THE PREOPERATIVE USE OF RESTRICTED ENERGY DIETS TO REDUCE LIVER VOLUME AND LIVER FAT CONTENT AND IMPROVE POSTOPERATIVE OUTCOME IN OBESE PATIENTS SCHEDULED FOR BARIATRIC SURGERY: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Co-study leader: Prof. C.M. Walsh

DECLARATION

I hereby declare that the work submitted in this document is my independent effort. Contributions from other researchers are appropriately referenced. I further declare that this work is submitted for the first time at University of the Free State towards a Magister degree and that it has never been submitted to any other university or faculty.

I hereby cede copyright of this work in favour of the University of the Free State.

Annelien Els

31 January 2014.

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- My study leader, Dr. V.L. van den Berg and co-study leader, Prof. C.M. Walsh at the Department of Nutrition and Dietetics, University of the Free State for their expert supervision and contributions;
- Nestlé Health Science in South Africa for allowing me the time to complete this research project;
- My family members for their support and motivation.

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GLOSSARY OF TERMS

Abdominal fat (Intra-abdominal fat)

Fat tissue deposited internally in the abdominal cavity around the abdominal organs.

Adjustable gastric banding

A surgical procedure to reduce stomach size by placement of an inflatable device around the top portion of the stomach.

Android obesity

See *central obesity.*

Bariatric surgery

Surgery performed on the stomach and/or intestines to facilitate weight loss.

Biliopancreatic diversion

A gastric bypass procedure involving removal of the lower portion of the stomach.

Biliopancreatic diversion with duodenal switch

Biliopancreatic diversion in which the pylorus is left intact.

Body mass index

A weight-for-height index used to classify weight status. The body mass index is calculated by dividing weight in kilogram by height in meters squared; and is interpreted in the context of underweight, normal weight, overweight and obese.

Central obesity

A form of obesity in which fat is localized around the waist area; when obesity is accompanied by an increased waist circumference.

Computed tomography

Radiographic procedure in which a three-dimensional image of a body structure is constructed from a series of plane cross-sectional images made along an axis with the use of a computer.

Hepatic steatosis (Fatty liver)

The accumulation of fat in liver cells.

Hepatomegaly

An abnormally enlarged liver.

Insulin resistance

A decreased responsiveness to the action of insulin.

Laparoscopic surgery

A surgical technique that makes use of multiple small incisions through which surgical instruments and a camera is inserted.

Low calorie diet

A restricted energy diet that limits daily energy intake to 800-1100 kilocalories (3300-5000 kilojoules) per day.

Magnetic resonance imaging

A radiology procedure in which a nuclear magnetic resonance spectrometer is used to produce an electronic image of a molecular structure.

Metabolic syndrome

The existence of a cluster of inter-connected metabolic disturbances which may include obesity, insulin resistance, glucose intolerance, dyslipidaemia, and hypertension.

Non-alcoholic fatty liver disease

A group of liver abnormalities defined by excessive fat accumulation in the liver in individuals who do not consume excessive amounts of alcohol.

Obesity

Excessive body fat accumulation that may impair health, as expressed by body mass index.

Proximal gastric bypass

Surgery combining the creation of a small stomach pouch to restrict food intake and construction of bypasses of the duodenum and other segments of the small intestine.

Roux-en-Y gastric bypass

A surgical procedure involving creation of a small stomach pouch and bypassing parts of the small intestine.

Spectroscopy

An imaging method that provides information about cellular activity.

Sleeve gastrectomy

A gastric bypass procedure in which stomach size is permanently restricted.

Very low calorie diet

A diet consisting of liquid formulations used to replace food intake, supplying 800 kilocalories (3300 kilojoules) or less per day.

Visceral fat

See *abdominal fat*

LIST OF ABBREVIATIONS

2hPG	Two hour plasma glucose
β	Beta
A1C	Glycated haemoglobin
AACE	American Association of Clinical Endocrinology
ACP	American Chest Physicians
ADA	Academy of Nutrition and Dietetics (previously known as the American Dietetic Association
AGB	Adjustable gastric banding
AHA	American Heart Association
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body mass index
BPD	Biliopancreatic diversion
CCK	Cholecystokinin
CHO	Carbohydrate
cm	centimeter
CT	Computed tomography
DNA	Deoxyribonucleic acid
ERAS	Enhanced recovery after surgery
FDA	Food and drug administration
FFA	Free fatty acid
FPG	Fasting plasma glucose
g	gram
GIP	Gastric inhibitory polypeptide
GLP-1	Glucagon-like peptide 1
HDL	High density lipoprotein
ICU	Intensive care unit
IDF	International Diabetes Federation
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
IL-6	Interleukin-6
kcal	kilocalorie
kg	kilogramme
kJ	kilojoule

L	liter
LCD	Low calorie diet
LDL	Low density lipoprotein
m	meter
m^2	square meter
MC4R	Melanocortin 4 receptor
mg/dl	milligram per deciliter
ml	milliliter
mmol/l	millimoles per litre
MRI	Magnetic resonance imaging
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NCEP:ATPIII	National Cholesterol Education Program Adult Treatment Panel III
NHBLI	National Heart, Lung and Blood Institute
OGTT	Oral glucose tolerance test
RCT	Randomized controlled trial
RYGB	Roux-en-Y gastric bypass
SG	Sleeve gastrectomy
TG	Triglycerides
TNF-α	Tumour necrosis factor- alpha
VBG	Vertical banded gastroplasty
VLCD	Very low calorie diet
VLDL	Very low density lipoprotein
WHO	World Health Organization

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CHAPTER 1: PROTOCOL

Chapter 1 presents the protocol that was used as a framework to execute the research.

1.1 Introduction

Obesity is the most prevalent metabolic disease world-wide and has been declared a global epidemic affecting both developed and developing countries (Tsigos et al., 2008:106). According to the World Health Organization (WHO), obesity is classified by body mass index (BMI) which is calculated as body weight in kilogramme (kg) divided by height in meter (m) squared. In adults over 18 years of age, obesity is defined as BMI ≥ 30 kg/m^2 (WHO, 2006: online).

Obesity-related health risks include a variety of complications such as metabolic disturbances (insulin resistance, type 2 diabetes mellitus, dyslipidaemia); cardiovascular disorders (hypertension, coronary heart disease, stroke); respiratory disease (asthma, sleep apnoea); hepatic disease (non-alcoholic fatty liver disease and non-alcoholic steatohepatitis); cancer; and reproductive health problems (Tsigos et al., 2008:109). In addition, obesity may also increase the risk associated with surgical procedures, leading to increased perioperative morbidity and mortality (Bamgbade et al., 2007:556).

The European Clinical Practise Guidelines for the management of obesity in adults (Tsigos et al., 2008:106-116) identify obesity management as a complex process including factors such as diet, cognitive behavioural therapy, physical activity, psychological support, pharmacological treatment and surgery. Of these, surgery has been identified as the most effective treatment for sustained long-term weight loss, improvement in co-morbidities and decreased overall mortality (Tsigos et al., 2008:2113; Snow et al., 2005: 528). Surgery reduces the incidence and severity of co-morbidities including type 2 diabetes mellitus, hypertension, dyslipidaemia and obstructive sleep apnoea (Buchwald et al., 2004:1724). As such, bariatric surgery is a popular treatment modality for obesity, which however is currently reserved only for those with a BMI ≥ 40 kg/m^2, or with BMI > 35 kg/m^2 and significant co-morbidities who failed previous dietary attempts to effective weight loss (SAGES, 2010: online).

Though associated with treatment success, the surgical procedure constitutes only one part of the comprehensive bariatric approach in which greatest success is achieved in patients who are physically and mentally well prepared, and who are able to comply with a long-term monitoring protocol. Pre- and postoperative follow-up and support is essential for optimal outcome, and patient education is important to ensure that patients are prepared to comply with permanent life-style changes (OPTIFAST Pre-Operative protocol: online).

Tsigos et al. (2008:113) classify common bariatric surgery techniques by method of action:

- Restrictive procedures (food limitation), such as adjustable gastric banding , proximal gastric bypass and sleeve gastrectomy;
- Absorption limiting procedures, such as biliopancreatic diversion; and
- Combined techniques, such as biliopancreatic diversion with duodenal switch and Roux-en-Y gastric bypass.

Though expected average weight loss and long term maintenance of weight loss is best following procedures such as biliopancreatic diversion and gastric bypass, these procedures are also associated with increased technical complexity and nutritional risk (Tsigos et al., 2008:113).

Although the less invasive use of laparoscopic technique is preferred (Tsigos et al., 2008:113), excessive intra-abdominal fat and increased liver volume, associated with hepatic steatosis, complicate the procedure and increase surgical difficulty. Excessive intra-abdominal fat and hepatomegaly are most often seen in patients with central obesity, metabolic disorders and in the super-obese (BMI > 50 kg/m^2). An enlarged left lobe of the liver obscures anatomical markers while traction of a large fatty liver may cause liver trauma with increased risk of bleeding. Large liver and excessive intra-abdominal fat reduces operating space and exposure (OPTIFAST Pre-Operative protocol: online). These difficulties explain why enlarged liver size is the most common reason for conversion from laparoscopic to open procedures (Schwartz et al., 2003:734; O'Brien et al., 2002:652;). In comparison to laparoscopic procedures, open surgery is associated with increased blood loss, longer intensive care unit (ICU) and hospital stay, risk for developing incisional hernia, as well as delayed recovery time before being able to resume daily activities of living (Colquitt et al., 2009:28; Nguyen and Wolfe, 2002:86).

Preoperative strategies to promote weight loss and reduce liver volume can therefore contribute to increased safety of surgery in obese patients undergoing bariatric surgery, in particular by reducing the likelihood of having to convert from laparoscopic to an open procedure. By, Preoperative weight loss can decrease operating time by decreasing surgical complexity (Dambrauskas et al., 2010:46) and reduce the incidence of postoperative complications (Van Nieuwenhove et al., 2011:1300).

Restricted energy diets, and very low calorie diets (VLCDs) in particular, have been used successfully in a number of studies to reduce weight, abdominal fat, liver size and liver fat content in the preoperative phase of bariatric surgery (Van Nieuwenhove et al., 2011: 1300-1305; Edholm et al., 2011:345-350; Colles et al., 2006:304-311; Lewis et al., 2006:697-701; Fris, 2004:1165-1170). VLCDs are defined by the Academy of Nutrition and Dietetics (previously known as the American Dietetic Association) (ADA) as liquid formulations used as exclusive food source for a period of active weight loss (thus designed to totally replace food intake), supplying a maximum of 800 kilocalories (kcal) or 6-10 kcal per kg body weight per day (equal to a maximum of 3300 kilojoules (kJ) per day). VLCDs are enriched with high biologic value protein and provide at least 100% of the daily value of essential vitamins and minerals (ADA, 2009:335). The definition for low calorie diets (LCDs) are not as clearly described in literature as that of VLDCs, and generally refer to restricted energy diets designed to achieve an energy deficit of 500-1000 kcal per day (ADA, 2002:1150); or 2090-4180 kJ per day. Similar to VLCDs, LCDs may also be in the form of liquid meal replacements used prior to bariatric surgery, and typical LCD will provide 800-1100 kcal (3300-4600 kJ) per day (Edholm et al., 2011:346). For the purpose of this review, LCDs will refer to meal replacement diets providing 800-1100 kcal (3300-4600 kJ)per day; and VLCDs will refer to meal replacement diets providing <800 kcal (3300 kJ) per day.

As a general strategy to weight loss, VLCDs may be appropriate to achieve weight loss of 5-15% of initial body weight over a period of 12-16 weeks, however concern exists in regard to weight-loss maintenance which seems to be no more successful than for traditional low energy diets (ADA, 2009:336).

The use of LCDs and VLCDs in bariatric surgery as part of preoperative management seems to be successful (Van Nieuwenhove et al., 2011: 1300-1305; Edholm et al., 2011:345-350; Colles et al., 2006:304-311; Lewis et al., 2006:697-701; Fris, 2004:1165-1170). The use thereof for different periods of preoperative duration may reduce intra-abdominal fat and liver fat content resulting in reduced liver size, therefore possibly incurring benefits for both the patient (due to improved outcomes) and the surgeon (due to reduced technical difficulty). Studies conducted to date have made use of commercial restricted energy diet products such as Optifast® VLCD (Nestlé Health Science, Switzerland) and Modifast® LCD (Inpolin AB, Sweden) for various preoperative periods ranging from 2-12 weeks. Positive outcomes on visceral and subcutaneous adipose tissue, liver volume, liver fat content and patient outcome are reported by individual studies but concerns exist in regard to increased cost and patient discomfort (Van Nieuwenhove et al., 2011: 1300-1305;

Edholm et al., 2011:345-350; Colles et al., 2006:304-311; Lewis et al., 2006:697-701; Fris, 2004:1165-1170). Further concerns are related to increased morbidity due to performing surgery on a catabolic patient (Gustafsson et al., 2011:571), even though earlier reports could not establish a link between preoperative VLCDs and poor wound healing or compromized immune function. No systematic review and/or meta-analysis to assess the benefits of preoperative LCDs and VLCDs in bariatric surgery patients have been published to date.

Furthermore, it is unclear what the optimal period for preoperative use of restricted energy diet programmes is since patient compliance and acceptability may be influenced by longer duration of use. Individual studies report outcomes based on durations of two weeks, four weeks, six weeks and 12 weeks (Van Nieuwenhove et al., 2011: 1300-1305; Edholm et al., 2011:345-350; Colles et al., 2006:304-311; Lewis et al., 2006:697-701; Fris, 2004:1165-1170). A study by Colles et al. (2006:304-311) suggested an ideal duration of six weeks, minimum two weeks, to achieve optimal reduction in liver volume.

The need therefore exist to conduct a systematic review and meta-analysis to explore the benefits of using a preoperative restricted energy diet protocol to reduce abdominal fat, liver size and liver fat content in obese patients scheduled for bariatric surgery. Before this practise can be considered as standard procedure, convincing evidence is needed to show that a clinically relevant reduction in liver size can be achieved in a time period that does not influence patient compliance and acceptance.

1.1.1 Rationale for the study

Excessive intra-abdominal fat and increased liver volume associated with hepatic steatosis increase surgical complexity of bariatric procedures due to obstruction of anatomical markers, reduced operating space and increased trauma with liver retraction (OPTIFAST Pre-Operative protocol: online). Hepatomegaly is the most common reason for converting from laparoscopic to open procedures (Schwartz et al., 2003:734; O'Brien et al., 2002:652), and is estimated to increase surgical difficulty in 10-20% of cases (Colles et al., 2006:304). These factors contribute to increased postoperative complications. Restricted energy diets (including both LCDs and VLCDs) have been used successfully in a number of individual studies to achieve significant reduction in liver volume and fat content in the preoperative phase of bariatric surgery (Van Nieuwenhove et al., 2011: 1300-1305; Edholm et al., 2011:345-350; Colles et al., 2006:304-311; Lewis et al., 2006:697-701; Fris, 2004:1165-1170). Convincing data based on a systematic review and meta-analysis is however lacking.

1.1.2 Aim of the study

The aim of the study is to review clinical trials conducted on the effect of preoperative restricted energy diets on hepatic steatosis and liver volume in adult obese patients scheduled for bariatric surgery; and to critically appraise the methods and findings of these trials by means of a systematic review. If feasible, a meta-analysis will be performed to quantify the outcomes.

1.1.3 Objectives

The primary objective of this review is to summarise outcomes on reductions in hepatic steatosis and liver volume following a preoperative commercial meal replacement restricted energy diet in adult obese bariatric surgery patients. The secondary objectives are to

(i) identify the optimal time period of LCDs and VLCDs to achieve clinically relevant reductions;
(ii) identify if VLCDs are associated with better outcome compared to LCDs; and
(iii) identify the effect of restricted energy diets on incidence of postoperative complications, surgical difficulty and operating time.

1.2 Methods and design

1.2.1 Study design

A systematic review of published clinical trials will be performed to investigate the effect of commercial preoperative restricted energy diets used as meal replacements on hepatic steatosis and liver volume in adult obese patients undergoing bariatric surgery; and/or reporting on operative outcomes. If appropriate, a meta-analysis will be performed.

1.2.2 Criteria for selecting studies

The following inclusion and exclusion criteria will be used to identify all relevant studies. In order to ensure that all possible studies are included in this review, broad inclusion criteria with regard to the study design will be used.

1.2.2.1 Inclusion criteria

i. Study design:

All relevant studies published from January 1980 to December 2012 in peer-reviewed journals will be included in this review. Randomized and non-randomized trials will be included since the number of studies conducted as randomized controlled trials may be limited due to the small amount of research done on this topic. Although randomized controlled trials are considered the gold standard in assessing the effects of an intervention, trials of different study designs will be included to ensure a sufficient study sample. If appropriate, data obtained from randomized trials will be interpreted separately.

ii. Population:

Obese (BMI ≥ 30 kg/m^2) adults (≥ 18 years) scheduled for bariatric surgery who participated in trials evaluating the effect of preoperative LCDs and VLCDs on operative outcomes (although bariatric surgery is usually reserved for those with a BMI ≥ 35 $kg/m^{2,}$ it may also be performed on those with a lower BMI with significant co-morbidities)

iii. Intervention:

All studies designed to evaluate the impact of preoperative restricted energy diets (LCDs and VLCDs, which for the purpose of this review, will refer to commercial meal replacement diets providing 800-1100 kcal (300-4600 kJ) per day in the case of LCDs, and meal replacement diets providing <800 kcal (3300 kJ) per day in the case of VLCDs) in obese individuals scheduled for bariatric surgery will be included. Only studies evaluating the effect of restricted energy diets applied for a time period of two to 12 weeks preoperatively will be included.

iv. Outcome measures:

Outcome measures to achieve primary and secondary objectives are as follows:

- Primary outcome variables: measurement criteria that indicate reduction in liver size (as measured by ultrasound and/or whole-body imaging and/or magnetic resonance imaging and/or manual segmentation) and liver fat content (as measured by spectroscopy); and
- Secondary outcome variables on measurement criteria related to intra-operative factors including operating time, blood loss, and surgical difficulty/complexity; postoperative complications; and patient compliance (adherence and/or acceptability).

1.2.2.2 Exclusion criteria:

The following research studies will be excluded:

- Studies reporting on the effects of LDCs and VLCDs in non-obese populations;
- Studies reporting on the effects of LDCs and VLCDs in populations other than those scheduled for bariatric surgery;
- Studies reporting on traditional LCDs and VLCDs such as a food based self-selection diet;
- Studies published outside of the stipulated time period; and
- Studies that include patients younger than 18 years of age.

Although the language of the publication will not serve as a means for exclusion, translation might not be viable within the time period allocated to this review. A list of all non-English studies will be listed in the report appendix. In the case of an English abstract containing sufficient scientific data, the results from the abstract will be included in the systematic review process.

1.2.3 Identification of eligible studies and data extraction

1.2.3.1 Search strategy, screening and review process

The following two-step search strategy will be applied to identify eligible studies:

1. Electronic bibliographic databases will be searched for appropriate studies;
2. Reference lists of all eligible studies will be screened for appropriate studiess.

Electronic databases will include EbscoHost (including MEDLINE, HealthSource (academic edition) and CINAHL), Cochrane (Cochrane Database of Systematic reviews, Cochrane controlled trials register), Pubmed and Science Direct.

The following search terms will be used to seek eligible studies from these databases:

- [very low calorie diet(s) OR low calorie diet(s) OR low energy diet(s) OR very low energy diet(s) or restricted energy diet(s)]

  AND
- [bariatric surgery OR laparoscopic gastric bypass OR Roux-en-Y gastric bypass OR gastric banding OR sleeve gastrectomy OR biliopancreatic diversion]

  AND

- [liver volume OR liver size OR liver fat OR hepatic volume OR (intra)hepatic fat OR hepatic steatosis OR liver steatosis]

  AND/OR

- [(post)operative complication(s) OR (post)operative outcome OR intra-operative outcome OR operating time OR blood loss OR surgical difficulty OR surgical complexity OR patient compliance OR patient adherence OR patient acceptability]

Two independent reviewers with experience in systematic reviews (the researcher and one of the study leaders), will screen all studies identified based on title, after which abstracts for eligible studies will be obtained. Full-text articles will be retrieved for all studies which adhere to the inclusion criteria. Although full-text articles are preferred for the data-extraction, abstracts which contain sufficient scientific data will also be included. All eligible studies will be evaluated and discussed by the two reviewers to ensure relevance.

