
Soop 2001	5.5	1.41	8	5.1	1.85	7	2.0%	0.40 [-1.28, 2.08]
Total (95% CI)			**63**			**66**	**100.0%**	**0.01 [-0.23, 0.25]**

Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 1 (P = 0.64); I² = 0%
Test for overall effect: Z = 0.07 (P = 0.95)



COMPARISON 4: ORAL CHO VERSUS ACTIVE CONTROL (IV CHO)

No analyses for this comparison.

Appendix 6.28: Fit for discharge analyses per comparison

COMPARISON 1: ORAL CHO VERSUS INACTIVE CONTROL (FASTING + PLACEBO)

No analyses for this comparison.

COMPARISON 2: ORAL CHO VERSUS FASTING

No analyses for this comparison.

COMPARISON 3: ORAL CHO VERSUS PLACEBO

No analyses for this comparison.

COMPARISON 4: ORAL CHO VERSUS ACTIVE CONTROL (IV CHO)

No analyses for this comparison.

Appendix 6.29: Results of trials assessing thirst

	INTRAGROUP COMPARISON				INTERGROUP COMPARISON			
	TRIAL	TIMING	RESULTS	P-VALUE	TRIAL	TIMING	RESULTS	P-VALUE
PREOP	A52	Baseline (i.e. day before surgery) to 1 – 2 hours before surgery	CHO group less thirsty	< 0.05	A6	Baseline (i.e. day before surgery) to 1 – 2 hours before surgery	CHO group less thirsty than fasting group	< 0.05
			Fasting group more thirsty	> 0.05	A16		CHO group less thirsty than fasting group	< 0.05
	A64		CHO group no change in thirst	0.921	A52		CHO group less thirsty than fasting group	< 0.05
			Fasting group more thirsty	0.001	A64		Difference in thirst between oral CHO, fasting and placebo group	0.005
			Placebo more thirsty	0.015			No difference in thirst between CHO and placebo groups	0.970
	A71		CHO group less thirsty	< 0.05	A74		CHO group less thirsty than fasting group	0.01
			Fasting group more thirsty	< 0.05	A94		CHO group less thirsty than other groups	?
			IV group more thirsty	< 0.05	A121		CHO group less thirsty than fasting group	< 0.001
	A121		CHO group less thirsty	?				
			Fasting group more thirsty	< 0.001				
			Placebo no consistent trend	?				
	A131		CHO group less thirsty for 60 minutes	< 0.01				
			Placebo group less thirsty for 40 minutes	< 0.05				
POSTOP		None of the trials assessed this comparison.			A15	Day 2	CHO group less thirsty than fasting group	> 0.05
					A16	2 hours	CHO group less thirsty than fasting group	< 0.05
						24 hours	No difference between CHO and fasting groups in thirst	> 0.05
PERIOP		None of the trials assessed this comparison.			A66	Preoperative to postoperative	No difference in thirst between CHO and placebo groups	> 0.05

Appendix 6.30: Results of trials assessing hunger

	INTERGROUP COMPARISON				INTRAGROUP COMPARISON			
	TRIAL	TIMING	RESULTS	P-VALUE	TRIAL	TIMING	RESULTS	P-VALUE
PREOP	A52	Baseline (i.e. day before surgery) to 1 – 2 hours before surgery	CHO group less hungry	< 0.05	A6	Baseline (i.e. day before surgery) to 1 – 2 hours before surgery	CHO group less hungry than fasting group	< 0.05
			Fasting group more hungry	> 0.05	A16		CHO group less hungry than fasting group	< 0.05
	A64		CHO group no change in hunger	0.147	A52		CHO group less hungry than fasting group	< 0.05
			Fasting group more hungry	0.006	A64		Difference in hunger between oral CHO, fasting and placebo group	0.041
			Placebo no change in hunger	0.291			No difference in hunger between CHO and placebo groups	0.146
	A71		CHO group less hungry	< 0.05	A74		CHO group less hungry than fasting group	0.04
			Fasting group more hungry	< 0.05	A94		CHO group less hungry than other groups	?
			IV group no change in hunger	> 0.05	A121		CHO group less hungry than fasting group	< 0.05
	A121		CHO group less hungry	?				
			Fasting group more hungry	< 0.05				
			Placebo no consistent trend	?				
	A131		CHO group no change in hunger	0.10				
			Placebo group less hungry for 20 minutes	< 0.05				
POSTOP					A16	2 hours	CHO group less hungry than fasting group	< 0.05
						24 hours	No difference in hunger between CHO and fasting groups	> 0.05
PERIOP					A66	Preoperative to postoperative	No difference in hunger between CHO and placebo groups	> 0.05