A table detailing all studies excluded during the systematic search process, as well as the reason for exclusion, will be compiled.

1.2.3.2 Quality assessment

A standard assessment form will be developed to assess the quality of each included publication (see appendix A for preliminary questionnaire). The quality will be judged according to the following criteria:

- Specification of target population;
- Sampling method (Was the sample chosen by consecutive inclusion, or whole population?);
- Specification of inclusion and exclusion criteria;
- Randomization criteria (How was the randomization done?);
- Similarity of treatment and control group (If baseline differences occur, is this accounted for?);
- Similarity in treatment other than intervention (Did co-intervention occur?);
- Effect of lost to follow-up (Were withdrawals described and did they occur with similar frequency between the intervention and control groups?);
- Intention to treat presentation of data (Were participants analysed according to the intervention to which they were allocated, whether they received it or not?);

- Blinding of investigators and/or data-collectors (Were outcome assessor independent from the individuals administrating/supervising the assigned intervention?).

The response options for the above criteria are as follows: yes (subdivided as criteria appropriately applied or inappropriately applied), unclear (criteria not described), and no (criteria not applied). After evaluating each study according to these criteria, all studies will be classified as:

- Low risk of bias: all criteria met;
- Moderate risk of bias: one or more of the criteria unclear; or
- High risk of bias: one or more of the criteria not met.

The results from the quality assessment will, in the case of a meta-analysis being conducted, impact on the methodological quality.

In the case of disagreement between the two reviewers on any specific aspect, a third party with expertise in the area will be consulted.

1.2.3.3 Data extraction

Data will be extracted independently by 3 reviewers using a screening and data extraction form (preliminary form attached in appendix B), and will be summarized in table format (preliminary table is attached in appendix C). If required data is not reported in the publication, an attempt will be made to contact the trial manager(s).

1.2.4 Data analysis

The results from the included studies will be evaluated according to:

1. Study design and quality;
2. Participants: type of surgery;
3. Intervention: duration of preoperative diet; and
4. Outcomes:
    a. Primary outcome, namely the hepatic steatosis and liver size; and
    b. Secondary outcomes, namely intra-operative factors including operating time, blood loss, surgical difficulty/complexity; postoperative complications, and patient compliance (adherence and acceptability).

The various dietary interventions will be assessed and compared to one another according to this analysis. The impact of dietary interventions will be determined statistically if there is sufficient homogeneity across the studies with regard to the target population, intervention, comparison groups, and outcomes measured. As different dietary interventions will be assessed, the homogeneity of each type of intervention will be assessed individually.

1.3 Ethics and communication

1.3.1 Ethics

This protocol will be submitted for ethical approval to the Ethics Committee of the Faculty of Health Sciences, University of the Free State (South Africa).

The researcher undertakes an oath not to commit plagiarism. Information obtained from included studies will be adequately referenced.

1.3.2 Reporting and implementation

The final report will be compiled in the form of a scientific publication for submission to a peer reviewed scientific journal; taking into account the publisher's submission instructions.

1.4 Logistics

1.4.1 Timeline

Estimates on the start and end dates for conducting the systematic review is as follows:

- Proposal development: 01 June 2012 – 31 July 2012
- Ethical approval: Before end 2012, in accordance with the meeting schedule of the Ethical Committee
- Writing of literature review: 01 January 2013 – 30 March 2013
- Data search: 02 January 2013 – 30 April 2013
- Analysis: 01 May 2013 – 15 July 2013
- Writing of results and dissertation: 15 July 2013 – 30 August 2013
- Writing of journal article: 01 September 2013 – 30 September 2013

- Editing: 01 October 2013 – 31 December 2013
- Submission: January 2014

1.4.2 Budget

Estimation of the cost to complete the study (all cost will be carried by the researcher):

- Inter-library loans; postage; on-line purchase of articles: R 800-00
- Stationary: R 150-00
- Printing: R 800-00
- Binding: R 50-00
- ***Total:*** ***R 1800-00***

1.5 Structure of dissertation

The mini-dissertation will include the following parts:

- Chapter 1: Protocol (as originally planned)
- Chapter 2: General literature review providing information on surgical interventions related to treatment of obesity, as well as surgical complications and the role on nutrition;
- Chapter 3: Systematic review. The research publication will include a description of the systematic review process, as well as a presentation and discussion of the findings; and
- Appendix.

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CHAPTER 2: LITERATURE REVIEW

Chapter 2 is a review of literature pertaining to obesity and bariatric surgery as the most effective intervention for obesity management.

2.1 Introduction

Obesity is defined by the World Health Organization (WHO) as excessive body fat accumulation that may impair health (WHO, 2013a: online). As per body mass index (BMI) classification of more than 30 kilogramme (kg) per square meter (m^2), obesity currently affects 500-600 million people worldwide (International Obesity Taskforce, 2013: online). BMI definition, calculation and classification are presented in Table 2.1.

The 2010 Global Status Report on non-communicable diseases identifies obesity as a global epidemic and states that overweight and obesity contributes to 2.8 million global deaths on an annual basis (WHO, 2011:22). This is linked to the fact that excessive body fat increases the risk for various health problems (see Table 2.2.), some of which represent major causes of death and disability. Risk factors associated with obesity include coronary heart disease, ischaemic stroke, type 2 diabetes mellitus, hypertension, certain types of cancer, as well as hepatic disease (WHO, 2011:22-23; Neuschwander-Tetri, 2005:327). Many of these associated comorbidities form part of the metabolic syndrome. Metabolic syndrome is not a disease *per se*, but a combination of metabolic abnormalities which can present in different ways in accordance to the various components that constitute the syndrome. Obesity, particularly central obesity which is indicated by increased waist circumference, is one of the main components of the metabolic syndrome. Other components of the metabolic syndrome include insulin resistance, glucose intolerance, dyslipidaemia, and hypertension. Glucose intolerance may lead to the development of type 2 diabetes mellitus; while all components individually and in combination are risk factors for the development of cardiovascular disease (Eckel et al., 2005:1415-1417). Metabolic syndrome can also present as non-alcoholic fatty liver disease (NAFLD), sometimes referred to as the hepatic manifestation of the syndrome (Hafeez and Ahmed, 2013:2).

Given the increasing prevalence of obesity, global weight management programmes aim to reduce or maintain BMI values within normal parameters, which will also reduce manifestation of comorbidities associated with metabolic syndrome. Preventative programmes are mainly targeted at national governments, authorities and policy makers with the aim to improve dietary and lifestyle behaviour on a global level; while evidence-based treatment approaches to weight management guide therapeutic interventions such as therapeutic diet programmes, pharmacotherapy and bariatric surgery applied to individual cases.

Of all treatment approaches, bariatric surgery is regarded as the most successful and durable option for long-term management of obesity. Bariatric surgery is associated with a significant decrease in body weight, fat mass and BMI; improvement in insulin sensitivity; remission of type 2 diabetes mellitus; and regression of NAFLD (Mechanick et al., 2013:160; Hafeez and Ahmed, 2013:2-3). Bariatric procedures may however be complicated by NAFLD since the presence of a large, fatty liver obscures the surgical view and restricts operative access (Colles et al., 2006:304; Lewis et al. 2006:698).

In this literature review, the pathophysiology of metabolic syndrome will be briefly explained. This will be followed by an overview of obesity and non-alcoholic fatty liver disease. Weight management strategies will be briefly reviewed, with special focus on the role of bariatric surgery and how an enlarged liver complicates surgical procedures. The potential role of restricted energy diets on reducing liver size pre-bariatric surgery will also be highlighted.

Table 2.1. Classification of body mass index and central obesity (WHO, 2013b: online; International Diabetes Federation, 2006: online).

BMI:

BMI is a weight-for-height index used to classify weight status in adults. It is calculated by dividing body weight (in kg) by the square of the height (in m).

Classification:

Classification	BMI (kg/m^2)
UNDERWEIGHT	< 18.5
Severe thinness	<16
Moderate thinness	16.0 – 16.9
Mild thinness	17.0 – 18.49
NORMAL RANGE	18.5 – 24.9
OVERWEIGHT	≥ 25
Pre-obese	25.0 – 29.9
OBESE	≥ 30
Obese class I	30.0 – 34.9
Obese class II	35.0 – 39.9
Obese Class III	≥ 40

Central obesity:

A BMI value ≥ 30 kg/m^2 together with an increased waist circumference indicates central obesity. For the identification of increased waist circumference, population and country-specific cut-off values apply. While currently there are no specific values for Sub-Saharan Africa, the IDF recommends using the same values as for Europides to identify increased waist circumference, namely ≥ 94 cm in males and ≥ 80 cm in females.

kg: kilogramme; m: meter; BMI: body mass index; IDF: International Diabetes Federation; cm: centimetre.

Table 2.2. Health outcomes associated with obesity (Hng and Ang, 2012:435).

Type 2 diabetes mellitus	Gallstones
Hypertension	Pseudotumour cerebri
Dyslipidemia	Osteoarthritis
Cardiovascular disease	Infertility
Obstructive sleep apnoea	Urinary incontinence
Obesity hypoventilation syndrome	Gastro-esophageal reflux
Cancer	Non-alcoholic fatty liver disease

2.2 Metabolic syndrome

Metabolic syndrome presents as a cluster of inter-connected metabolic disturbances. Various international organizations and expert groups have attempted to define metabolic syndrome by incorporating the different components thereof. These include (amongst others) definitions by the National Cholesterol Education Program Adult Treatment Panel III (NCEP:ATPIII), American Association of Clinical Endocrinology (AACE), International Diabetes Federation (IDF), and American Heart Association (AHA) in collaboration with National Heart, Lung and Blood Institute (NHLBI). These definitions are presented in Table 2.3. A consensus definition put forward in 2009 by a working group representing various professional organizations (Alberti et al., 2009:1640) defines metabolic syndrome as the prevalence of any three of the following:

- Elevated waist circumference (according to ethnic and country-specific values);
- Triglyceride level ≥ 150 milligram per decilitre (mg/dl) or 1.69 millimoles per litre (mmol/l);
- High density lipoprotein (HDL) cholesterol < 40 mg/dl (1.03 mmol/l) in men and < 50 mg/ dl (1.29 mmol/l) in women;
- Blood pressure reading ≥ 130/85 mmHg;
- Fasting glucose ≥ 100 mg/dl (5.56 mmol/l).

2.2.1 Underlying disorders and manifestations

Eckel et al. (2010:182) states that metabolic syndrome is an "outgrowth" of insulin resistance. This indicates that the individual factors which in co-existence constitutes metabolic syndrome, are all primarily caused by insulin resistance. Insulin resistance is a subnormal biologic response to insulin in which a given concentration of insulin will produce a less-than-expected biological effect.

Figure 1 is based on the current model of metabolic syndrome as explained by Eckel et al. (2005:1418-1420) and represents the main components of metabolic syndrome (insulin resistance, glucose intolerance, dyslipidaemia, hypertension and NAFLD) and how these are inter-related, with central obesity as the main starting point.

Table 2.3. Metabolic syndrome definitions (Kassi et al., 2011:9).

National Cholesterol Education Program Adult Treatment Panel III (NCEP:ATPIII):

Any three or more of the following:

- Waist circumference > 102 cm in men and > 88 cm in women;
- TG ≥ 150 mg/dl (1.69 mmol/l);
- HDL-cholesterol < 40 mg/dl (1.03 mmol/l) in men and < 50 mg/dl (1.29 mmol/l) in women;
- BP ≥ 130/85 mmHg;
- Fasting glucose ≥ 100 mg/dl (5.56 mmol/l).

American Association of Clinical Endocrinology (AACE):

Impaired glucose tolerance plus two or more of the following:

- BMI ≥ 25 kg/m^2;
- TG ≥ 150 mg/dl (1.69 mmol/l) and/or HDL-cholesterol < 40 mg/dl (1.03 mmol/l) in men and < 50 mg/dl (1.29 mmol/l) in women;
- BP ≥ 130/85 mmHg.

International Diabetes Federation (IDF):

Central obesity (defined by waist circumference with ethnicity-specific values[#], but can be assumed if BMI > 30 kg/m^2), plus two of the following:

- TG ≥ 150 mg/dl (1.69 mmol/l);
- HDL-cholesterol < 40 mg/dl (1.03 mmol/l) in men and < 50 mg/dl (1.29 mmol/l) in women;
- BP ≥ 130/85 mmHg;
- Fasting glucose ≥ 100 mg/dl (5.56 mmol/l).

American Heart Association in collaboration with National Heart, Lung and Blood Institute (AHA/NHLBI):

Any three of the following:

- Waist circumference ≥ 102 cm in men, and ≥ 88 cm or greater in women;
- TG ≥ 150 mg/dl (1.69 mmol/l);
- HDL-cholesterol < 40 mg/dl (1.03 mmol/l) in men and < 50 mg/dl (1.29 mmol/l) in women;
- BP ≥ 130/85 mmHg;
- Fasting glucose ≥ 100 mg/dl (5.56 mmol/l).

TG: Triglyceride; HDL: High density lipoprotein; BP: blood pressure: BMI: body mass index

[#]*See Table 2.1.*

2.2.1.1 Insulin resistance and hyperinsulinaemia

Insulin resistance is marked by high serum insulin concentrations (hyperinsulinaemia) in association with normal or high blood glucose concentrations (Olatunbosun and Dagogo-Jack, 2013: online) in both postprandial and fasting states. In the context of metabolic syndrome, insulin resistance is strongly associated with obesity. Growing adipose cells release an overabundance of fatty acids into the circulation, and this interferes with insulin action. The various manifestations of metabolic syndrome is thus all directly or indirectly caused by insulin resistance, which is brought about by an overabundance of intra-abdominal fat (Eckel et al., 2005:1418).

Lipolysis of visceral adipose stores increases the amount of circulating fatty acids, which in turn is associated with the development of insulin resistance. The mechanism by which an increase in fatty acids cause reduced biologic response to insulin is related to modification of insulin signalling. Normal action of insulin is linked to the binding of insulin to specific insulin receptors which initiates a cascade of events: insulin receptor tyrosine kinase is activated, which leads to the phosphorylation of insulin receptor substrates. This in turn activates other pathways which eventually stimulates glucose uptake. The presence of high circulating concentrations of free fatty acids interferes with the signalling pathway, and hampers insulin-stimulated glucose uptake (Ragheb and Medhat, 2011:1). Other mechanisms by which fatty acids may impair insulin action is explained by Delarue and Magnan (2007:143-144) and involves defects created by fatty acids in glucose oxidation and in glucose transport receptors, and by an increase in fatty acid substrate availability. The latter is supported by the reciprocal metabolic relationship between glucose and fatty acid whereby increased glucose availability increases glucose oxidation and storage while inhibiting fatty acid oxidation; and fatty acid availability promotes fatty acid oxidation and storage while inhibiting glucose oxidation.

Since insulin acts as an anti-lipolytic agent, insulin resistance that develops as a result of increase fatty acid availability, creates a feedback system leading to an even higher release of fatty acids through lipolysis (Eckel et al., 2005:1418). Under normal metabolic conditions, postprandial insulin release will inhibit lipolysis of adipose tissue. When insulin resistance is present however, lipolysis is not constrained and therefor the production of fatty acids increases beyond normal circulating levels.

2.2.1.2 Glucose intolerance

In addition to all the aforementioned effects of insulin resistance, glucose intolerance may result. This can be attributed to both a decrease in insulin sensitivity (the impaired ability of insulin to decrease glucose production by the liver and to mediate glucose uptake by tissue cells); as well as damage to insulin-producing pancreatic-beta (β) cells (Eckel et al., 2005:1420). Therefor insulin resistance may cause impaired fasting glucose and impaired glucose tolerance (both of which indicate a state of prediabetes), as well as type 2 diabetes mellitus.

Under normal metabolic circumstances, insulin that is released by pancreatic β-cells closely control blood glucose levels. A feedback-loop between insulin–sensitive tissue (such as liver and muscle) and β-cells regulate the release of insulin based on blood glucose levels and cellular demand. In case of insulin resistance, a greater insulin response is needed to maintain normal glucose levels, and hyperinsulinaemia may develop. Failure in the feedback-mechanism will cause glucose intolerance with high plasma glucose levels. In addition to increased release of insulin by pancreatic cells, hepatic clearance of insulin is also lowered in individuals who are insulin resistant, and this furthers the development of hyperinsulinaemia (Kahn et al., 2006:840-844).

Not all obese, insulin–resistant individuals develop type 2 diabetes mellitus as β-cells can compensate for decreased insulin sensitivity by increasing insulin release. However, high circulating levels of fatty acids induce a state of lipotoxicity which causes damage to pancreatic β-cells and a continued decline in β-cell function (Kahn et al., 2006:842-844). Failure of β-cells to adapt leads to a rise in postprandial and fasting plasma glucose levels, resulting in prediabetes and eventually type 2 diabetes mellitus (see diagnostic criteria for diabetes and prediabetes in Table 2.4.).

Table 2.4. Diagnostic criteria for diabetes-related conditions (Canadian Diabetes Association Clinical Practice Guidelines Expert Committee, 2013:S9)

Criteria for the diagnosis of diabetes:	***Criteria for the diagnosis of prediabetes:***
FPG ≥ 7 mmol/l **OR** A1C ≥ 6.5% (adults) **OR** 2hPG in a 75g OGTT ≥ 11.1 mmol/l **OR** Random PG ≥ 11.1 mmol/l	**IFG:** FPG = 6.1-6.9 mmol/l **IGT:** 2hPG in a 75g OGTT = 7.8-11 mmol/l **Prediabetes:** A1C = 6-6.4%
FPG: fasting plasma glucose (no caloric intake for at least eight hours); A1C: glycated haemoglobin; 2hPG: 2 hour plasma glucose; OGTT: oral glucose tolerance test; PG: plasma glucose; IFG: impaired fasting glucose; IGT: impaired glucose tolerance	

2.2.1.3 Hepatic complications of the metabolic syndrome

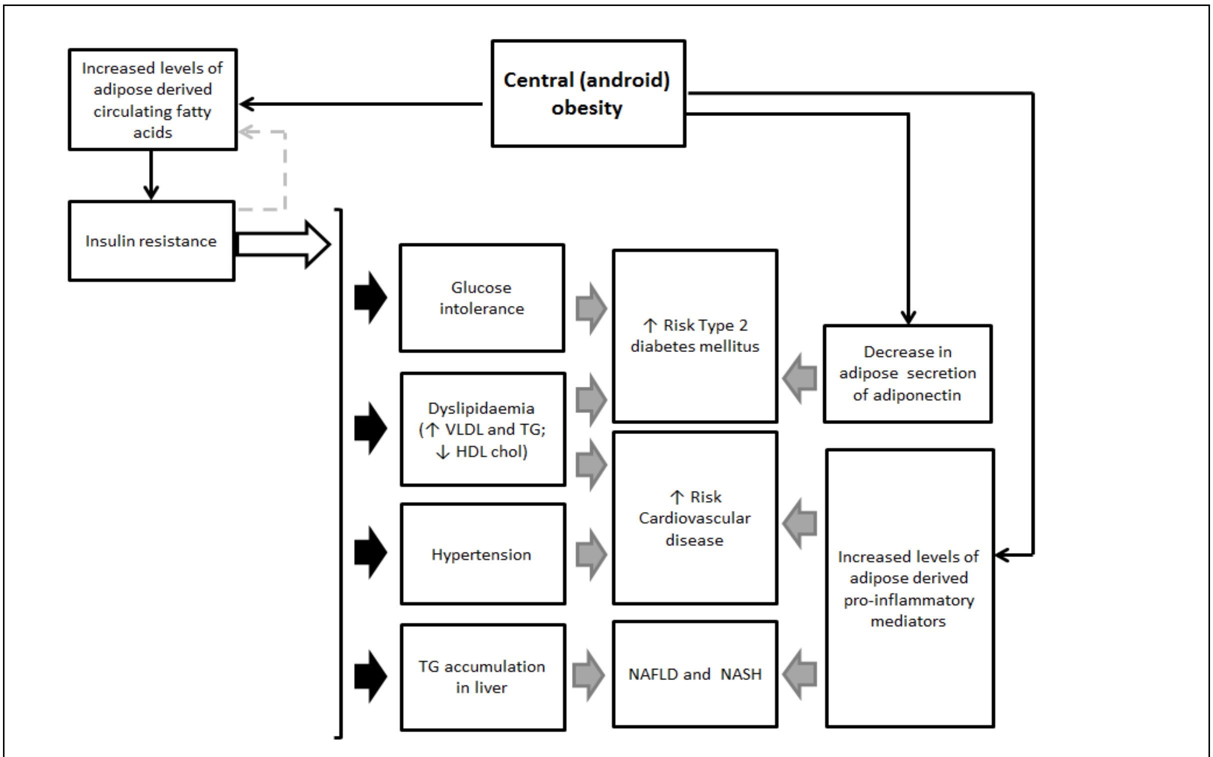
Fatty acids derived from lipolysis of visceral adipose tissue result in an increased flux to the splanchnic circulation, compared to lipolysis of subcutaneous fat which tend to be released into the systemic circulation. The splanchnic circulation delivers fatty acids to the liver where it either accumulates in hepatocytes as triglyceride droplets (causing NAFLD); or are secreted as very low density lipoprotein (VLDL) into the circulation. As with all other manifestations of metabolic syndrome, the process of liver steatosis is initiated by insulin resistance and the excessive release of fatty acids from visceral adipose tissue. Chronic hyperinsulinaemia, as a result of insulin resistance, impairs the release of triglycerides into circulation, causing accumulation thereof in hepatocytes. Thus, insulin resistance constantly feeds more fatty acids into the liver while simultaneously hampering the release thereof (Neuschwander-Tetri, 2005:327-328). The prevalence and treatment of NAFLD is discussed in more detail in section 2.3

2.2.1.4 Hypertension

Metabolic syndrome is also associated with development of hypertension. The relationship between blood pressure control and insulin resistance is explained mainly through (i) the action of insulin on stimulating endothelin-1 release by vascular endothelial cells, thereby causing constriction of blood vessels and hence an increase in blood pressure; and (ii) the fact that insulin stimulates renal sodium reabsorption. While the vasoconstriction effect may be lost in case of insulin resistance, the latter effect remains and leads to increase in blood pressure as a result of higher sodium concentration (Eckel et al., 2005:1420).

2.2.1.5 Other manifestations

In addition to the effect of lipolysis of visceral adipose tissue and the resultant effects of increased fatty acids and insulin resistance, changes in adipose tissue secretions may further increase the risk of developing conditions associated with metabolic syndrome. Adipose tissue, in particular visceral fat, can be viewed as an endocrine organ which secretes various bioactive substances acting as biomarkers and biosensors. Collectively, these substances are referred to as adipokines and includes amongst others adiponectin, leptin, as well as the inflammatory mediators tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). In the presence of obesity, changes in the release of these adipokines may also contribute to the development of metabolic syndrome (that is, in addition to the metabolic effects of increased circulating fatty acids). The most notable change in adipokine release is the change in adiponectin release which is decreased in case of excessive visceral fat stores. Adiponectin functions as an insulin sensitizer, therefor hypoadiponectonemia is implicated in the development of insulin resistance and associated co-morbidities including type 2 diabetes mellitus, hypertension and cardiovascular disease (Deng and Scherer, 2010:E1-E2).



VLDL: very low density lipoprotein; TG: triglycerides; HDL: high density lipoprotein

Figure 1. A simplified model of the metabolic syndrome (based on Eckel et al., 2005:1415-1428)

This explanation briefly highlights the main inter-related components of metabolic syndrome for the purpose of clarifying the context of the following sections, as in totality, the metabolic pathways involved in metabolic syndrome are much more intricate.

2.2.2 Management

The fact that insulin resistance and central obesity are regarded as the main underlying causes of metabolic syndrome motivates weight control as the key focus in management of the syndrome and its manifestations. Weight reduction has a positive impact on all components of metabolic syndrome, mainly through improvement in insulin sensitivity. The underlying mechanism appears to be a reduction in fatty acid mobilization brought about by reduction in body weight (Schenk et al., 2009:4949). Weight management is discussed in more detail in section 2.5.

2.3 Obesity

Obesity is a global epidemic which also affects a great proportion of the local population: in South Africa it is estimated that 50% of adults are currently obese. This represents 10.6% of the South African male population and 39.2% of females. High obesity figures are also found in the paediatric population. Locally, 16.2% of all boys and 23.6% of girls under the age of 18 years are obese (International Obesity Taskforce, 2013: online).

As mentioned, the WHO classification of overweight and obesity is based on BMI, while central obesity is diagnosed based on increased waist circumference (Table 1). Both overweight and obesity are major contributors to chronic diseases and present a major public health challenge, increasing healthcare cost, morbidity as well as mortality rates. Compared with normal weight individuals, obese patients require more medical treatment episodes, incur higher costs for both in-hospital and outpatient visits and also spend more on prescription medicine (Jensen et al., 2013:9). In addition, mortality rates increase with increasing degrees of overweight (WHO, 2011:23).

2.3.1 Causes of obesity

Control of whole-body energy balance is dependent on the relationship of energy intake to energy output, with a net excess intake leading to weight gain. The balance between energy intake and expenditure is controlled by a series of neuro-hormonal mechanisms, environmental components and genetic factors. Disturbance in one or a combination of these can decrease the ability of the body to ensure proper energy homeostasis and may result in the accumulation of body fat.

Clément (2011:S8) describes three phases in the development of obesity:

- In the *static phase*, the individual is in energy balance and the weight is stable. Healthy body weight is defended by intrinsic control mechanisms;
- In the *dynamic phase*, weight is gained as a result of positive energy balance. This can happen gradually as even a minor positive energy imbalance in the short term can potentially lead to persistent weight gain over time. Increased fat mass release hormonal signals which interferes with appetite control;
- In the *obese static phase*, energy balance is regained. A new, stable (though increased) body weight is established which will, again, be vigorously defended by intrinsic regulators.

Tight regulation of the newly established weight creates the potential to add a fourth phase, the *resistance phase* where increased effort is required to sustain weight loss. Rapid weight regain following reduction of body weight is not uncommon as neuro-hormonal weight regulation by the hypothalamus favours weight increase in response to weight loss (Clement, 2011:S8).

2.3.1.1 Neuro-hormonal control of body weight

Yüksel (2009:58) describes neuro-hormonal regulation of appetite and body weight in the context of central and peripheral regulation. Hormonal and metabolic signals from the periphery are received by the central nervous system, which determine energy homeostasis within the hypothalamus. Peripheral regulators include hormonal signals by adipose tissue (adipokines, such as adiponectin and leptin) and gut hormones (enterokines, such as ghrelin, peptide YY, glucagon-like peptide-1 (GLP-1), gastric inhibitory polypeptide (GIP) and cholecystokinin (CCK). Release of these bioactive substances regulates multiple aspects of energy homeostasis in a coordinated way to maintain a stable degree of body weight and whole-body energy balance. However, disturbance in one or more of these mechanisms is associated with metabolic syndrome and weight gain. For example, adiponectin levels are decreased in individuals with high proportions of visceral fat. Since adiponectin protects against development of type 2 diabetes mellitus and cardiovascular disease, low levels associated with central obesity is causally related to development of the metabolic syndrome (Kassi et al., 2011:4).

The origins and effects of adipokines and enterokines are summarised in Table 2.5.

Table 2.5. Neuro-hormonal control of body weight through the action of adipokines and enterokines (Hng and Ang, 2012:437-438; Yüksel, 2009:58-64).

Hormone	Site of secretion	Effect
Adipokines		
Adiponectin	Adipose tissue	Improves insulin sensitivity Anti-atherogenic, anti-inflammatory, cardioprotective effects
Leptin	White adipose tissue	Low leptin levels induces hunger High leptin levels increase lipogenesis
Enterokines		
Ghrelin	Stomach	Appetite stimulator Increase gut motility Promotes lipid accumulation and weight gain Inhibits insulin secretion and impairs glucose tolerance
Peptide YY	Pancreas, small intestine, colon	Appetite suppressant Promotes satiety Delays gastric emptying Enhances insulin sensitivity
GLP-1 and Oxyntomodulin	Distal intestine	Appetite suppressant Promotes satiety Delays gastric emptying Potentiates glucose-stimulated insulin secretion and enhance insulin biosynthesis Inhibits glugagon release
GIP	Duodenum	Promotes lipogenesis Stimulate insulin release
CCK	Duodenum and ileum	Inhibits food intake Induces gall bladder contraction Delays gastric emptying
GLP: Glucagon-like peptide; GIP: gastric inhibitory polypeptide; CCK: cholecystokinin)		

2.3.1.2 Environmental control of body weight

Clément (2011, S7-S15) describes the obesogenic environment as a complex network of multiple environmental factors which have caused a rapid progression in obesity prevalence over the past 20-30 years. These environmental factors include eating habits in favour of energy dense food and increased portion sizes, in conjunction with sedentary lifestyle. The WHO confirms a global increase in the intake of energy-dense, high-fat food, coupled with decreased levels of physical activity linked to the increasingly sedentary nature of work, transportation and urbanization (WHO, 2013a:online). In addition to these, environmental factors may interact with biological weight control mechanisms, such as environmental temperature rise and increase in pollutants that interfere with regulators of lipogenesis and disrupt metabolic control mechanisms (Clément, 2011:S7-S15). Exposure to high levels of stress with a chronic hypersecretion of stress mediators may lead to visceral fat accumulation (Kassi et al., 2011:5). Similarly, neuro-hormonal changes associated with sleep deprivation may increase cortisol and ghrelin levels, decrease leptin levels and impair glucose metabolism (AlDabal and BaHammam, 2011:31).

2.3.1.3 Genetic factors

Genetic factors may increase an individual's biological susceptibility to develop obesity. Mutations in genes coding for leptin, the leptin receptor, pro-opiomelanocortin, prohormone convertase 1, and the melanocortin 4 receptor (MC4R), disrupt neuro-hormonal signalling to the hypothalamic centres that control energy balance. Defects in one (monogenic obesity) or more (polygenic obesity) of these genes lead to a phenotype of abnormal eating behaviour followed by severe, early-onset obesity. Mutations of MC4R represent the most common cause of monogenic obesity: MC4R mutations have a population prevalence of at least 1 in 2000, and is believed to be accountable for 6% of all severe cases of childhood obesity. Obesity associated mutations in MC4R influence early weight gain with various degrees of severity (Logan and Pepper, 2010:45).

The interaction between genetic expression and environmental factors is known as epigenetics. Certain environmental factors influence cellular mechanisms that affect gene expression without changing deoxyribonucleic acid (DNA) sequence. Haemer et al. (2009:3) explains that epigenetic modifications during early developmental periods can determine phenotype expression later in life. For example, prenatal smoking or excess weight gain during pregnancy, discontinuation of breastfeeding of an infant before twelve months of age, and poor infant sleeping patterns, may all increase a person's risk of becoming obese in subsequent years. Similarly, a strong correlation exists between maternal undernutrition and the development of obesity later in life (Tanner and Hanganu-Bresch, 2013:44).

2.3.2 Management

As mentioned in previous sections, central obesity is regarded as an important contributor towards development insulin resistance and its associated metabolic disturbances. Hence, weight management is a key recommendation in the therapeutic goals of overweight or obese patients with metabolic syndrome. An overview of various therapeutic approaches to weight management, with special focus on bariatric surgery, is discussed in section 2.6.

2.4 Non-alcoholic fatty liver disease

As mentioned, NAFLD is viewed as the hepatic manifestation of metabolic syndrome. NAFLD includes a spectrum of subtypes ranging from steatosis to non-alcoholic steatohepatitis (NASH). Simple steatosis represents fatty acid accumulation within hepatocytes to an extent of making up > 5% of liver weight while NASH is, in addition to steatosis, also characterized by lobular inflammation and hepatocellular ballooning. NASH has the potential to progress to fibrosis, cirrhosis, hepatocellular carcinoma, and terminal liver failure (Hafeez and Ahmed, 2013:1; Younossi, 2008:3).

While NAFLD resembles symptoms associated with alcohol-induced liver abnormalities, it occurs in individuals who do not consume excessive amounts of alcohol. Instead, NAFLD is strongly associated with characteristics of metabolic syndrome. Given the relationship between NAFLD and the various other components of metabolic syndrome, it is not surprising that NAFLD prevalence is steadily on the increase, parallel to the global increase in obesity (Younossi et al., 2011:524). Currently, NAFLD is the most common liver disease in Western Countries (Carvalhana et al., 2012:468) with a growing prevalence of 24% in non-obese, 74% in obese, and 90% in morbidly obese (obese class III) individuals (Brody et al., 2011:491; Hafeez and Ahmed, 2013:2). From 1998 to 2008, the contribution of NAFLD to overall prevalence of chronic liver diseases, doubled from 5.5% to 11%. The rising prevalence of NAFLD coincides with the rise in prevalence of obesity and type 2 diabetes mellitus (Younossi et al., 2011:524).

2.4.1 Clinical presentation and diagnosis

Patients with NAFLD are generally asymptomatic. Neuschwander-Tetri (2005:326) explains that because liver injury is typically symptom free in its progression, the presence of NAFLD in patients with insulin resistance may stay unrecognized until patients develop other manifestations of metabolic syndrome. Liver enzymes may be mildly increased, especially aminotransferase (alanine aminotransferase (ALT) and aspartate aminotransferase (AST)) indicatinghepatocyte injury and inflammation (De Ridder et al., 2007:196). Hepatomegaly is present in up to 75% of patients (Neuschwander-Tetri, 2005:327). While radiologic tests such as ultrasound, computerized tomography (CT) and magnetic resonance imaging (MRI) can reveal hepatic steatosis, it cannot differentiate NASH from NAFLD and therefore liver biopsy remains the gold standard for diagnosis (Younossi, 2008:4).

2.4.2 Pathophysiology

The development of NAFLD is linked to insulin resistance and the increased release of fatty acids from growing adipose cells. In the presence of insulin resistance, there is increased influx of fatty acids into the liver where it accumulates and causes liver steatosis. An additional factor that may cause the progression of steatosis to NASH involves the release of inflammatory proteins by adipose tissue which causes hepatocellular oxidation and injury (Rahimi and Landaverde, 2013:43). Increased influx of inflammatory agents such as IL-6 and TNF-α (released from visceral fat) increase oxidative stress and activates other inflammatory pathways (Hafeez and Ahmed, 2013:7), causing lipid peroxidation. While liver steatosis can thus be seen as the first hit; increased inflammation and oxidative damage is the second hit which could potentially cause progression of simple steatosis to NASH, fibrosis, and hepatic cancer.

2.4.3 Management

The impact of dietary and lifestyle patterns in the development of obesity and insulin resistance is well described, and since these are closely related to development of NAFLD, it would be logical to reason that an association exist between lifestyle and NAFLD. Weight loss, whether induced by lifestyle modification, drug therapy or bariatric surgery is key in the management of NAFLD. Zelber-Sagi et al. (2012:1145) describe the association between weight gain and weight loss on NAFLD development and remission, respectively. A remission rate of 75% in individuals who lost ≥ 5% body weight has been reported, while in the case of 7% weight loss significant improvements in steatosis, lobular inflammation and ballooning was also noted (Musso et al., 2012:885). Weight management strategies, with focus on bariatric surgery, is discussed in detail in section 2.6.

2.5 Weight management

Insulin resistance, brought about by high levels of body fat, underlies development of the metabolic syndrome and therefor current emphasis in the management thereof is sustained, long-term weight loss. Weight reduction can be achieved by behavioural and lifestyle modification aimed at reducing energy intake and increasing energy expenditure. Bariatric surgery is however the most effective therapeutic intervention for effective and sustained weight loss. In addition, bariatric surgery reduces the incidence and severity of co-morbidities including type 2 diabetes mellitus, hypertension, dyslipidaemia, obstructive sleep apnoea, and NAFLD (Hafeez and Ahmed, 2013:1-11; Buchwald et al., 2004:1724). Bariatric surgery is discussed in more detail in section 2.6.

2.5.1 Approaches to weight management

Various approaches to weight control is explained by the European Clinical Practise Guidelines for the Management of Obesity in Adults (Tsigos et al., 2008:106-116), including factors such as diet, cognitive behavioural therapy, physical activity, psychological support, pharmacological treatment and surgery. Of these, surgery is the most effective treatment for sustained long-term weight loss, improvement of co-morbid conditions and decreased overall mortality (Tsigos et al., 2008:2113; Snow et al., 2005: 528).

Approaches to weight management can be viewed as traditional patient-centred approaches (life-style modification where factors such as dietary intake and physical activity is addressed), and medical interventions (very low calorie diets (VLCDs), drug therapy and bariatric surgery procedures). Medical intervention in the form of VLCD and bariatric surgery are often reserved for those who either failed traditional attempts to weight loss, or for those with a high BMI value (at least 30 kg/m^2 for VLCD or at least 35 kg/m^2 for bariatric surgery).

Whichever strategy is decided upon, the goals of weight management need to be individualized and adapted to a comprehensive approach that takes into account other health parameters such as blood pressure and blood glucose levels in addition to actual body weight. It is important to create realistic expectations by putting more emphasis on achievement of a more healthful weight versus achievement of ideal body weight (ADA, 2009:331; Snow et al., 2005:526). Hamby (2013: online) describes a paradigm shift in the medical management of obesity where the focus is placed on achieving and maintaining the highest possible weight that will eliminate or minimize obesity-related co-morbidities. According to Eckel et al. (2005:1423), the goal for management of abdominal obesity is a decrease of 10% weight loss in the first year followed by further reduction, or at least maintenance of weight loss, thereafter. The rate of weight loss needs to be closely monitored and build into the overall goal, since uncontrolled weight loss or weight cycling is associated with health risks such as cardiac arrhythmia, electrolyte disturbances, cholelithiasis, hyperuricemia and the potential to develop eating disorders. In patients with NAFLD, concern exists when rapid weight loss of more than 1.6 kg per week occurs. This has been linked to a risk of portal inflammation and fibrosis (Younossi, 2008:5). Rapid fat mobilization increases visceral free fatty acids and accelerates the inflammatory process, which may negatively affect patients with advanced liver disease (Rafiq and Younossi, 2008:430). A reasonable goal may be based on 0.4-0.5 kg weight-loss per week as part of the overall goal. It is however advised that each patient's goal is individualized (Hamby, 2013: online).

Maintenance of weight loss is another aspect that needs to be considered. Since body weight and fat content is closely regulated by internal control mechanisms, weight-loss initiatives needs to override internal systems that will by default favour return to initial start-off weight. Energy restriction results in acute compensatory changes including lower levels of circulating leptin and higher levels ghrelin. These hormonal changes stimulate appetite and may remain present for at least one year following diet-induced weight loss, without returning to initial levels (Sumithran et al., 2011:1598). This will result in increased hunger perception and possible food consumption which may hamper weight-loss maintenance. In addition, the fact that energy expenditure is related to weight can dampen the effect of energy restriction over time. In order to maintain weight loss, self-monitoring is of high importance. Together with other factors such as daily physical activity and consumption of most meals at home rather than away from home, this can contribute to successful weight maintenance (Hamby, 2013: online).

2.5.1.1 Dietary intervention

Creating a negative energy balance is the most important factor affecting amount and rate of weight loss (ADA, 2009:333). A reduction in energy intake of 500 to 1000 kilocalories (kcal) (2090- 4180 kilojoules (kJ)) per day can achieve 0.5-1.0 kg weight loss per week. In order to achieve negative energy balance, various dietary and life-style strategies have been explored from decreasing intake to increasing output, or both. Dietary energy restriction strategies vary from simple calorie counting, to diet composition, to the use of meal replacements or VLCDs. In addition, strategies may include changes to meal frequency, meal timing and portion control (ADA, 2009:333).

i. Diet composition

A low-fat, reduced-energy, portion-controlled diet is the best studied weight-loss diet strategy and is the type of diet most often recommended by health care professionals who prescribe weight management strategies (Hamby, 2013: online). Fat is the most energy-dense macronutrient and therefore is the main focus when calculating energy restricted diet plans. In addition to the reduction in energy intake, reduced fat intake complements general health. Since obesity and metabolic syndrome are associated with increased risk factors for type 2 diabetes mellitus and cardiovascular disease, focus on reducing saturated fat, dietary cholesterol as well as trans-fatty acid content are recommended.