Appendix 6.31: Results of trials assessing nausea

	INTERGROUP COMPARISON				INTRAGROUP COMPARISON			
	TRIAL	TIMING	RESULTS	P-VALUE	TRIAL	TIMING	RESULTS	P-VALUE
CONTINUOUS DATA								
PREOP	A64	Baseline (i.e. day before surgery) to 1 – 2 hours before surgery	CHO group no change in nausea	0.139	A52	Baseline (i.e. day before surgery) to 1 – 2 hours before surgery	No difference in nausea between CHO and fasting groups	> 0.05
			Fasting group no change in nausea	0.116	A64		No difference in nausea between CHO fasting and placebo groups	> 0.05
			Placebo group no change in nausea	0.135	A94		CHO group less nauseous than other groups	?
	A121		CHO group no change in nausea	> 0.05				
			Fasting group no change in nausea	> 0.05				
			Placebo more nauseous	< 0.0001				
POSTOP		None of the trials assessed this comparison			A14	Day 1	CHO group less nauseous than fasting group	< 0.001
					A15	Day 2	CHO group less nauseous than fasting group	> 0.05
					A115	Day 1	No difference between CHO and placebo groups	0.871
PERIOP	A105	Preoperative + Postoperative	Fasting group more nauseous	0.018	A16	Preoperative + Postoperative	No difference in nausea between CHO and fasting groups	> 0.05
			Placebo group more nauseous	< 0.001	A66		No difference in nausea between CHO and placebo groups	> 0.05
					A105		No difference in nausea between CHO, fasting and placebo groups	> 0.05

	IN GROUP COMPARISON				BETWEEN GROUP COMPARISON			
	TRIAL	**MEASUREMNT**	**RESULTS**	**P-VALUE**	**TRIAL**	**MEASUREMENT**	**RESULTS**	**P-VALUE**
DICHOTOMOUS DATA								
PREOP	None of the trials assessed this comparison				None of the trials assessed this comparison			
POSTOP	A105	Number of patients	CHO less nausea	< 0.001	A15	Number of episodes	CHO group less nauseous than fasting group	> 0.05
			Fasting no difference	0.067	A75	Number of patients	Fewer patients nauseous in CHO group than in fasting group (on day 2 to 4)	< 0.05
			Placebo less nausea	0.006	A90	Number of patients	More patients nauseous in CHO group than in fasting group (on day 1)	0.044
					A105	Number of patients	No difference between CHO, fasting and placebo groups (on day 1)	0.305
					A115	Number of episodes	No difference between CHO and placebo groups (on day 1)	1.000
PERIOP	None of the trials assessed this comparison				None of the trials assessed this comparison			

Appendix 6.32: Results of trials assessing vomiting

	INTRAGROUP COMPARISON				INTERGROUP COMPARISON			
	TRIAL	TIMING	RESULTS	P-VALUE	TRIAL	TIMING	RESULTS	P-VALUE
CONTINUOUS DATA								
PREOP	None of the trials assessed this comparison				None of the trials assessed this comparison			
POSTOP	None of the trials assessed this comparison				A14	Day 1	CHO group less vomiting than fasting group	< 0.001
					A15	Day 2	CHO group less vomiting than fasting group	> 0.05
					A115	Day 1	No difference between CHO and placebo groups	0.278
PERIOP	None of the trials assessed this comparison				None of the trials assessed this comparison			