The law of thermodynamics (the law of conversion of energy) underlies the traditional approach of simply reducing energy intake as opposed to manipulating macronutrient contribution to total energy intake. This means that, according to traditional weight management diet plans, it is believed that an energy-restricted diet will result in weight loss, independent of macronutrient composition. New research in support of ketogenic diets indicating the opposite however remains controversial. The ketogenic diet involves severe carbohydrate (CHO) restriction of < 50 gram (g) per day together with a relative increase in protein and fat intake. In the scarcity of dietary CHO, there are insufficient glucose reserves available to sustain cellular energy demand, and therefor alternative fuel sources are utilized. As indicated by the term ketogenic diet, ketone bodies (including acetoacetate, acetone and β-hydroxybutyric acid) are used as fuel source in the absence of sufficient glucose. These are produced in the liver mitochondria through overproduction of acetyl coenzyme A (Paoli et al., 2013:789).

A review by Paoli et al. (2013:789-796) indicates that there are strong evidence to support the use of ketogenic diets to induce weight loss. One of the major contributing factors to the favourable effects of ketogenic diets on weight management is appetite suppression. Appetite is reduced not only because of a higher satiety value of fat and protein in the diet, but also due to a direct appetite-reducing effect of ketone bodies. In addition, ketosis is an energy-expensive process therefor contributes to energy consumption. In the context of metabolic syndrome, positive effects follow severe restriction of CHO intake since insulin resistance manifests as CHO intolerance. In addition to weight loss, improved glycaemic control, reduced triglyceride and low density lipoprotein (LDL) cholesterol levels, and increased HDL cholesterol levels improve the metabolic profile of overweight or obese individuals with metabolic syndrome.

Controversy with regards to ketogenic diets for weight management revolves around a lack of long-term safety data. A high protein and fat intake is encouraged which is often unrestricted and this may not be ideal for patients with cardiovascular-related co-morbidities (ADA, 2009:333).

ii. Eating frequency and portion control

Despite general belief that eating frequency is an important consideration in weight management diets, the American Dietetic Association (ADA) (2009:334-335) states that convincing evidence to support this practise is lacking. General concern with regard to an erratic eating schedule is that it leads to poor food choices from easily available, energy dense, nutrient poor foods; and that it may lead to excessive consumption later during the day as a form of compensation for lost meals. A recommendation from the ADA evidence base library is that total energy intake should be distributed throughout the day, with the consumption of four to five meals or snacks per day inclusive of breakfast (ADA, 2009:335). Further recommendation from the ADA is that portion control should be included as part of a comprehensive weight management program. Examples of portion control strategies include the use of premeasured foods; replacing volume of higher energy-density foods with lower energy-density foods; and education on size of serving containers and second-portion helpings.

iii. Meal replacements

Meal replacements provide a specific, controlled amount of energy within a prefixed portion size. Meal replacements can be useful to eliminate problematic food choices by reducing the number of daily decisions a person has to make regarding food intake; and by reducing exposure to tempting foods that might result in overeating. Heymsfield et al., (2003:538) describe a partial meal replacement plan as one or two portion-controlled, nutrient fortified meal replacements along with traditional low energy meal(s) and snacks. Partial meal replacement plans are usually designed to decrease energy intake by 500–1000 kcal (2090-4180 kJ) per day. In a systematic review of randomized controlled trials (RCT) utilizing partial replacement plans for weight management, it is reported that partial meal replacement interventions can safely and effectively produce significant, sustainable weight loss and improve weight-related risk factors (Heymsfield et al., 2003:537).

Despite concern that a meal replacement strategy may result in over-reliance on artificial nutrients and may hamper the learning process on selection of healthy food in appropriate portion sizes, the ADA recommends partial meal replacement as an option for people who have difficulty with self-selection and/or portion control (ADA, 2009:335).

2.5.1.2 Physical activity

In order to achieve 0.5-1.0 kg weight loss per week, an energy deficit of 500 to 1000 kcal (2090-4180 kJ) per day needs to be achieved (ADA, 2009:336). To maintain this level of energy deficit through exercise alone is challenging since the contribution of exercise to creating a negative energy balance is small in comparison to dietary restriction. While it requires effort to burn 1000 kcal (4180 kJ) per week through increased activity, it is relatively easy to consume 1000 kcal less by omitting a few additional portions of snacks or beverages. The best approach is thus to combine increased energy expenditure through physical activity with reduced food intake.

In addition to weight management, physical activity is an important factor to improve general health and obesity related co-morbidities, as well as for the prevention of weight regain. For this reason it is recommended that physical activity goals are included in weight management programmes (ADA, 2009:336). Specific exercise targets are included in three categories:

i. 30 minutes of moderate-intensity physical activity on most days of the week to reduce the risk of chronic disease;
ii. 60 minutes of moderate- to vigorous intensity activity on most days of the week to help manage body weight and prevent weight gain in adulthood;
iii. 60-90 minutes of daily moderate-intensity physical activity while not exceeding energy requirements in order to prevent weight regain after weight loss (United States department and Health and Human Service, 2008: online).

2.5.1.3 Very low calorie diets

VLCDs are defined by the ADA as liquid formulations that are used to replace total food intake for a pre-determined period of time when active weight loss is required, and supplies a maximum of 800 kcal (3345 kJ) or 6-10 kcal (25-42 kJ) per kg body weight per day. Low calorie diets (LCD) are less restrictive and allow calorie intake of 1200-1600 kcal (5015-6690 kJ) per day (Heymsfield et al., 2003:537). These diet programmes are typically available as commercial food items (such as shakes, soups and food bars) and are enriched with high biologic value protein to preserve lean body mass.

Commercially available programmes provide at least 100% of the daily value of essential vitamins and minerals to address any potential or existing micronutrient deficiencies (ADA, 2009:335).

VLCDs are used in medically supervised programmes aimed at achieving a substantial weight loss while providing adequate nutrition and preserving lean body mass. A rapid weight loss of up to 15% body weight in 12-16 weeks can be achieved, but involves medical risks such as gallstone formation, cholecystitis, and disturbance in fluid-electrolyte balance. For this reason, VLCDs are indicated only for those with a BMI > 30 kg/m^2 (ADA, 2009: 336). Though effective on the short term, maintenance of weight loss achieved through VLCD plans is problematic. A meta-analysis by Tsai and Wadden (2006:1283-1293) analysed data from six RCTs and indicated that despite significantly greater short-term weight loss, VLCDs do not offer any better outcomes on the long term as compared to normal low energy diets. In addition, compliance to VLCD plans is poor (Hamby, 2013: online)

The use of VLCDs has however been increasingly investigated as a short-term measure to reduce liver volume and surgical risk pre-operatively in patients scheduled to undergo bariatric surgery. The application of LCDs and VLCDs for different periods of preoperative duration seems to be successful in reducing hepatic volume and steatosis, but it is unclear if this translates to improved patient outcome (Van Nieuwenhove et al., 2011:1300-1305; Edholm et al., 2011:345-350).

2.5.1.4 Behaviour modification

The ADA recognizes that behaviour modification constitutes one aspect within a comprehensive approach to weight management (ADA, 2009:337), however Hamby (2013: online) explains that it is a challenging and time consuming effort to addressing the behaviours that contribute to excessive food intake and sedentary lifestyle. Certain activities or circumstances may act as cues that stimulate inappropriate intake of food, and it may require in-depth evaluation by a committed, trained professional to identify and change the reaction to cues. Cognitive behavioural therapy is advantageous in the sense that it has measurable outcomes and advocates small changes (ADA, 2009:337). Changing behaviour relating to food intake patterns appear to be more important early in the weight loss journey, whereas physical activity behaviour support changes in dietary behaviour during weight loss maintenance (Stubbs and Lavin, 2013:17).

2.5.1.5 Pharmacotherapy

Guidelines by the American College of Physicians (ACP) on the Management of Obesity in Primary Care state that drug therapy may be offered to obese patients who failed to achieve their weight loss goals through diet and exercise alone (Snow et al., 2005:526). When weight loss drugs are incorporated in obesity management, patients should be made aware of the side effects of drug therapy, as well as the temporary nature of weight loss effects. Since the use of any type of medication includes risks, the benefits related to pharmacological treatment needs to outweigh the potential risk. The patient needs to understand that the effect of weight loss drugs is limited to palliation only; meaning that it can induce or maintain weight loss but that it is not a long-term solution that will cure the condition (Hamby, 2013: online).

Criteria for the approval of weight-loss drugs by the United States Food and Drug Administration (FDA) require proof of placebo-adjusted weight loss of ≥ 5% at one year; or that ≥ 35% of patients on the drug should achieve a ≥ 5% weight loss with at least twice as many patients losing ≥ 5% relative to those treated with placebo (Shin and Gadde, 2013:131). Current FDA approved drugs for long-term treatment of obesity include orlistat, lorcaserin, and phentermine-topiramate combination. A previously approved drug, sibutramine, has been recalled following reports that indicate an increased risk of heart attack and stroke (FDA, 2010: online).

Orlistat is a pancreatic lipase inhibitor that inhibits the digestion and absorption of dietary fat. Side effects of orlistat use include steatorrhoea, bloating, distension and anal leakage. Since fat absorption is restricted, deficiencies of fat soluble vitamins may arise. Despite these unfavourable side-effects, orlistat have a proven long-term safety record with sustained weight loss of up to 10% over a two year period (Hamby, 2013: online; ADA, 2009:339).

Lorcaserin as well as phentermine-topiramate was FDA approved in 2012 for long-term weight management of individuals with BMI ≥ $30kg/m^2$ or BMI ≥ 27 kg/m^2 with at least one co-morbid condition. The method of action for lorcaserin is related to the selective activation of serotonin 5-HT_{2C} receptor, which in turn promotes satiety (FDA, 2010: online).

Phentermine is an appetite suppressing agent, which is approved for the short-term treatment of obesity, while topiramate is approved for seizure disorders and migraine prophylaxis. Phentermine affects food intake by enhancing the release of norepinephrine while also blocking re-uptake of norepinephrine. The mechanism whereby topiramate induce weight loss is not clearly understood, but is postulated to increased energy expenditure and decrease energy intake and the amount of weight loss achieved with combination therapy is of a greater magnitude than what could be achieved with either agent alone (Shin and Gadde, 2013:131).

With regard to improvement of insulin sensitivity, metformin and thiazolidinediones can reduce the risk of developing type 2 diabetes mellitus in patients with impaired fasting glucose or impaired glucose tolerance. However, thiazolidinediones have unfavourable effects on body weight (cause weight increase), and so does insulin secretagogues such as sulphonylureas. This is mainly due to increased caloric intake as a result of hypoglycaemia, therefor close monitoring is important (Eckel et al., 2005:1424).

2.5.1.6 Bariatric surgery

Surgery is the most successful strategy to achieve long-term weight loss and is believed to be superior to conservative weight management options in obese patients. A recent review by Hafeez and Ahmed (2013:2) concludes that bariatric surgery is safe; effective to reduce weight; improves quality of life; decreases obesity related disease; and increases life expectancy. Bariatric surgery is explained in more detail in the following section.

2.6 Bariatric surgery

As bariatric surgery is currently deemed as the most successful strategy to achieve long-term weight loss in obese patients, bariatric surgery figures are on the increase. In the United Kingdom the number of bariatric surgery procedures increased by 720% from 2003/2004 to 2009/2010 (Rickers and McSherry, 2012:41. Worldwide a similar increase of 760% over the past ten years is reported (Hafeez and Ahmed, 2013:2). The increase in bariatric surgery procedures have also been fuelled by the development of centres of excellence, laparoscopic techniques, improved safety records and better documentation of clinical effectiveness (Hng and Ang, 2012:435). Bariatric surgery has been shown to be not only effective in reducing body weight, but also improving co-morbidities and quality of life (ADA, 2009:240).

Currently, bariatric surgery is reserved for patients with severe disease who have failed previous weight loss attempts, and have a BMI ≥ 40 kg/m^2; or a BMI ≥ 35 kg/m^2 with significant co-morbidities (Mechanick et al., 2013: 163; SAGES, 2010: online). Bariatric surgery for individuals with a BMI of 30-34.9 kg/m^2 with co-morbidities is currently under investigation (Neff et al., 2013:5). For this patient group the term *metabolic surgery* has emerged, and describes bariatric procedure intended to treat type 2 diabetes mellitus in individuals with a BMI of 30-35 kg/m^2 (Mechanick et al., 2013:161).

Candidates are assessed by a multi-disciplinary team of health professionals in a complex process involving psychological, surgical, dietetic and medical aspects. Patients need to be both physically and psychologically fit; have realistic expectations; and be determined to comply with post-operative instructions and care. As with any type of surgery, bariatric surgery involves risk, and for every individual patient the benefits of bariatric surgery should outweigh potential risk (Neff et al., 2013:5)

2.6.1 Surgical techniques

Bariatric surgery techniques can be classified in three categories based on method of action (Hafeez and Ahmed, 2013:2):

- Restrictive procedures aim to limit the volume of food eaten by surgically reducing stomach capacity. Such procedures include vertical banded gastroplasty (VBG), adjustable gastric banding (AGB), proximal gastric bypass, and sleeve gastrectomy (SG);
- Absorption limiting procedures are less popular than restrictive procedures as they are technically more demanding to perform, and patients often develop nutritional deficiencies. Procedures such as biliopancreatic diversion (BPD), with or without duodenal switch, aim to bypass segments of the small intestine in order to reduce nutrient absorption;
- Hybrid procedures are a combination of above techniques. The Roux-en-Y gastric bypass (RYGB) procedure restricts food intake by means of creating a small gastric pouch, while it also decrease nutrient absorption through bypassing a section of the small bowel. Refer to Figure 2 for images of some of the more commonly performed procedures.

According to Neff et al. (2013:1), the most commonly performed procedures are AGB, RYGB and SG. BPD is performed less commonly, but often considered in the morbid obese (obese class III) individual. All procedures can be performed by laparoscopic technique which is preferred as the complication rate is lower (Edholm et al., 2011:345-346). However, as mentioned earlier, hepatomegaly and hepatic steatosis linked to NAFLD, may complicate procedures and result in the need to convert to open technique.

2.6.1.1 Adjustable gastric band

When laparoscopically performed, AGB is the least-invasive procedure, completely reversible with the lowest mortality. An inflatable silicone band is placed around the stomach, at the site immediately distal to the gastroesophageal junction. A subcutaneous port is connected to the silicone band to allow adjustment. This procedure is purely restrictive, since the band generates a feeling of satiety which in turn reduces appetite and restricts food intake (Hng and Ang, 2012:435).

2.6.1.2 Roux-en-Y gastric bypass

This combination procedure, also performed laparoscopically, involves the formation of a small gastric pouch of 20-30 millilitre (ml) capacity that is connected to the jejunum to form the Roux limb. The disconnected duodenal limb is anastomosed 75-150 centimetre (cm) along the Roux limb, forming a Y configuration. The Roux limb may be extended to increase the section of the small intestine that is bypassed (Hng and Ang, 2012:435).

2.6.1.3 Sleeve gastrectomy

The stomach is transected vertically to create a gastric tube, leaving a pouch of 100-200 ml capacity (Neff et al., 2013:1).

2.6.1.4 Biliopancreatic diversion and duodenal switch

BPD is a procedure that results in malabsorptive through bypass of most of the small intestine. When performed with duodenal switch, the procedure starts off with a sleeve gastrectomy which leaves the pylorus intact. The duodenum is disconnected and the stomach is directly anastomosed to the distal small bowel. The biliopancreatic limb is then connected to the ileum (75-100 cm proximal to the ileocaecal valve). When performed without the duodenal switch, a partial gastrectomy is performed, leaving a 400 ml gastric pouch. The common channel where digestion and absorption takes place, is shortened to 50 cm (Hng and Ang, 2012:436).

2.6.2 Effectiveness

Expected average weight loss and long term maintenance of weight loss has been found to be better after absorptive limiting and combination procedures, however these procedures are also associated with increased technical complexity and nutritional risk (Tsigos et al., 2008:113). Comparing the effectiveness of the different types of surgical procedures, expected outcomes range from 47.5% excessive weight loss for AGB, to 70% for BPD (ADA, 2009:340). Weight loss reaches a maximum within 12 months post-operative.

In addition to the effect on weight, bariatric surgery is also associated with significant improvement in co-morbidities. Remarkable effects on resolution of type 2 diabetes mellitus have been documented with 77-86% of patients achieving complete remission. Improved blood glucose control occurs within days following RYGB – even before a significant amount of weight is lost – indicating that mechanisms other than weight loss and its effect on insulin resistance is involved (Hng and Ang, 2012:437). Furthermore, bariatric surgery is associated with improvements in hyperlipidemia (improved in ≥ 70% of patients); hypertension (resolved or improved in 79% of patients); obstructive sleep apnoea (resolved in 84% of patients); and decreased risk of developing cardiovascular disease, cancer and new co-morbid conditions (Hng and Ang, 2012:437). Positive effects on functional status, body image and economic outcomes have also been reported (Neff et al., 2013:8-9). RYGB is associated with histological improvement in steatosis, inflammation and fibrosis. Data from individual studies indicate a 50-60% resolution in fibrosis and NASH respectively; and 83% complete regression of NAFLD. Similar to RYGB, VBG procedure is also associated with improvements in steatosis, inflammation and fibrosis. Improvement in biochemical markers has also been reported (Hafeez and Ahmed, 2013:2-3).

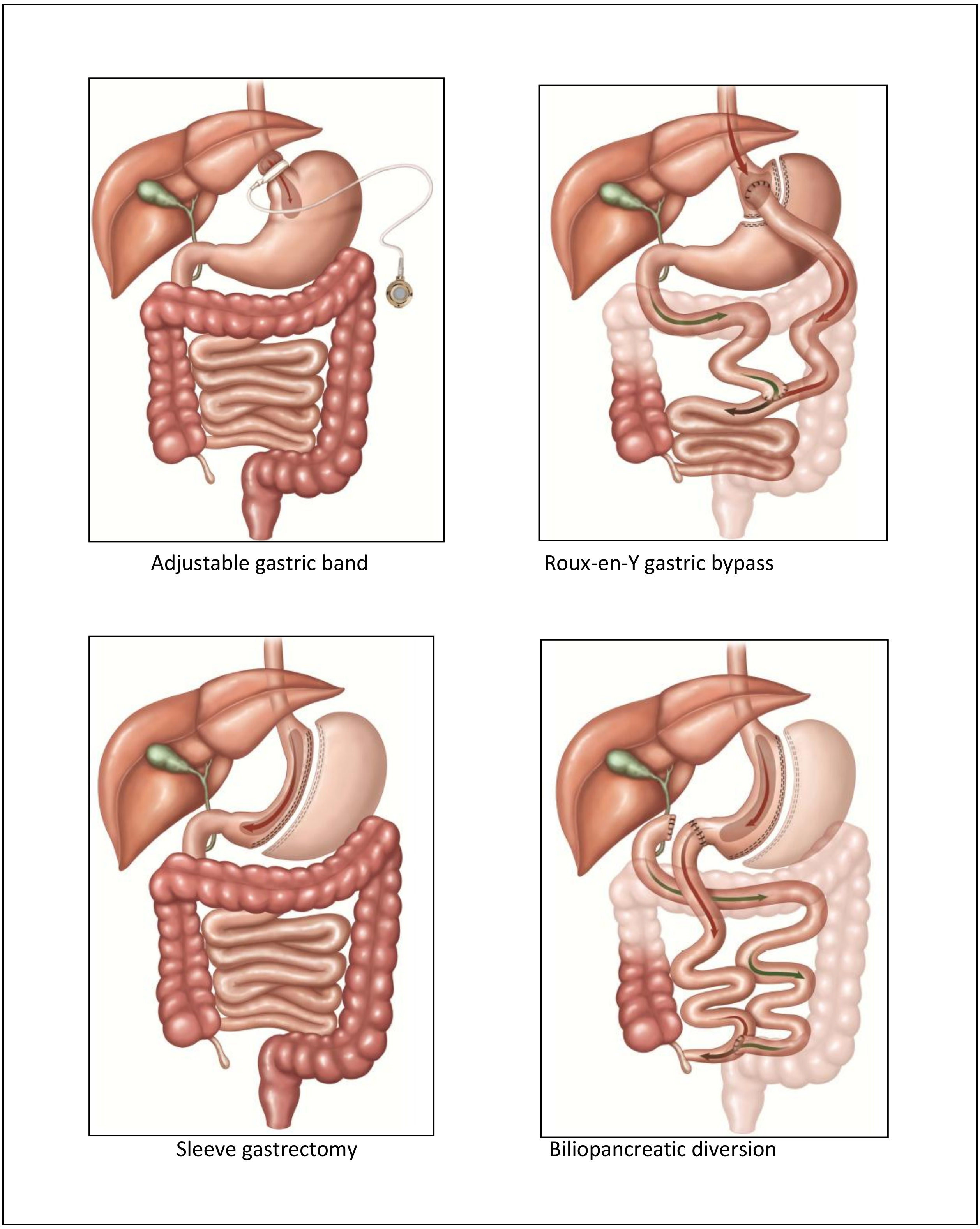


Figure 2. Schematic representation of commonly performed bariatric procedures (Neff et al., 2013:1-17).

2.6.3 Mechanism of action

The weight-loss effect of bariatric surgery is only partially related to restriction and malabsorption. In fact, malabsorption accounts for only 5% of weight lost following RYGB. Changes in neuro-hormonal systems is believed to contribute to weight loss through changes in appetite, satiety, food preference and eating patterns (Hng and Ang, 2012:437).

2.6.3.1 Changes to the neuro-hormonal control of energy balance

As explained previously, hypothalamus action relies on hormonal signals by adipokines and enterokines which provide information relating to energy status. Bariatric surgery influences the release of gut hormones. The neuro-hormonal effects of bariatric surgery are supported by the existence of two hypotheses: the hindgut theory and the foregut theory. .These are briefly described below (Hng and Ang, 2012:438):

- Hindgut theory: rapid delivery of undigested food increase Peptide-YY and GLP-1 release in the distal gut, contributing to early satiety, reduced meal size, improved glucose control and resolution of type 2 diabetes mellitus;
- Foregut theory: bypassing of the duodenum and proximal jejunum leads to improved glucose control via reduced secretion of anti-incretin, which is normally released by the small bowel when it comes in contact with food.

2.6.3.2 Changes in microbiota

Changes in gut microbiota, brought about by procedures such as RYGP, affect host-microbial interaction which may contribute to the weight loss effect of bariatric surgery. An animal study confirmed changes in the microbiota of mice after RYGP surgery and also found that transfer of the microbiota from RYGB-treated mice to non-operated, germ-free mice resulted in weight loss and decreased fat mass in the recipient animals. This effect is potentially due to altered production of short-chain fatty acids and provides the first empirical support for the hypothesis that changes in gut microbiota may be one of the mechanisms through which RYGB surgery decrease weight and adiposity (Liou et al., 2013:1).

2.6.4 Hepatomegaly as a challenge to performing bariatric surgery

The incidence of large, fatty liver is common in the obese population which presents a physical challenge to performing bariatric surgery, especially when laparoscopic procedure is used. A large liver in combination with excessive layers of abdominal fat, obscures the surgical field and restricts exposure of anatomic markers, and is one of the main reasons from conversion from laparoscopic to open surgery (Colles et al., 2006:304).

Successfully decreasing liver size pre-operatively (also described as liver shrinking) may be an important strategy to minimize the challenges of bariatric surgery to the surgeon, thereby also bringing a supposed benefit to the patient in terms of reduced complications in the post-operative phase. Though several clinical trials have examined the value of pre-operative strategies to reduce liver volume (mainly the use of VLCDs for two to 12 weeks before surgery), few studies could actually link it to improved patient outcome and/or reduction in post-operative complications. The practise of liver shrinking is suggested to positively impact the degree of surgical difficulty. Unfortunately reporting is subjective in most trials done to date (Van Nieuwehove et al., 2011:1300; Lewis et al., 2006:697; Rao et al., 2005:199,). In terms of intra-operative blood loss and operating time, there does not seem to be any benefit related to liver shrinking before bariatric surgery is performed, except for a modest improvement in operating time in patients with BMI > 48 kg/m^2 (Dambrauskas et al. 2010:46). In addition, compliance may become problematic when VLCD needs to be followed for an extended period of time (Colles et al., 2006:304-311; Edholm et al., 2011:345-350)

Section 2.6.7 provides more information on the role of VLCD in the pre-operative liver shrinking approach.

2.6.5 Morbidity and mortality

Mortality rates for bariatric surgery are low, ranging from 0.3 - 1% for RYGP, and 0.02-0.4% for AGB. Though no significant differences has been reported among different procedures, it is interesting to note that mortality rates decrease as surgeon skill improves. Surgeons who had performed < 20 procedures have a patient mortality rate of 5% while a close to 0% rate is applicable to surgeons who had performed > 250 procedures (Snow et al., 2005:529). Bariatric surgery should therefore be performed by experienced surgeons at high-volume bariatric centres since an evident learning curve exist. Better patient outcome can be expected as the skill of the surgeon improves. Furthermore, high-volume centres are likely to have better capacity to care for the patient post-operatively, which can also improve patient outcome (Snow et al., 2005:527).

Acute complications occur in 5-10% of patients and include haemorrhage, obstruction, anastomotic leak, wound infection, cardiac arrhythmia, pulmonary emboli, respiratory failure and rhabdomyolysis (breakdown of muscle tissue). Long-term complications include internal hernias, anastomotic stenosis, marginal ulceration, fistulae, diarrhoea, gallstones, emotional disorders and nutritional deficiencies (Hng and Ang, 2012:437). Complications relating specifically to AGB include band migration, band erosion, and infection of the adjustment port (Neff et al., 2013:11).

Dumping syndrome is a potential complication following bariatric surgery due to the fact that the pyloric sphincter is bypassed, allowing undigested food to empty rapidly from the stomach pouch into the lower part of the small intestine. Hyperosmolar lumen content causes a movement of fluid from the intravascular space into the gut. In addition, vasoactive gastrointestinal hormones such as pancreatic polypeptide, intestinal polypeptide and GLP are released, resulting in a series of symptoms including nausea, vomiting, bloating, cramping, diarrhoea, dizziness and fatigue. Early dumping as explained above can occur immediately after food intake, while intermediate dumping occurs between 20 minutes and one hour after food intake. Late dumping occurs one to three hours after a meal and has a different pathophysiology which is related to reactive hypoglycaemia following excessive insulin release. Symptoms include weakness, sweating, palpitations and dizziness (Frantz et al., 2012:429). Simple dietary changes such as avoiding food with high fat or high sugar content may help to prevent dumping (Rickers and McSherry, 2012:44). Small, regular meals containing protein and carbohydrate and low in glycaemic index is recommended by Neff et al. (2013:12). In the case of late dumping, 2-3 kg weight gain often abolish symptoms secondary to a small increase in insulin resistance (Neff et al., 2013:17). Though unpleasant, dumping syndrome can actually be a beneficial side effect as it may deter patients from consuming food with high fat or high sugar content.

2.6.6 Nutritional considerations before and after surgery

Despite an excess of body fat, obese patients might not have a good nutritional status at the time of surgery. Though excess energy intake precedes obesity, patients may present with nutritional deficiencies. These deficiencies may develop as a result of overconsumption of energy-dense, nutrient poor food together with increased nutrient requirements as a consequence of obesity and its co-morbid conditions (Rickers and McSherry, 2012:42). Pre-operative nutritional status may affect wound healing, post-operative infection risk and overall recovery rate. In this regard it is quite interesting to revisit the practise of preoperative VLCD to reduce liver volume prior to bariatric surgery. Concerns are related to increased morbidity when performing surgery on a catabolic patient (Gustafsson et al., 2011:571), although none of the reviewed RCTs reported an association between preoperative VLCDs and poor wound healing, compromized immune function or mortality (Van Nieuwenhove et al., 2011: 1300-1305; Edholm et al., 2011:345-350; Colles et al., 2006:304-311; Lewis et al., 2006:697-701; Fris, 2004:1165-1170). Studies were however not designed to specifically evaluate this, and a possible relationship cannot be totally excluded.

Development of nutritional deficiencies is common following bariatric surgery, especially in the case of absorption restrictive procedures. Deficiencies due to poor absorption may be exacerbated by poor food choice. Rickers and McSherry (2012:44) summarize the risk of developing deficiencies for specific bariatric surgery procedures as indicated in Table 2.6.

Table 2.6. Risk of developing micronutrient deficiencies after different bariatric surgery procedures (Rickers and McSherry, 2012:44).

Micronutrient	Laparoscopic AGB	RYGB	BPD
Calcium	Medium	Medium	High
Copper	Low	Low	Low
Folate	Low	Low	Low
Iron	Medium	High	High
Selenium	Low	Low	Low
Vitamin B_1	Low	Low	Low
Vitamin A	Low	Low	Medium
Vitamin B_{12}	Low	High	Medium
Vitamin D	High	High	High
Vitamin E	Low	Low	Low
Vitamin K	Low	Low	Medium
Zinc	Low	Medium	Medium
AGB: adjustable gastric banding; RYGB: Roux-en-Y gastric bypass; BPD Biliopancreatic diversion			

Symptoms of vitamin or mineral deficiency are non-specific. Biochemistry analysis is recommended both before and after surgery. Frequency of post-operative monitoring is dependent on the surgical procedure as it is unlikely that purely restrictive procedures would result in deficiencies unless poor dietary habits exist. In case of suspected deficiency, micronutrient supplementation must be considered via oral or intravenous route (Rickers and McSherry 2012:44).

Following surgery, there is little evidence and varying practise with regard to introduction of food textures. Guidelines from the American Endocrine Society recommend post-operative progression of food consistency over weeks to months, to minimise vomiting and damage to the surgical site (Heber et al., 2010:4823). It is reasoned that a gradual progression from fluids to puree to solid food allows patients to adjust to a restricted portion size and new eating habits. Initial volume of fluid/food is small, and progression will depend on individual tolerance (Rickers and McSherry, 2012:43).

Sufficient protein intake post-operatively can be particularly challenging, mainly due to the development of intolerances to protein-rich foods. Almost one in five patients, who had undergone RYGB procedures, experience persistent intolerance to protein-rich food, and this only improves after one year following surgery (Bock, 2003:142). For this reason patients should be counselled about food choices and protein supplements to maximise intake.

2.6.7 Very low calorie diets and bariatric surgery

Laparoscopically performed bariatric surgery is complicated by increased liver volume which may also contribute to the development of postoperative complications (Van Nieuwehove et al., 2011:1300). Large liver and excessive intra-abdominal fat reduces operating space and exposure, making laparoscopic surgery difficult to perform. Even during open surgery procedures it remains a challenge since liver traction may cause hepatic trauma with increased risk of bleeding. These difficulties explain why enlarged liver size is the most common reason for conversion from laparoscopic to open procedures (Schwartz et al., 2003:734; O'Brien et al., 2002:652). In comparison to laparoscopic procedures, open surgery is associated with increased blood loss, longer intensive care unit and hospital stay, risk for developing incisional hernia, as well as delayed recovery time before being able to resume daily activities of living (Colquitt et al., 2009:28; Nguyen and Wolfe, 2002:86).

This highlights the potential benefit in preoperative reduction of liver volume. The use of VLCDs has been increasingly investigated to reduce liver volume and surgical risk pre-operatively in patients undergoing bariatric surgery. The application of LCDs and VLCDs for periods ranging from two to 12 weeks of preoperative duration seems to be successful in reducing intra-abdominal and hepatic fat content.

Colles et al. (2006:304-311) investigated the efficacy of preoperative VLCD for 12 weeks in 32 obese patients. In addition to reduction in body weight, a significant reduction in liver volume of 0.56 litre (L) was reported. .This was directly related to the reduction in body weight and initial liver volume. Moreover, researchers analysed the reduction in liver volume in a subgroup of patients with initial liver volume ≥ 2.8L. In this group an overall 27.8% decrease in liver volume was reported, of which 80% of the reduction occurred during the first two weeks of VLCD implementation. Lewis et al. (2006:697-701) reported findings of a six-week VLCD intervention on 18 morbidly obese patients. Significant reduction in both liver volume (14.7%) and liver fat content (43%) is reported.

In a similar study by Edholm et al. (2011:345-350), patients who received a four-week preoperative LCD intervention showed significant reduction in liver volume (12%) and liver fat (40%). A similar finding is reported in a study on 15 morbidly obese women by Kullberg et al. (2011:1-8). In this study, a four-week intervention with a LCD decreased liver fat content by 41%. Fris (2004:1165-1170) managed to show that a significant reduction in liver size and –fat content can be achieved with a VLCD, taken for as little as two weeks prior to surgery.

A reduction in liver volume could potentially translate to a reduction in technical difficulty of BS procedure and fewer postoperative complications. Rao et al., (2005:199-204) reports a decrease in difficulty scoring for laparoscopic adjustable gastric banding. Van Nieuwenhove et al. (2011:1300-1305) reported findings of a two-week preoperative VLCD approach in 298 obese patients in five high-volume bariatric centres across Europe. Surgeon's perceived difficulty of the operation was lower in patients who a underwent preoperative VLCD plan; and these patients also had a significant reduction in complications at 30-day follow-up. Though individual studies report on positive outcomes as stated above, sample sizes of these studies are small, and this highlights the need for a systematic review and/or meta-analysis to confirm beneficial effects of LCD and VLCD prior to surgery. Before this practise can be considered standard procedure, convincing evidence is needed to show that a clinically relevant reduction in liver size can be achieved in a time period that does not influence patient compliance and acceptance.

2.7 Conclusion

Obesity is a world-wide epidemic with serious health risks. Central obesity is the main causative factor in the development of insulin resistance which in turn is the main underlying factor for development of the metabolic syndrome. Metabolic syndrome can manifest in the liver as NAFLD.

Traditional weight management efforts are patient-centred, focussing on diet restriction, exercise and life-style modification. These strategies have limited ability to maintain long-term effects and are difficult to maintain. The use of surgical techniques to restrict food intake and limit nutrient absorption is more effective than traditional approaches to weight management, though comes with a series of risks and complications of its own. One such complication is the high degree of surgical difficulty associated with increased liver volume and intra-abdominal fat which obscures the surgical field. VLCDs have been examined as a possible mechanism to induce pre-operative liver shrinking. It is assumed that liver shrinking can improve surgical outcome through benefit to the surgeon (decreased complexity) and to the patient (decreased intra- and post-operative complications). Though VLCD seem to effectively reduce liver size when used pre-operatively, data is lacking to convincingly argue that it should be implemented as standard practice. Data obtained from a systematic review and/or meta-analysis will help establish the rational for VLCDs to induce liver shrinking; and whether this translates to improved surgical outcome.

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CHAPTER 3: SYSTEMATIC REVIEW

Chapter 3 presents the systematic review in article format. The first article (original article) is a comprehensive description of the research; while the second article is more condensed in order to meet requirements for journal publication.

3.1 Original article

3.1.1 Abstract

Introduction

Excessive abdominal fat and increased liver volume associated with liver steatosis increase surgical complexity of bariatric procedures in obese individuals due to obstruction of anatomical markers, reduced operating space and increased trauma with liver traction. Hepatomegaly is the most common reason for converting from laparoscopic to open procedure. Pre-operative restricted energy diets have been used successfully in small individual trials to achieve reduction in liver volume and fat content. However, few studies have been able to convincingly report a link between pre-operative restricted diet approach and improved intra- and postoperative patient outcome.

Objective

This review was undertaken to report on the effectiveness of commercial pre-operative restricted energy diet programmes to induce liver-shrinking, both volume and fat content, before bariatric surgery. Secondary objectives were to identify the optimal time period needed to achieve clinical reductions; and to identify possible benefits in terms of intra- and postoperative outcomes.

Methods

A systematic literature search was undertaken to identify published studies related to the study objective. A two-step search was conducted on trials published from 1980 to 2012. Initial search yielded 33 studies. Twenty-one studies were excluded based on title or level one screening and three more were excluded based on level two screening. To be included trials had to report on at least one of the following outcome measures: effect on liver size, liver fat, surgical difficulty, operating time, blood loss, post-operative complication and patient compliance.

Results

The final review included nine trials, of which most were of poor quality with moderate to high risk of bias. Six studies reported on data relevant to the primary study objective and indicated that preoperative energy restriction significantly reduces liver volume and liver fat content. Studies that reported on intra-operative factors (surgical complexity, operating time and blood loss) could not confirm that liver shrinking is of benefit to the surgeon or to the patient. One study indicated that patients may have better 30-day postoperative outcome. The optimal time for pre-operative energy restriction is two to four weeks. Any period longer than four weeks is unlikely to result in additional reduction in liver size or fat content.

Conclusion

Restricted energy diets, used for two to four weeks before bariatric surgery, significantly reduce liver volume and fat content in obese patients. Data is lacking to confirm whether these changes to liver morphology improve other outcome parameters.

3.1.2 Introduction

While the prevalence of obesity is rising in South Africa as well as across the world, bariatric surgery procedures are increasingly performed (Rickers and McSherry, 2012:41). Besides the fact that bariatric surgery is now recognized as the most successful approach in obesity management, reports are indicating that bariatric surgery improves glycaemic control and can potentially reverse type 2 diabetes mellitus (Hng and Ang, 2012:437). Of concern to operating surgeons, is the high incidence of an enlarged liver presenting as non-alcoholic fatty liver disease (NAFLD). Hepatomegaly caused by liver steatosis obscures anatomical markers and reduces operating space. Managing liver morphology prior to surgery may impact on surgical complexity and outcome.

Obesity now affects more than 500 million of the world population. In South Africa, approximately 30% of the population is currently overweight or obese (International Obesity Taskforce, 2013: online). The World Health Organization (WHO) classifies obesity based on body mass index (BMI) which is an expression of body weight in relation to height. According to the WHO, obesity is diagnosed when the BMI of an individual over 18 years is equal to or exceeds 30 kilogramme (kg) per meter squared (m^2) (WHO, 2013: online). Excess body weight is often accompanied by insulin resistance and the distribution of body fat around the abdominal area (central or android obesity) which are indicative features of metabolic syndrome. Metabolic syndrome is a complex network of metabolic abnormalities that increase the risk of cardiovascular disease and type 2 diabetes mellitus. While excess body weight and insulin resistance represents core manifestations of metabolic syndrome, NAFLD can be viewed as the hepatic manifestation of the syndrome (Hafeez and Ahmed, 2013:2).

NAFLD is estimated to affect 74% of obese individuals and can be defined as the accumulation of fat in the liver in the absence of excessive alcohol intake (Hafeez and Ahmed, 2013:1-2). Deposition of fat in hepatic tissue results in the development of an enlarged, fatty liver (Larson et al., 2007:1329). The process of hepatic fat accumulation is the result of a combination of metabolic changes related to insulin resistance and excess body fat. An increased release of free fatty acid (FFA) by adipose tissue together with a decrease of FFA metabolism within the liver is mainly responsible for fatty infiltration that causes liver enlargement. The presence of > 5% steatotic hepatocytes in a section of liver tissue is the minimum criterion for the histological diagnosis of NAFLD (Brunt and Tiniakos, 2010:5288). Additional metabolic changes such as the release of various immune and inflammatory mediators can cause further complications, resulting in the progression of simple steatosis to steatohepatitis, fibrosis, cirrhosis and cancer (Hafeez and Ahmed, 2013:1).

Obesity management is central in the treatment of metabolic syndrome and NAFLD. Reduction in excess body fat can improve insulin sensitivity as well as fatty liver infiltration. For these reasons, emphasis is placed on the value of significant and sustainable weight loss in obese individuals. In addition to the traditional approach which addresses factors such as diet, cognitive behaviour, physical activity and psychological problems, weight management strategies may also involve pharmacological treatment and bariatric surgery.

Bariatric surgery is proven to be the most effective treatment for sustained long-term weight management, while also bringing about improvement in co-morbidities and decrease overall mortality (Tsigos et al., 2008:2113; Snow et al., 2005: 528). A recent review by Hafeez and Ahmed (2013:1-11) states that bariatric surgery is also an effective treatment option for NAFLD management. Currently, surgery is considered for those with a BMI ≥ 40 kg/m^2, or with BMI > 35 kg/m^2 and significant co-morbidities who failed previous dietary attempts to successful weight loss (SAGES, 2010: online). Surgery for individuals with lower BMI and co-morbidities, is under investigation (Mechanick et al., 2013:161).