	IN GROUP COMPARISON				BETWEEN GROUP COMPARISON			
	TRIAL	**MEASUREMNT**	**RESULTS**	**P-VALUE**	**TRIAL**	**MEASUREMENT**	**RESULTS**	**P-VALUE**
DICHOTOMOUS DATA								
PREOP	None of the trials assessed this comparison				None of the trials assessed this comparison			
POSTOP	A105	Number of patients	CHO less vomiting	< 0.001	A15	Number of episodes	CHO group less vomiting than fasting group	> 0.05
			Fasting no difference	0.067	A75	Number of patients	Less patients vomiting in CHO group than in fasting group (on day 2)	< 0.05
			Placebo less vomiting	0.006	A90	Number of patients	No difference between CHO and fasting groups (on day 1)	0.437
					A105	Number of patients	No difference between CHO, fasting and placebo groups (on day 1)	0.305
					A115	Number of episodes	No difference between CHO and placebo groups (on day 1)	0.336
PERIOP	None of the trials assessed this comparison				None of the trials assessed this comparison			

Appendix 6.33: Results of trials assessing anxiety

	INTRAGROUP COMPARISON				INTERGROUP COMPARISON			
	TRIAL	TIMING	RESULTS	P-VALUE	TRIAL	TIMING	RESULTS	P-VALUE
PREOP	A52	Baseline (i.e. day before surgery) to 1 – 2 hours before surgery	CHO group decrease in anxiety	< 0.05	A14	Baseline (i.e. day before surgery) to 1 – 2 hours before surgery	CHO group less anxious than fasting group	0.035
	A64		CHO group no change in anxiety	0.080	A16		No difference between CHO and fasting groups	> 0.05
			Fasting group no change in anxiety	0.278	A52		CHO group less anxious than fasting group	< 0.05
			Placebo group no change in anxiety	0.712	A64		Difference in thirst between oral CHO, fasting and placebo groups	0.104
	A71		CHO group no change in anxiety	> 0.05			No difference in anxiety between CHO and placebo groups	0.940
			Fasting group increase in anxiety	< 0.05	A74		CHO group less anxious than fasting group	0.01
			IV group increase in anxiety	< 0.05	A94		CHO group less anxious than other groups	?
	A121		Fasting group no change in anxiety	> 0.05	A121		CHO group less anxious than fasting group	< 0.001
			Placebo group no change in anxiety	> 0.05				
	A131		CHO group no change in anxiety for 90minutes	0.11				
			Placebo group decrease in anxiety for 90 minutes	< 0.05				
POSTOP		None of the trials assessed this comparison				None of the trials assessed this comparison		
PERIOP		None of the trials assessed this comparison			A6	Preoperative to postoperative	No difference in anxiety between CHO and fasting groups	> 0.05
					A66		No difference in anxiety between CHO and placebo groups	> 0.05

Appendix 6.34: Results of trials assessing pain

	INTRAGROUP COMPARISON				INTERGROUP COMPARISON			
	TRIAL	TIMING	RESULTS	P-VALUE	TRIAL	TIMING	RESULTS	P-VALUE
PREOP	A121	Baseline (i.e. day before surgery) to 1 – 2 hours before surgery	CHO group no change in pain	> 0.05	A52	Baseline (i.e. day before surgery) to 1 – 2 hours before surgery	No difference in pain between CHO and fasting groups	> 0.05
			Fasting group no change in pain	> 0.05	A71		No difference in pain between CHO, fasting and IV groups	> 0.05
			Placebo group no change in pain	> 0.05				
POSTOP		None of the trials assessed this comparison.			A15	Day 2	CHO group less pain than fasting group	> 0.05
					A75	Day 0 - 5	CHO group less pain than fasting group	< 0.05
PERIOP		None of the trials assessed this comparison.			A66	Preoperative to postoperative	No difference in pain between CHO and placebo groups	> 0.05
					A105		No difference in pain between CHO, fasting and placebo groups	> 0.05
					A115		No difference in pain between CHO and placebo groups	0.228