The high incidence of large, fatty liver in obese patients presents a physical challenge to performing bariatric surgery, especially when a laparoscopic procedure is performed. A large liver in combination with excessive layers of abdominal fat obscures the surgical field, restricting exposure of anatomic markers. This has been cited as one of the main reasons for conversion from laparoscopic to open bariatric surgery procedures (Colles et al., 2006:304).

Successfully decreasing liver size pre-operatively may be an important strategy to minimize the challenges of surgery, thereby also bringing a supposed benefit to the patient in terms of reduced complications intra-operatively and in the post-operative phase. The 2013 Clinical Practise Guidelines for Bariatric Surgery (Mechanick et al., 2013:165) address preoperative approaches to reduce liver volume and states that reduction in liver volume may help to improve the technical aspects of surgery. However, the guideline was downgraded due to inconsistent results. This emphasizes the need for convincing evidence indicating that a clinically relevant reduction in liver size can be achieved, and that such reduction positively impacts on the outcome of surgery.

Restricted energy diets, which may include both very low calorie diets (VLCDs) and low calorie diets (LCDs), have been used successfully in a number of studies to reduce weight, abdominal fat, liver size and liver fat content in the preoperative phase (Van Nieuwenhove et al., 2011: 1300-1305; Edholm et al., 2011:345-350; Colles et al., 2006:304-311; Lewis et al., 2006:697-701; Fris, 2004:1165-1170). Despite the reported effectiveness in reducing liver size, few studies could link the shrinking of the liver to reduction in post-operative complications and/or improved patient outcome. In addition, compliance may become problematic when severely restrictive diets need to be followed for an extended period of time (Colles et al., 2006:304-311; Edholm et al., 2011:345-350)

To date, no systematic review have been published to explore the benefits of using a preoperative restricted energy diet protocol to reduce liver size and liver fat content in obese patients, scheduled for bariatric surgery. Before this practise can be considered as standard procedure, convincing evidence is needed to show that a clinically relevant reduction in liver size can be achieved in a time period that does not influence patient compliance and acceptance. This review was undertaken to appraise and compare results of individual clinical trials in order to provide evidence in support of this practise. As secondary objectives, researchers aimed to identify the optimal time period of liver-shrinking diets to achieve clinically relevant reductions; and to identify the effect of restricted energy diets on incidence of postoperative complications, surgical difficulty and operating time.

3.1.3 Methods

Literature search strategy

Following approval by the University of the Free State Ethics Committee, a systematic literature search was conducted from April to June 2013 in a two-step approach. Initially, electronic bibliographic databases were screened by means of a systematic on-line literature search. Databases included EBSCO (including MEDLINE), Cochrane (Cochrane Database of Systematic reviews, Cochrane controlled trials register), Pubmed, ScienceDirect, and Controlled Trials Registry using the following search terms:

- [very low calorie diet(s) OR low calorie diet(s) OR low energy diet(s) OR very low energy diet(s) or restricted energy diet(s)]
  AND

- [bariatric surgery OR laparoscopic gastric bypass OR Roux-en-Y gastric bypass OR gastric banding OR sleeve gastrectomy OR biliopancreatic diversion]
  AND
- [liver volume OR liver size OR liver fat OR hepatic volume OR (intra)hepatic fat OR hepatic steatosis OR liver steatosis]
  AND/OR
- [(post)operative complication(s) OR (post)operative outcome OR intra-operative outcome OR operating time OR blood loss OR surgical difficulty OR surgical complexity OR patient compliance OR patient adherence OR patient acceptability]

In step two of the search strategy, reference lists of all identified studies were manually checked to identify other possible sources of relevant information. Figure 3 shows a schematic representation of the procedure followed to search, screen and select studies.

The electronic search was initially done by one reviewer. A second reviewer followed the same procedure to confirm if all applicable studies have been identified. All randomized and non-randomized publications on the study topic, published in peer-reviewed journals, were included. No unpublished studies were included, and abstract reports were only included if reported data was sufficient according to the inclusion criteria in Table 3.1.

Table 3.1 Inclusion and Exclusion criteria	
Inclusion criteria	Exclusion criteria
Study design: Randomized and non-randomized trials related to the study objective, published from January 1980 to December 2012 in peer-reviewed journals. **Intervention:** Studies reporting on obese (BMI ≥ 30 kg/m^2) adults (≥ 18 years) scheduled for BS who were participating in trials evaluating the effect of preoperative LCDs or VLCDs on liver morphology and/or operative outcomes. **Outcome measures:** Studies that reported on at least one of the following measures: • reduction in liver size and/or liver fat content; • intra-operative factors (operating time, blood loss, and surgical difficulty/complexity); • postoperative complications; and • patient compliance (adherence and/or acceptance).	• Studies reporting on non-obese population; or population other than those scheduled for bariatric surgery; • studies that include patients younger than 18 years of age; • studies reporting on a food based self-selection diet (even if it was energy restricted); • studies published outside of the stipulated time period; • animal studies; and • Language other than English

Screening, selection and data extraction

A screening and data extraction form was used to evaluate the studies initially identified by the literature search. In the first section of the form, studies were screened based on abstract and type of publication. Studies were excluded if the abstract clearly indicated that it was irrelevant to the study objective; or irrelevant publication type (any type of publication other than an intervention study, were eliminated). When eliminated at this level, publications were not listed as excluded. Remaining studies were screened based on the second section of the form dealing with eligibility criteria. If it did not meet the necessary criteria, studies were listed as excluded and reason for exclusion was documented (Table 3.2.). Data were then extracted from all remaining studies based on the third and fourth sections of the form which dealt with research method, sample characteristics, intervention and outcome measures.

Though the screening and data extraction process was undertaken by the principle investigator only, uncertainties were discussed and resolved to ensure agreement amongst all reviewers.

Risk of bias

To ascertain validity of eligible studies, the principle reviewer evaluated the quality of each included study. The assessment form developed as part of the protocol could not be used, since the literature search revealed that more than 50% of trials included were non-randomized trials. The original form was developed to assess randomized trials since it was expected that most trials would be based on randomized intervention, thus this form was not applicable. Since the potential bias is greater for non-randomized studies compared with randomized trials it was necessary to change the evaluation criteria to an instrument specifically designed for assessing methodological quality of non-randomized studies. In this regard, guidelines published by the Cochrane Collaboration (Reeves et al., 2011: online) was consulted for an appropriate assessment tool. Though these guidelines do not state a specific recommendation on appropriate method to assess such studies, there is indication that the Newcastle-Ottawa Scale or the Downs and Black questionnaire may be modified to suit the study objective. For the purpose of this review, the Newcastle-Ottawa Scale would not be suitable, since most included studies did not have a control group. Therefor the Downs and Black instrument was used as a guide to modify the original quality assessment form (Refer to Appendix D for a copy of the adapted assessment form).

3.1.4 Results

Literature search and data selection

The initial electronic literature search yielded 29 studies, of which three were immediately excluded based on topic. Through screening of the reference lists, four more studies were identified.

The 30 publications were screened and 18 were excluded based on level one screening. Of the remaining 12 trials, three were excluded based on level two screening. One more potential publication was identified as cited in the article by Rao et al. (2005). However, the publication details of this specific study were not included in the reference list though it was referred to in the discussion section. A search was done, using Google search engine, using the surname (Toouley) and a combination of search terms, but the outcome was unsuccessful.

Nine publications were included in this review, of which one in abstract form (the abstract was accepted based on the fact that it reported on relevant data). From a total of nine, six studies reported on data related to the primary objective (assessing the effect of pre-operative restricted energy diet on liver volume and/or liver fat content), and five on data related to the secondary objectives (assessing the effect of pre-operative restricted energy diet on intra- and post-operative outcome and patient compliance).

Table 3.2 provides a summary of studies that were excluded based on level two screening and Table 3.3 summarizes characteristics of the nine publications that were included in this review.

Reviewers initially attempted to analyze data of the six trials reporting on liver volume and/or fat content by means of a meta-analysis. This was however not possible for several reasons. Main reasons included variations in treatment period (ranging from two weeks to 12 weeks) and variations in data reporting (mean versus median values). Though it would have been possible to contact original researchers to obtain data based on two-week period intervals as well as raw data on reduction in liver volume and fat content, it was decided that for the purpose of this review, data analysis would be done in the form of a narrative review only.

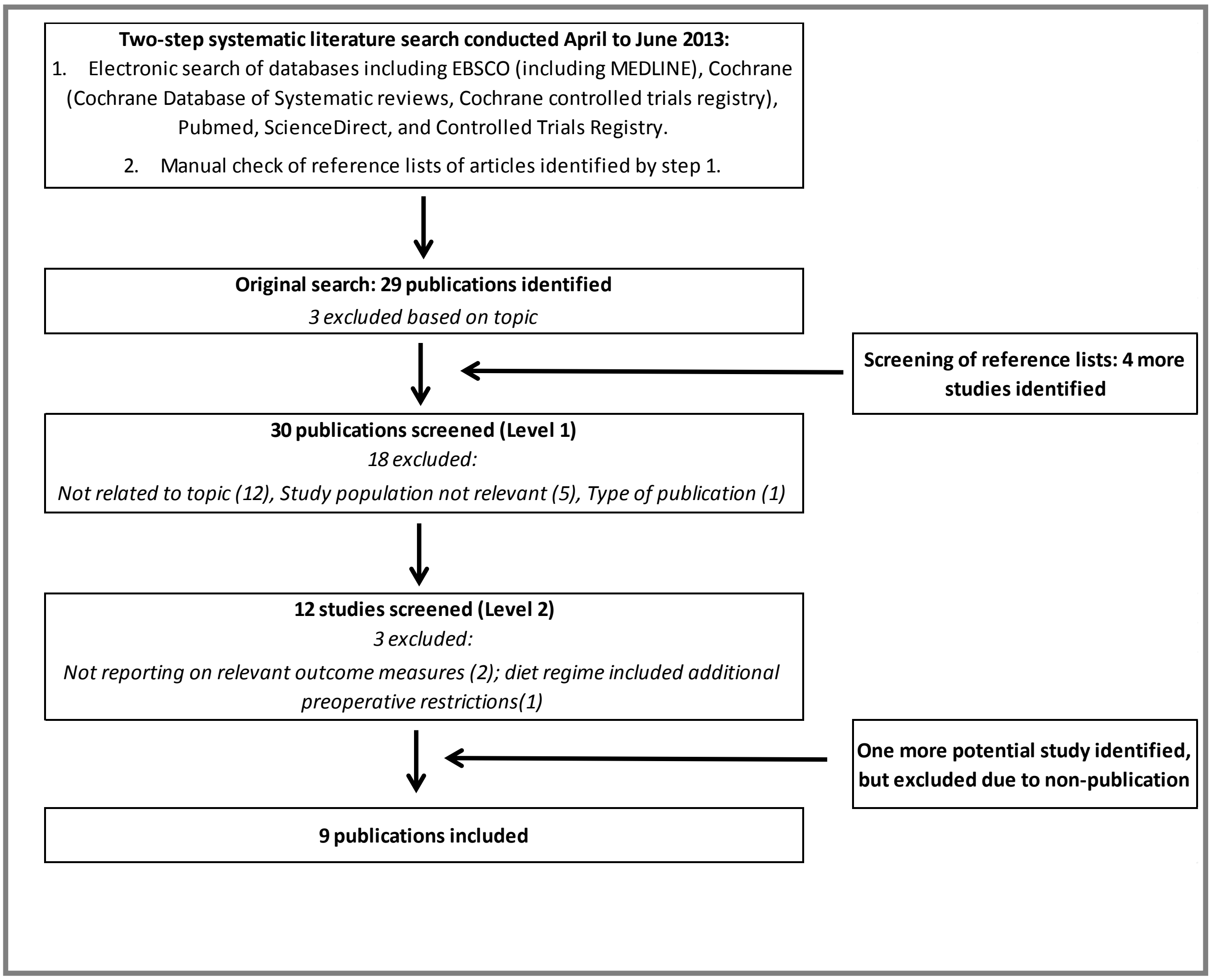

Figure 3. Flow chart representing the search, screening and selection of studies.

Table 3.2. Summary of studies excluded at level two screening.

Author reference	Description and reason for exclusion
Andersen et al., 1987.	Study objective: To compare horizontal and vertical banded gastroplasty to their effectiveness and side-effects in patients pre-treated for morbid obesity with a very-low-calorie formula diet. Reason for exclusion: Did not report on relevant outcome measures.
Benjaminov et al., 2007.	Study objective: To determine the effect of a four-week pre-operative low carbohydrate diet on liver volume and surgical complexity. Reason for exclusion: No restriction on dietary calorie intake.
Carbajo et al., 2010.	Study objective: To determine the effectiveness and tolerance of a balanced energy formula diet in comparison to low calorie regular diet. Reason for exclusion: Additional period of food-based restricted diets followed intervention for an additional eight days prior to surgery.

Study characteristics and quality

Assessment of studies based on the modified Downs and Black questionnaire, classified all nine studies as either moderate or high risk of bias. Potential biases are likely to be greater for non-randomized studies compared with randomized ones, and since only three of nine publications were based on the latter, results were interpreted with caution. These three studies reported only on data relevant to the secondary objectives. This means that all studies, from which data were extracted to fulfil the primary objective of this review, were non-randomized and had no control group. This increases the risk of biased reporting and limits the value of the data-analysis outcome.

A further limitation to individual study quality is that sample size was generally small. Only two studies included ≥ 130 patients (Dambrauskas et al., 131 patients; and Van Nieuwenhove et al., 294 patients). These two studies were not related to meeting the primary objective. The six publications from which data were obtained to meet the primary research question all had very small sample size (146 patients in total). This emphasizes again the limited value of the results of the systematic review.

In terms of the study population, studies reported that selection of participants was based on either consecutive patients or recruitment/invitation from waiting list. Only one publication mentioned a randomized recruitment method that was followed (Rao et al., 2005). It is not clear to assess whether those included by means of simple recruitment or by invitation were truly representative of the general obese population. It may be possible that those invited or recruited were more motivated to achieve success, which would cause better dietary compliance and hence potentially better results.

Only three studies reported on blinding or attempted blinding of those measuring the main outcomes (Van Nieuwenhove et al.,2011 Rao et al.,2005 and Fris et al., 2004). Most studies that reported on surgical difficulty used subjective methods to collect information, which increases the risk of reporting bias.

Patient characteristics

In accordance with the study objective, only studies that included obese participants were included, thus all patients in the individual trials had a BMI of > 30kg/m^2. Patients of various age groups (>18 years) were included. Both males and females were included, except in the trials conducted by Edholm et al., 2011 and Kullberg et al., 2011. These trials included only female subjects, in an attempt to reduce gender impact. There was no consistency in included trials with regard to patient co-morbidities.

Diet restriction

Not all publications indicated the exact amount of calories that was consumed as part of the pre-operative restricted energy diet plan. The lowest intake reported was 450 kcal per day (Rao et al., 2005) From this minimum, intake ranged up to a maximum of 1900 kcal per day (Van Nieuwenhove et al., 2011). Type of commercial product used to replace food intake was stated in eight of the trials, and included Optifast® (Nestlé Health Science S.A., five studies), Modifast® (Inpolin AB, two studies), and Nuvista® (Nutricia trading division of SHS International, one study). In some trials the commercial product was used as sole source of nutrition to replace total dietary intake, in other studies only some meals were replaced. Most studies allowed the intake of low-calorie food items and calorie-free drinks to be used in conjunction with the meal replacement diets. The macronutrient distribution of the pre-operative diet was not mentioned in any of the publications.

The duration of pre-operative restricted energy diets varied from the shortest period of two weeks to the longest of 12 weeks. Other studies report on the effect of a four-week or six-week pre-operative diet.

Surgical procedure

Type of procedure included adjustable gastric banding and gastric bypass procedures. All procedures were done laparoscopically.

Table 3.3 provides a summary of trials that were included.

Table 3.3. Study characteristics of included trials as reported in included publications

Author reference	Sample characteristics (baseline)				Procedure	Preoperative diet	
	n#	BMI§	Age§	%male		Duration	Description*
Brody et al., 2011	21	44.5±3.9	47.6±9.5	14	Laparoscopic bariatric surgery	4 weeks	Nuvista 2 meal replacements per day as part of a low calorie diet. Total energy intake 1000-1800 kcal/day
Colles et al., 2006	37	47.3±5.3	47.9±9.1	59	Laparoscopic adjustable gastric banding	12 weeks	Optifast 456-680 kcal/day
Dambrauskas et al., 2010	131	45.3 ± 6.7 Control: 43.2 ± 8.6	38±8 Control: 39±9	27.5 Control: 35.5	Laparoscopic Roux-en- Y gastric bypass	2 weeks	Optifast 800 kcal/day
Edholm et al., 2011	33	42.9±3.02 Control: 40.8±3.63	34.3±7.53 Control: 42.2±7.05	0	Laparoscopic gastric bypass	4 weeks	Modifast 800-1100 kcal/day
Fris, 2004	50	Median 47±6.8 (range 34.5-62)	Median 41 (range 25-74)	10	Laparoscopic adjustable gastric banding	2 weeks	Optifast 3 sachets per day to replace 3 meals (@152 kcal per sachet)
Kullberg et al., 2011	15	42.9±3.02	34.7±7.88	0	Laparoscopic gastric bypass	1 month	Modifast Actual intake: 959±146 kcal/day
Lewis et al., 2006	23	Median 44 (range 40-51)	Median 50 (range 34-57)	5.5	Laparoscopic adjustable gastric banding	6 weeks	Optifast 450-800 kcal/day
Rao et al., 2005	10	47 Control: 41.6	Not specified	Not specified	Laparoscopic adjustable gastric banding	6 weeks	Brand not specified 3 sachets per day @ 152 kcal per sachet Protein 46%, CHO 40%, Fat 14% of total energy
Van Nieuwenhove et al., 2011	273	43.4±10 Control: 43.3±8.2	39.7±9.5 Control: 30.4±9.5	29 Control: 30	Laparoscopic Roux-en- Y gastric bypass	2 weeks	Optifast Actual intake: 1906 kcal/day

Number of patients recruited to participate. § Mean value unless otherwise stated. * Calories refer to planned intake, unless otherwise stated as actual intake.

CHO: carbohydrates. BMI: body mass index

Study outcomes

Reduction in liver volume

Six studies reported on the effect of an acute pre-operative restricted energy diet (VLCD or LCD) on liver volume, of which three studies also reported on liver fat content. All six trials in which liver volume were monitored, reported a significant decrease in comparing the baseline data with that obtained after a period of following a VLCD or LCD. This period ranged between two and 12 weeks, making it difficult to directly compare results. Different measurement techniques were used, some more sensitive than others to reveal acute changes. A summary of the findings is presented in Table 3.4.

Only one study reported effects of a two-week pre-operative liver-shrinking diet plan (Fris, 2004). Reported reduction in liver volume (of the left lobe only) after two weeks, was 5.1% (95% CI 3.3-6.8). There is no other study reporting on two–week outcome data to compare this finding with. Though the study performed by Colles et al. (2006) employed a 12-week diet plan, the authors reported two-week data for a subgroup of patients with an initial large liver volume. The two-week data indicated an estimated 22% reduction which is much higher than the data reported by Fris, but this cannot be directly compared to Fris's finding since it represented total liver volume and Fris only measured the left liver lobe. The left liver lobe differs from the right lobe in that it is smaller and has more capsule per unit area, however there is minimal variability in steatosis between right and left liver lobes (Larson et al., 2007:1329), therefor a decrease in fatty deposition should affect both lobes alike. As one would expect to see proportionally similar effects to both liver lobes, this extreme difference is unexplained, unless it related to initial liver volume. Notwithstanding the differences, the data by both Fris (2004) and Colles et al. (2006) indicate significant reduction in liver volume after a short period of two weeks VLCD. Both studies also reported a correlation between reduction in liver size and decrease in body weight or BMI.

Three studies reported on the effects of a four-week pre-operative diet. Brody et al., (2011) reported a significant mean reduction of 43.4±17.2% of the left segment of the liver following four weeks of a restricted energy diet plan. This is much higher compared to the two other trials (Edholm et al., 2011 and Kullberg et al., 2011) both reporting a 12% decrease in liver volume. Similar to the above scenario, a substantial difference (43% vs. 12%) could not be explained. Different measuring techniques were used (ultrasound used by Brody et al., and magnetic resonance imaging used by Edholm et al. and Kullberg et al.) and these could have impacted on the sensitivity to measure any change, but the difference is most likely related to initial liver size. Unfortunately it was not possible to establish whether the initial liver volume could be responsible for the variation, since baseline volume were reported in some trials in total while other only measured volume of the left lobe.