Appendix 6.35: Results of trials assessing fatique

	INTRAGROUP COMPARISON				INTERGROUP COMPARISON			
	TRIAL	TIMING	RESULTS	P-VALUE	TRIAL	TIMING	RESULTS	P-VALUE
PREOP		None of the trials assessed this comparison			A16	Baseline (i.e. day before surgery) to 1 – 2 hours before surgery	CHO group less fatigue compared to fasting group	< 0.05
POSTOP		None of the trials assessed this comparison.			A16	Day 1	No difference in fatigue between CHO and fasting groups	> 0.05
PERIOP	A66	Preoperative to postoperative	CHO group increase in fatigue	< 0.05	A66	Preoperative to postoperative	No difference in fatigue between CHO and placebo groups	> 0.05
			Placebo group increase in fatigue	< 0.05	A115		No difference in fatigue between CHO and placebo groups	> 0.05

Appendix 6.36: Results of trials assessing weakness

	INTRAGROUP COMPARISON				INTERGROUP COMPARISON			
	TRIAL	TIMING	RESULTS	P-VALUE	TRIAL	TIMING	RESULTS	P-VALUE
PREOP	A64	Baseline (i.e. day before surgery) to 1 – 2 hours before surgery	CHO group no change in weakness	0.198	A16	Baseline (i.e. day before surgery) to 1 – 2 hours before surgery	CHO group less weak than fasting group	< 0.05
			Fasting group no change in weakness	0.775	A64		No difference in weakness between CHO, fasting and placebo groups	0.832
			Placebo group no change in weakness	0.868			No difference in weakness between CHO and placebo groups	0.584
	A71		CHO group no change in weakness	> 0.05	A94		CHO group less weak than other groups	?
			Fasting group increase in weakness	< 0.05				
			IV group no change in weakness	> 0.05				
	A121		CHO group no change in weakness	> 0.05				
			Fasting group increase in weakness	< 0.05				
			Placebo group no change in weakness	> 0.05				
POSTOP		None of the trials assessed this comparison.				None of the trials assessed this comparison.		
PERIOP		None of the trials assessed this comparison				None of the trials assessed this comparison.		

Appendix 6.37: Results of trials assessing tiredness

	INTRAGROUP COMPARISON				INTERGROUP COMPARISON			
	TRIAL	**TIMING**	**RESULTS**	**P-VALUE**	**TRIAL**	**TIMING**	**RESULTS**	**P-VALUE**
PREOP	A64	Baseline (i.e. day before surgery) to 1 – 2 hours before surgery	CHO group no change in tiredness	0.150	A52	Baseline (i.e. day before surgery) to 1 – 2 hours before surgery	No difference in tiredness between CHO and fasting groups	> 0.05
			Fasting group no change in tiredness	0.299	A64		No difference in tiredness between CHO, fasting and placebo groups	0.615
			Placebo group no change in tiredness	0.223			No difference in tiredness between CHO and placebo groups	0.509
	A71		CHO group no change in tiredness	> 0.05	A94		CHO group less tired than other groups	?
			Fasting group increase in tiredness	< 0.05				
			IV group no change in tiredness	> 0.05				
	A121		CHO group no change in tiredness	> 0.05				
			Fasting group increase in tiredness	< 0.0001				
			Placebo group increase in tiredness	< 0.001				
POSTOP		None of the trials assessed this comparison.				None of the trials assessed this comparison.		
PERIOP		None of the trials assessed this comparison.				None of the trials assessed this comparison.		

Appendix 6.38: Results of trials assessing malaise

	INTRAGROUP COMPARISON				INTERGROUP COMPARISON			
	TRIAL	TIMING	RESULTS	P-VALUE	TRIAL	TIMING	RESULTS	P-VALUE
PREOP	A52	Baseline (i.e. day before surgery) to 1 – 2 hours before surgery	CHO decrease in malaise	< 0.05	A16	Baseline (i.e. day before surgery) to 1 – 2 hours before surgery	No difference in malaise between CHO and fasting groups	> 0.05
	A121		Fasting group no change in malaise	> 0.05	A52		CHO group experienced less malaise than fasting group	< 0,.05
			Placebo group decrease in malaise	< 0.01	A66		No difference in malaise between CHO and placebo groups	> 0.05
					A121		CHO group experienced less malaise than fasting group	< 0.01
POSTOP		None of the trials assessed this comparison.			A16	Day 1	CHO group experienced less malaise than fasting group	< 0.05
PERIOP		None of the trials assessed this comparison.			A115	Preoperative to postoperative	No difference between CHO and placebo groups	0.349