The remaining studies reported on effects after a six-week restricted energy diet (Lewis et al., 2006) and a 12-week restricted energy diet (Colles et al., 2006). Results indicated significant reduction in liver volume: 14.7% and 18.7% respectively. Subgroup analyses were done in both trials of those patients with a higher baseline liver volume. Reported decrease was higher for the subgroup (16.3% after six weeks and 28.7% after 12 weeks) confirming that more pronounced effects can be expected for those with larger liver volumes.

Reduction in liver fat content

Three studies reported on the effect of preoperative restricted energy diet on liver fat content (Edholm et al., 2011; Kullberg et al., 2011; Lewis et al. 2006). Measurement techniques were comparative, all reported using ^{1}H-spectroscopy to determine hepatic fat content.

Results from the two trials that investigated the effects of four-week preoperative energy restriction reported a 40% decrease in liver fat content; while a slightly higher reduction of 43% was reported after six weeks of diet restriction.

By means of subgroup analysis, Lewis et al. (2006), reported that reduction in hepatic fat content was only observed in patients with a large baseline liver volume indicative of fatty liver. For this group, the reduction was found to be 72.5% whereas 0% decrease was reported for those with normal size liver.

Only one study differentiated between liver fat percentage and liver fat volume (Kullberg et al., 2011). This is an important differentiation, since liver size or volume is a variable that will influence liver fat percentage. If the liver volume decrease due to reasons other than a reduction in fat content (such a depletion of glycogen stores), the fat percentage will increase even though the actual amount of fat might remain constant. A decrease of about 10-40% in liver volume can be expected when glycogen stores become depleted in patients who do not have hepatic steatosis prior to VLCD (Colles et al., 2006:310; Lewis et al., 2006:700). This means that, even in patients who do have fatty liver, actual reduction in fat content may be higher than reported when expressed as a percentage of the liver volume.

Table 3.4. Results of included trials on reduction in liver volume and liver fat		
Author reference	**Summary of findings related to liver volume**	**Summary of findings related to liver fat content**
Brody et al., 2011	Mean reduction of 43.4% Measured by ultrasonography (only left lateral segment measured). Percentage of volume reduction did not correlate with initial liver volume or with initial body weight or BMI.	N/A
Colles et al., 2006	Mean reduction of 18.7% for all patients; and 28.7% for subgroup of 9 patients. Measured by CT planimetric technique for all patients and by MR for subgroup of 9 patients. Overall the decrease in liver size was predicted by decrease in body weight and by initial liver volume.	N/A
Edholm et al., 2011	Reduction of 12% Measured by MR.	40% decrease in liver fat content. Measured by ^{1}H-spectroscopy.
Fris, 2004	Mean reduction of 5.1% Measured by Duplex ultrasound (only left lobe of liver measured). Change in liver volume was not related to loss of body fat, but was related to reduction in BMI.	N/A
Kullberg et al., 2011	Reduction of 12% Measured by MR.	40% decrease in liver fat content. Measured by ^{1}H-spectroscopy.
Lewis et al., 2006	Reduction of 14.7% for all patients; and 16.3% for subgroup of 11 patients Measured by MR. Change in liver volume predicted by change in liver fat.	43% decrease in liver fat content for all patients; and 72.5% reduction in subgroup of 11 patients Measured by ^{1}H-spectroscopy.
BMI: Body mass index; CT: computed tomography; MR: magnetic resonance		

Intra- and postoperative benefits

All trials reported significant decreases in liver fat and volume. In an attempt to establish if this relates to a decrease in intra- and/or postoperative benefits, reviewers evaluated effects on surgical difficulty, intra-operative blood loss, and the occurrence of post-operative complications.

In terms of surgical difficulty, the assumption is that a smaller-sized liver will increase visibility of anatomic structures and junctions, thus reducing the complexity of the procedure for the surgeon. Four studies reported on surgeon-perceived difficulty of which all found that the pre-operative energy restriction was effective to reduce surgical effort needed (Edholm et al., 2011; Lewis et al., 2006; Rao et al., 2005; Van Nieuwenhove et al., 2011). Recorded benefits included: improved exposure of the hiatal region; better/easier surgical access; and an improved ability to retract the liver. It is important to note that for three out of four trials, the surgeons who reported on the degree of difficulty were not blinded to the preoperative management; and that the data were obtained using subjective scoring methods. Only one study reported on objective and blinded surgeon feedback (Van Nieuwenhove et al., 2011). In this randomized trial, both subjective and objective data were obtained from blinded surgeons. Data were collected by means of a visual analogue scale (subjective), and by grading of liver lacerations (objective) to indicate surgical difficulty. Subjectively, the surgical difficulty was significantly lower for those subjects who received a VLCD for two weeks prior surgery; however there were no difference when objective data were compared. The study by Dambrauskas et al. (2010), available in abstract form, also reported that no difference was observed in liver lacerations between a group of patients who received preoperative VLCD and a control group. Thus, there is no firm indication that liver shrinking preoperatively brings about a true and objective benefit to the effort required by the surgeon.

To assess potential patient benefit, researchers looked at operating time and intra-operative blood loss. Two publications reported on operating time (Dambrauskas et al., 2010 and Van Nieuwenhove et al., 2011). Neither reported an overall reduction in operating time, though the abstract publication of Dambrauskas reported that operating time decreased in a subgroup of patients with BMI > 48kg/m^2, from 96±18 minutes to 80±15 minutes for those patients who underwent preoperative diet restriction. It is not clear why operating time decreased specifically in this group of patients since the estimated surgical difficulty was reported to be the same compared to the control patients.

With respect to intra-operative blood loss, Dambrauskas et al. (2010) and Van Nieuwenhove et al. (2011) both reported no difference in blood loss for patients who followed a preoperative reduced energy diet versus those who did not. This is not surprizing since both these trials also found no reduction in liver injury intra-operatively. The only other trial that reported on blood loss, was the study by Edholm et al. (2011) where 33 patients received preoperative VLCD and were compared to 18 control patients. In this trial, reported blood loss was higher in the group who followed diet restriction (130±41.4ml compared to 75±42.9ml). The authors did not state any reason for this finding, however mentioned that it was based on anaesthetist estimation. Estimating blood loss during laparoscopic surgery is difficult and to a great extent subjective. It is based on a combination of measures such as content in suction devices and visual estimation.

To determine post-operative benefit, 2 trials included information about 30-day patient follow-up. Edholm et al. (2011) reported that patients who received preoperative diet restriction were more likely to develop anastomotic ulcers in the 30-day post-operative period (three out of 15 patients on preoperative VLCD versus one out of 18 patients in control group); and questioned athe practice of operating on patients who are in catabolic state after severe energy restriction. In contrast, Van Nieuwenhove et al. (2011) reported a significant reduction of post-operative complication in a much larger study with a total of 294 patients, as reported by a nurse who was blinded to pre-operative intervention. Complications most commonly experienced by patients in the control group included wound infection, pyrexia of unknown origin and pulmonary infection.

Patient acceptance and compliance

Studies reported various measures to determine compliance and acceptance of commercial restricted diet preparations. Overall, compliance and tolerance was reported to be satisfactory. Product acceptance was influenced by the duration of restriction, and decreased over time. Colles et al. (2006) suggests a maximum duration of eight weeks and Edholm et al. (2011) states that the duration should not exceed four weeks to ensure satisfactory compliance.

3.1.5 Discussion

As the hepatic manifestation of metabolic syndrome, NAFLD is affecting a large proportion of obese individuals who undergo bariatric surgery. As the prevalence of obesity is on the increase, a parallel increase in NAFLD can be expected, and thus it is inevitable that the number of obese patients with fatty liver undergoing bariatric surgery in the future will increase. The prevalence of a large fatty liver complicates surgery and is the most common reason for conversion from laparoscopic to open surgery (Schwartz et al., 2003:734; O'Brien et al., 2002:652). As compared to open surgery, laparoscopic surgery is associated with less pain, reduced risk of incisional hernia, better postoperative pulmonary function and shorter hospital stay (Edholm et al., 2011:345-346). Data revealed that preoperative energy restriction was associated with significant reductions in both liver volume and fat content, and none of the trials included in this review reported the need to convert to open surgery. All procedures were performed laparoscopically. This finding can be supported by what is currently known about the metabolic effects of long-term energy restriction: when glycogen stores are depleted, oxidation of FFA in the liver mitochondria is increased to produce ketone bodies as alternative source of fuel used by body cells. The increase in oxidation of fat decreases the amount of fatty deposit in the liver, which in turn affects liver size, which is is confirmed by findings of studies that measured both liver volume and fat content.

It is however not clear whether these changes to the liver morphology translate to any benefit – whether to the surgeon or to the patient. That is, despite the assumption that it decreases the likelihood that open surgery would be needed. Data obtained from studies that reported on outcome measures related to surgical complexity and operative outcomes, are not convincing. Two studies could not find any change in the perceived difficulty of laparoscopic performed bariatric surgery. Those who reported benefit, based their finding on subjective reporting by surgeons, who were not blinded to pre-operative treatment. Thus, although a reduction in the operative complexity seems to be a logic consequence to liver shrinking, it remains questionable. The only benefit reported objectively and through blinded research, is a reduction in 30-day post-operative complications.

The fact that there is no real indication that pre-operative liver shrinking brings any intra-operative benefit, is an unexpected finding since one would assume if the visibility is better, that the procedure would be quicker to complete and that there would be less blood loss related to liver traction. Two reasons have been considered to explain this. First, the experience of the surgeon could potentially outweigh the benefits of liver shrinking. Bariatric surgery is mostly performed by skilled surgeons in high-volume bariatric units. It is possible that the surgeons who were involved in the trials were highly skilled so that they managed to handle all situations well without necessarily needing more time or encounter more blood loss when dealing with patients under conditions of poor visibility due to hepatomegaly. None of the studies except one (Van Nieuwenhove et al.) mention the skill level or experience of the surgeons involved. It is possible that decreasing the size of a large fatty liver may benefit a less-skilled surgeon more. Secondly, one need to consider the assumption that patients that was included in the trials that reported on intra-operative benefits, had NAFLD. Only three studies reported on intra-operative outcomes (operating time and blood loss). Of these, two studies did not measure liver volume or fat content at baseline thus it is not clear what percentage of patients truly presented with large, fatty liver when the diet restriction was initiated. The estimated incidence of NAFLD in the obese population is 74% (Hafeez and Ahmed, 2013:2), therefore it is likely to assume that patients who were evaluated had NAFLD. This however remains an assumption.

A concern related to preoperative diet restriction is performing surgery on a catabolic patient, which may increase post-operative morbidity. Obese patients may not have a good nutritional status at the time of surgery as nutritional deficiencies may develop when an individual have an overconsumption of energy-dense, nutrient poor food. In addition, nutrient requirements may increase as a consequence of obesity and its co-morbid conditions (Rickers and McSherry, 2012:42). A poor pre-operative nutritional status may delay wound healing and overall recovery rate while also increase infection risk. The fact that only two studies reported on 30-day outcome, makes it difficult to draw firm conclusions in this regard especially since the results of the two studies are conflicting. It is unlikely that commercial LCDs or VLCDs will result in the development of nutritional deficiencies since these products are designed to provide 100% of the daily requirement for vitamins and minerals. A sufficient supply of protein helps preserve lean body mass and therefore, if anything, the nutritional status of some patients may actually improve. Post-operative outcome will also depend on a number of other factors, so in order to really answer this question a randomized, controlled trial where all aspects of care are similar except for preoperative energy restriction is required. In this regard it would be interesting to follow future developments of Enhanced Recovery After Surgery (ERAS) protocols. When ERAS is applied appropriately, enhanced recovery protocols are associated with significant reduction in post-operative complications as well as shorter hospital stay (McFie, 2013:4). The development of bariatric surgery-specific ERAS protocols may improve post-operative outcome and duration of hospital stay.

In consideration of the optimal time period that can be recommended, it seems as though a period longer than two to four weeks will not result in a greater reduction in liver fat. Results on liver fat reduction documented after four weeks dietary restriction correlates well with that reported following six-week dietary restriction. The fact that 80% of the expected reduction in liver volume after a 12-week preoperative diet occurred within the first two weeks, supports the recommendation that two to four weeks of pre-operative energy restriction should be sufficient to bring about the desired effects. Longer periods may impact on patient acceptance and therefore compliance. Although compliance was overall good, one cannot ignore the fact that in some studies sample selection was based on invitation to participate. Patients who accepted the invitation may have been more motivated to comply to study protocol. On the other hand, Van Nieuwenhove et al. assigned patients to VLCD or control group by means of randomization and still reported good compliance rate of 90% in the VLCD (n=149) group.

Limitations of this systematic review include the small sample size and varying research design of individual studies. The value of this review could have been increased if reviewers contacted the corresponding authors of individual trials in an attempt to obtain data necessary for a meta-analysis. As this review was done in completion of a post-graduate degree, time limitations applied which did not allow contacting authors to obtain data that could potentially provide statistical power.

3.1.6 Conclusion and Recommendations

This study was undertaken to establish if there is sufficient evidence to support the practice of pre-operative liver shrinking diet plans. The setting in which individual trials were performed; outcomes that were measured; and how it was measured and reported, makes it impossible to state a recommendation for or against the use of preoperative restricted energy diets for obese patients undergoing bariatric surgery. While it is unlikely to cause harm, there is no true reported benefit in terms of intra- or postoperative outcomes. Only one study reported benefit in terms of 30-day post-operative complication rate. Albeit a well-designed blinded randomized trial, it is not sufficient to recommend the use of preoperative restricted energy diets as standard procedure. The only recommendation that can be made confidently is that well-designed randomized, blinded trials are needed to truly establish the value of preoperative liver shrinking. Ideally trials should randomly recruit patients in established centres where skilled surgeons operate. Patients should be randomly assigned to a pre-operative treatment or control group, and researchers should be blinded to treatment. Where possible, objective reports on surgical complexity should be recorded, and follow-up to assess post-operative complications should be done by a blinded, independent health care practitioner.

In conclusion, preoperative restricted energy diets in the form of commercial LCD or VLCD plans may significantly reduce liver volume and fat content in obese patients when used for an optimal period of two to four weeks. There is no evidence to link a decrease in liver size to benefits in terms of decreased surgical complexity, surgical time or blood loss. Patients may however experience improved 30-day outcome in terms of fewer complications.

3.1.7 Conflict of interest

The author is a paid employee of Nestlé Health Science S.A., global manufacturer and supplier of Optifast® Very Low Calorie Diet.

3.1.8 Reference list

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3.2 Article prepared for publication submission

The original article was adapted according to suit the requirements for publications as per author instructions of the international journal, Obesity Surgery. Refer to Appendix E for manuscript requirements and author instructions of this journal. For this part of the mini-dissertation, the format used for numbering of tables and figures stand separate, and the format of the references different than the rest of this manuscript; in compliance with journal requirements. See Appendix F for the required title page for the article (as per manuscript requirement).

3.2.1 Abstract

Introduction

Increased liver volume associated with liver steatosis, increases surgical complexity of bariatric procedures. Pre-operative restricted energy diets have been used successfully in small individual trials to achieve reduction in liver volume and fat content. This review was undertaken to report on the effectiveness of pre-operative restricted energy diet programmes to induce liver-shrinking and evaluate the effect thereof on intra- and postoperative outcomes.

Methods

a systematic literature search was undertaken in a two-step approach to identify studies published between 1980 and 2012 related to the objective. Initial search yielded 33 studies, of which 24 were excluded. Trials had to report on at least one of the following measures: liver size, liver fat, surgical difficulty, operating time, blood loss, post-operative complication and patient compliance.

Results

Nine trials were included; all with moderate to high risk of bias. Six studies reported that preoperative energy restriction significantly reduces liver volume and liver fat content. Studies that reported on intra-operative factors could not confirm that liver shrinking is of benefit to the surgeon or to the patient. One study indicated that patients may have better 30-day postoperative outcome. The optimal time indicated for pre-operative energy restriction is two to four weeks.

Conclusion

Preoperative restricted energy diets used for a short period before surgery significantly reduce liver volume and fat content in obese patients. Such programmes may improve patient outcome.

Randomized, blinded trials are needed to establish benefit in terms of decreased surgical complexity, operating time and blood loss.

3.2.2 Introduction

While the prevalence of obesity is rising across the world, bariatric surgery procedures are increasingly performed [1]. Besides the fact that bariatric surgery is now recognized as the most successful approach to obesity management, reports are also indicating that bariatric surgery improves glycaemic control and can potentially reverse type 2 diabetes mellitus [2]. Of concern to operating surgeons, is the high incidence of an enlarged liver presenting as non-alcoholic fatty liver disease (NAFLD). Hepatomegaly caused by liver steatosis obscures anatomical markers, reduces operating space and has been cited as one of the main reasons for the need to convert from laparoscopic to open procedure [3]. Managing liver morphology prior to surgery may therefore impact on surgical complexity and outcome, especially when laparoscopic procedure is used.

Currently, bariatric surgery is reserved for patients with a body mass index (BMI) ≥ 40 kg/m^2; or BMI ≥ 35 kg/m^2 with significant co-morbidities. Surgery for individuals with lower BMI and co-morbidities is under investigation [9]. For this patient group the term *metabolic surgery* has emerged, and describes bariatric procedure intended to treat type 2 diabetes mellitus in individuals with BMI 30-35 kg/m^2 [4].

The 2013 Clinical Practise Guidelines for Bariatric Surgery [4] address preoperative approaches to reduce liver volume and state that reduction in liver volume may help to improve the technical aspects of surgery. However, the guideline was downgraded due to inconsistent results. This emphasizes the need for convincing evidence indicating that a clinically relevant reduction in liver size can be achieved, and that such reduction positively impacts on the outcome of surgery.

Restricted energy diets (very low calorie diets (VLCDs) and low calorie diets (LCDs)), have been used successfully in individual trials to reduce weight, abdominal fat, liver size and liver fat content in the preoperative phase [5,6,7]. Despite the reported effectiveness in reducing liver size, few studies could establish a link to reduction in post-operative complications and/or improved patient outcome. In addition, compliance may become problematic when severely restrictive diets need to be followed for an extended period of time.

To date, no systematic review has been published to explore the benefits of using a preoperative restricted energy diet protocol to reduce liver size and fat content in obese patients scheduled for bariatric surgery. This review explores literature relating to the effect of preoperative diet restriction to establish effects on liver volume and fat content in order to provide evidence in support of this practise. As secondary objectives, this review aim to identify the optimal time period for pre-operative programmes and to identify the effect thereof on intra- and postoperative complications.

3.2.3 Methods

Following approval by the University of the Free State Ethics Committee, a systematic literature search was conducted (April to June 2013). Electronic bibliographic databases were screened by an on-line literature search. Databases included EBSCO (including MEDLINE), Cochrane, Pubmed, ScienceDirect, and Controlled Trials Registry using pre-identified search terms. Reference lists of identified publications were manually screened to identify other sources of relevant information. Figure 1 shows a schematic representation of the procedure followed to search, screen and select studies.

A screening and data extraction form was used to evaluate all trials based on eligibility criteria (see Table 1). To ascertain validity, the quality of included studies was evaluated based on a modified version of the Newcastle-Ottawa Scale. This tool was chosen since most of trials included were non-randomized trials.

3.2.4 Results

Literature search and data selection

Electronic search yielded 29 studies, and four more were identified through manual screening. After excluding 21 studies based on level one screening, a further three were eliminated based on level two screening [8,9,10]. Finally, nine publications were included (one in abstract form) of which six studies reported on data relevant to the primary objective. A meta-analysis was not possible due to variations in treatment period and data reporting.

Table 2 summarizes characteristics of the nine publications that were included in this review [5-7, 11-16].

Study characteristics and quality

Quality assessment revealed a moderate or high risk of bias for all studies. Only three trials were randomized [13,15,16]. Individual sample size was generally small. Majority of studies reported participant selection based on either consecutive recruitment or invitation. Only three studies [6,15,16] reported on blinding or attempted blinding of those measuring the main outcomes.

Patient characteristics and diet intervention

Only studies that included obese, adult participants were included. There was no consistency with regard to patient co-morbidities. Pre-operative intake ranged from 450 to 1900 kcal per day, for a duration of two to 12 weeks. Type of commercial product used to replace food intake included Optifast® (Nestlé Health Science S.A., five studies), Modifast® (Inpolin AB, two studies), and Nuvista® (Nutricia trading division of SHS International, one study). In some trials the product was used as sole source of nutrition, in other studies only some meals were replaced. Most studies allowed the intake of low-calorie food items and calorie-free drinks to be used in conjunction with the meal replacement diets.

Surgical procedure

All procedures were done laparoscopically and included adjustable gastric banding and gastric bypass procedures.

Study outcomes

<u>Reduction in liver volume</u>

Six studies reported on the effect of an acute pre-operative restricted energy diet (VLCD or LCD) on liver volume, of which three also included data on liver fat content (Table 3). All six trials, reported a significant decrease in liver volume.

One study reported effects of a two-week pre-operative diet plan (Fris [6]). Reduction in liver volume (left lobe only) was 5.1% . In the study performed by Colles *et al* [11], two-week data was reported for a subgroup of patients with an initial large liver volume in which a 22% reduction (full liver volume) was reported. Three studies reported on the effects of a four-week pre-operative diet. Brody *et al* [12] reported a significant mean reduction of 43.4% (left lobe only) versus 12% (full liver volume) decrease reported by other trials [5,14]. It was not possible to assess why these differences were found. It is unlikely to be related to measurement of left lobe only versus full liver volume as there is minimal variability for steatosis between right and left liver lobes [17] and decrease in fatty deposition should affect both lobes alike. The differences might be related to initial liver volume and that a greater reduction can be expected for those with a larger baseline liver size. Remaining two studies reported on effects of a six-week and a 12-week restricted diet period [7,11]. Results indicated significant reduction in liver volume of 14.7% and 18.7% respectively. Subgroup analyses were done in both trials of those patients with a higher baseline liver volume. Reported decrease was higher for the subgroup (16.3% after six weeks and 28.7% after 12 weeks) confirming that more pronounced effects can be expected for those with larger baseline liver volumes.

Reduction in liver fat content

Three studies measured the effect of four to six weeks diet restriction on liver fat content [5,7,14] and reported significant reductions of 40-43% . By means of subgroup analysis, Lewis *et al* [7] reported that reduction in hepatic fat content was only observed in patients with a large baseline liver volume indicative of fatty liver (72.5% reduction).

Only one study differentiated between liver fat percentage and liver fat volume [14]. This is an important differentiation, since liver volume influence liver fat percentage – if the volume decrease due to reasons other than a reduction in fat content (such a depletion of glycogen stores), the fat percentage will increase even though the actual amount of fat might remain constant. A decrease of 10-40% in liver volume can be expected when glycogen stores become depleted in patients without steatosis [7,11].

Intra- and postoperative benefits

Four studies reported on surgeon-perceived difficulty, and all found that the pre-operative energy restriction was effective to reduce surgical complexity [5,7,15,16]. Unfortunately two factors limit this finding. First, in all but one trial the surgeons who reported on the degree of difficulty were not blinded to preoperative management; and secondly, reporting was based on subjective scoring methods. Only one study reported on objective and blinded surgeon feedback [16], and found that there was no difference in surgical difficulty comparing patients who followed preoperative diet restriction versus those who did not.

To assess potential patient benefit, two publications reported on operating time and blood loss [13,16]. Neither reported any overall change in operating time related to preoperative diet restriction, though Dambrauskas *et al* found that time decreased in a subgroup of patients with BMI > 48kg/m^2 (96±18 versus 80±15 minutes). In these two trials there were also no changes observed with respect to intra-operative blood loss. The only other trial that reported on blood loss, was the study by Edholm *et al* [5] in which reported blood loss was higher in the group who followed diet restriction (130±41.4ml *versus* 75±42.9ml). The reason for this is not clear, although the authors state that higher blood loss was estimated by anaesthetist only.

To determine post-operative benefit, two trials reported on 30-day patient follow-up. Edholm *et al* [5] reported that patients who received preoperative diet restriction were more likely to develop anastomotic ulcer and raises a question about operating on patients who are in a catabolic state after severe energy restriction. In contrast, Van Nieuwenhove *et al* [16] reported significant reduction in post-operative complications in a much larger study and by means of blinded reporting.

Patient acceptance and compliance

Different measures were used to determine compliance and acceptance of commercial restricted diet preparations. Overall, compliance and tolerance was satisfactory. Product acceptance was influenced by the duration of restriction which decreased over time.

3.2.5 Discussion

Preoperative energy restriction was associated with significant reductions in both liver volume and fat content. This could be the reason why conversion to open surgery was not necessary in any of the trials. Reduction in liver size and fat content is supported by what is currently known about the metabolic effects of energy restriction: In response to high glucagon and low insulin concentrations, oxidation of fatty acids within the liver is increased to produce ketone bodies as alternative fuel source. The increase in oxidation decreases the amount of fatty deposit in the liver, which in turn affects liver size. This is confirmed by findings of studies that measured both liver volume and fat content.

It is not clear whether these changes to the liver morphology translate to any benefit to the surgeon or to the patient. That is, despite the fact that it may decrease the likelihood that open surgery would be needed [5]. Data obtained from those studies that reported on outcome measures related to surgical complexity and operative outcomes, are not convincing since it is based on subjective and non-blinded reporting. Although a reduction in the operative complexity seems to be a logical consequence to liver shrinking, it remains unproven. The only benefit reported objectively and through blinded research, is reduction in 30-day post-operative complications.

The fact that there is no real indication that pre-operative liver shrinking brings any intra-operative benefit is an unexpected finding. Two reasons have been considered to explain this. First, the experience of the surgeon could potentially outweigh the benefits of liver shrinking. It is possible that the surgeons who were involved in the trials were highly skilled and managed to handle all situations well without needing more time or encounter more blood loss when dealing with patients under conditions of poor visibility due to hepatomegaly. Secondly, one need to consider the assumption of NAFLD in patients that was included in the trials that reported on intra-operative benefits. Only three studies reported on intra-operative outcomes and of these, two studies did not report on baseline liver volume or fat content - thus it is not clear what percentage of patients truly presented with large, fatty liver when the diet restriction was initiated. The estimated incidence of NAFLD in obese population is 74% [18] therefore it is likely to assume that most patients who were evaluated had NAFLD. This however remains an assumption.

A concern related to preoperative diet restriction, is performing surgery on a catabolic patient. Obese patients may present with poor nutritional status and nutrient deficiencies which may delay wound healing and overall recovery rate while also increase infection risk. The fact that only two studies reported on 30-day outcome, makes it difficult to draw any conclusions especially since the results of the two studies are conflicting. It is unlikely that commercial LCDs or VLCDs will result in the development of nutritional deficiencies since these products are designed to provide 100% of the daily requirement for vitamins and minerals. A sufficient supply of protein helps preserve lean body mass and therefore, if anything, the nutritional status of patients may actually improve.

In consideration of the optimal time period that can be recommended, results on liver fat reduction documented after four weeks diet restriction correlates well with that reported following longer periods. Colles *et al* [11] reported that 80% of expected reduction in liver volume after a 12-week preoperative diet occurred within the first two weeks. Two to four weeks of pre-operative energy restriction should therefore be sufficient to bring about desired effects. Longer periods may impact on patient acceptance and compliance.

Limitations of this systematic review include the small sample size and biased design of individual studies. The value of this review could have been increased by contacting the corresponding authors of individual trials to obtain data necessary for a meta-analysis.

3.2.6 Conclusion and Recommendations

This systematic review was undertaken to establish if there is sufficient evidence to support the practice of pre-operative liver shrinking diet plans prior bariatric surgery. The setting in which individual trials were performed; outcomes that were measured; and how they were measured and reported, varied greatly and renders it impossible to make a recommendation in this regard. An acute pre-operative period (two to four weeks) of LCD or VLCD can bring about significant reductions in liver volume and fat content. While the effect on liver morphology is clearly established, there is no objective data indicating benefit in terms of intra- or postoperative outcomes, except for possible reduction in 30-day post-operative complication rate. Randomized, blinded trials are needed to establish if liver-shrinking holds any additional intra- or postoperative benefits. Where possible, objective reports on surgical complexity should be recorded, and follow-up to assess post-operative complications should be done by a blinded, independent health care practitioner.

In conclusion, preoperative restricted energy diets in the form of commercial LCD or VLCD plans significantly reduce liver volume and fat content in obese patients when used for an optimal period of two to four weeks. There is insufficient evidence to link the decrease in liver size to benefits in terms of decreased surgical complexity, surgical time or blood loss. Patients may experience fewer complications at 30-day follow-up.

3.2.7 Conflict of interest

- A Els: Employee of Nestlé Health Science S.A., global manufacturer and supplier of Optifast® Very Low Calorie Diet.
- VL van den Berg: No conflict of Interest
- CM Walsh: No conflict of interest

3.2.8 Reference list

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3.2.9 Tables and images:

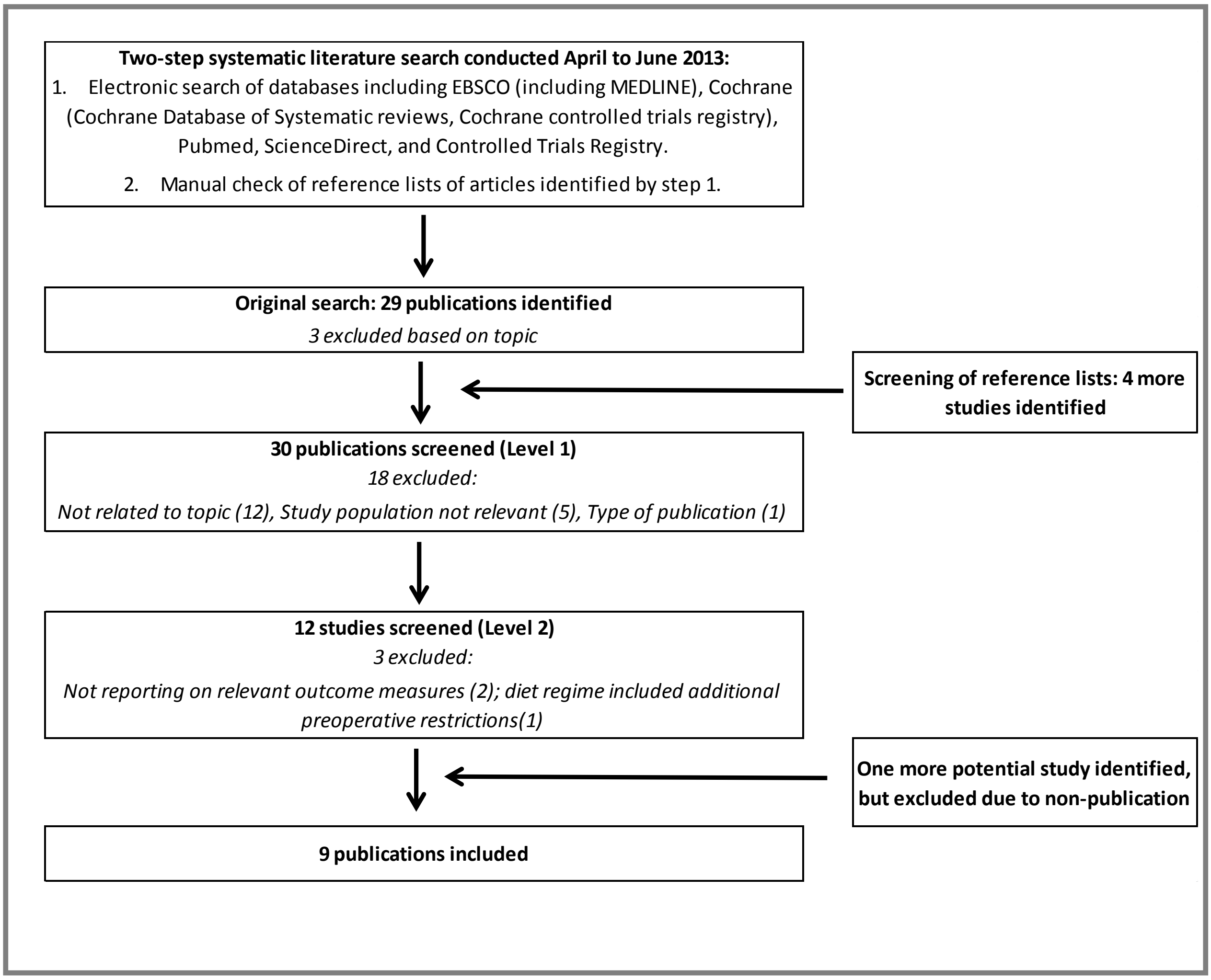

Figure 1. Flow chart representing the search, screening and selection of studies.

Table 1. Inclusion and Exclusion criteria	
Inclusion criteria	Exclusion criteria
Study design: Randomized and non-randomized trials related to the study objective, published from January 1980 to December 2012 in peer-reviewed journals. **Intervention:** Studies reporting on obese (BMI ≥ 30 kg/m^2) adults (≥ 18 years) scheduled for bariatric surgery who were participating in trials evaluating the effect of preoperative LCDs or VLCDs on liver morphology and/or operative outcomes. **Outcome measures:** Studies that reported on at least one of the following measures: • reduction in liver size and/or liver fat content; • intra-operative factors (operating time, blood loss, and surgical difficulty/complexity); • postoperative complications; and • patient compliance (adherence and/or acceptance).	• Studies reporting on non-obese population; or population other than those scheduled for bariatric surgery; • studies that include patients younger than 18 years of age; • studies reporting on a food based self-selection diet (even if it was energy restricted); • studies published outside of the stipulated time period; • animal studies; and • language other than English..

Table 2. Study characteristics of included trials as reported in included publications

Author reference	Sample characteristics (baseline)				Procedure	Preoperative diet	
	n[#]	BMI[ø]	Age	%male		Duration	Description*
Brody *et al* [12]	21	44.5±3.9	47.6±9.5	14	Laparoscopic bariatric surgery	4 weeks	Nuvista 2 meal replacements per day as part of a low calorie diet. Total energy intake 1000-1800 kcal/day
Colles *et al* [11]	37	47.3±5.3	47.9±9.1	59	Laparoscopic adjustable gastric banding	12 weeks	Optifast 456-680 kcal/day
Dambrauskas *et al* [13]	131	45.3 ± 6.7 Control: 43.2 ± 8.6	38±8 Control: 39±9	27.5 Control: 35.5	Laparoscopic Roux-en- Y gastric bypass	2 weeks	Optifast 800 kcal/day
Edholm *et al* [5]	33	42.9±3.02 Control: 40.8±3.63	34.3±7.53 Control: 42.2±7.05	0	Laparoscopic gastric bypass	4 weeks	Modifast 800-1100 kcal/day
Fris [6]	50	Median 47±6.8 (range 34.5-62)	Median 41 (range 25-74)	10	Laparoscopic adjustable gastric banding	2 weeks	Optifast 3 sachets per day to replace 3 meals (@152 kcal per sachet)
Kullberg *et al* [14]	15	42.9±3.02	34.7±7.88	0	Laparoscopic gastric bypass	1 month	Modifast Actual intake: 959±146 kcal/day
Lewis *et al* [7]	23	Median 44 (range 40-51)	Median 50 (range 34-57)	5.5	Laparoscopic adjustable gastric banding	6 weeks	Optifast 450-800 kcal/day
Rao *et al* [15]	10	47 Control: 41.6	Not specified	Not specified	Laparoscopic adjustable gastric banding	6 weeks	Brand not specified 3 sachets per day @ 152 kcal per sachet Protein 46%, CHO 40%, Fat 14% of total energy
Van Nieuwenhove *et al* [16]	273	43.4±10 Control: 43.3±8.2	39.7±9.5 Control: 30.4±9.5	29 Control: 30	Laparoscopic Roux-en- Y gastric bypass	2 weeks	Optifast Actual intake: 1906 kcal/day

Number of patients recruited to participate. [ø] Mean value unless otherwise stated. * Calories refer to planned intake, unless otherwise stated as actual intake.

SD: standard deviation. CHO: carbohydrates.

Table 3. Results of included trials on reduction in liver volume and liver fat		
Author reference	**Summary of findings related to liver volume**	**Summary of findings related to liver fat content**
Brody *et al* [12]	Mean reduction of 43.4% Measured by ultrasonography (only left lateral segment measured). Percentage of volume reduction did not correlate with initial liver volume or with initial body weight or BMI.	N/A
Colles *et al* [11]	Mean reduction of 18.7% for all patients; and 28.7% for subgroup of 9 patients. Measured by CT planimetric technique for all patients and by MR for subgroup of 9 patients. Overall the decrease in liver size was predicted by decrease in body weight and by initial liver volume.	N/A
Edholm *et al* [5]	Reduction of 12% Measured by MR.	40% decrease in liver fat content. Measured by ^{1}H-spectroscopy.
Fris [6]	Mean reduction of 5.1% Measured by Duplex ultrasound (only left lobe of liver measured). Change in liver volume was not related to loss of body fat, but was related to reduction in BMI.	N/A
Kullberg *et al* [14]	Reduction of 12% Measured by MR.	40% decrease in liver fat content. Measured by ^{1}H-spectroscopy.
Lewis *et al* [7]	Reduction of 14.7% for all patients; and 16.3% for subgroup of 11 patients Measured by MR. Change in liver volume predicted by change in liver fat.	43% decrease in liver fat content for all patients; and 72.5% reduction in subgroup of 11 patients Measured by ^{1}H-spectroscopy.

CT: computed tomography; MR: Magnetic resonance

APPENDIX A

Draft quality assessment for assessing research publications on the preoperative use of restricted energy diets to reduce liver volume and fat content; and improve postoperative outcome in obese patients scheduled for bariatric surgery

Author(s):	
Publication date (year):	
Title:	

Criteria	Yes		Un-clear	No
	Appr	Inappr		
Is the target population specified?				
Is the sampling method adequate? Type of sampling method ____				
Is inclusion and exclusion criteria specified?				
Randomisation				
Are the intervention and control groups similar at baseline?				
If no, are differences accounted for in data analysis?				
Are treatments similar for intervention and control groups?				
Are withdrawals adequately described?				
Is data presented based on intention-to-treat principle?				
Were outcome assessors independent from the individuals administrating/ supervising the assigned intervention?				

Response options:

Yes: Criteria appropriately applied; or criteria inappropriately applied

Unclear: Criteria not described

No: Criteria not applied

<u>QUALITY OUTCOME: check appropriate box</u>

- ☐ Low risk of bias (All criteria met)
- ☐ Moderate risk of bias (One or more of the criteria unclear)
- ☐ High risk of bias (One or more of the criteria was not met)

APPENDIX B

Draft screening and data extraction form for research publications on the preoperative use of restricted energy diets to reduce liver volume and fat content; and improve postoperative outcome in obese patients scheduled for bariatric surgery

Author(s):	
Publication date (year):	
Title:	

LEVEL 1: INITIAL SCREENING

1. Is this paper about the effect of a pre-operative restricted energy diet on liver size and/or fat content; OR on the postoperative outcome of obese patients undergoing bariatric surgery (perhaps in addition to other topics)?

☐	1. Yes	☐	1
☐	2. No		
☐	3. Cannot tell		

2. What kind of article is this?

☐	1. Randomized or non-randomized intervention study	☐	2
☐	2. Case Report		
☐	3. Review article		
☐	4. Theoretical or position statement, editoria, book review		
☐	5. Practical guideline or treatment protocol		
☐	6. Other (Specify ____)		
☐	7. Cannot tell		

If excluded at this level, do not list in table as excluded

LEVEL 2: ELIGIBILITY CRITERIA

1. Does this study include a clearly described dietary intervention in the form of a pre-operative restricted energy diet ?

☐ 1. Yes ☐ 3

☐ 2. No

☐ 3. Cannot tell

2. Does the study include adult obese patients with BMI ≥ 30kg/m^2 scheduled to undergo bariatric surgery?

☐ 1. Yes ☐ 4

☐ 2. No

☐ 3. Cannot tell

3. Does this study report on any one or more of the following outcomes?
liver size; liver fat content; operating time; blood loss; surgical difficulty/complexity; postoperative complications; patient compliance

☐ 1. Yes ☐ 5

☐ 2. No

☐ 3 Cannot tell

If excluded at this level, list in table as excluded

LEVEL 3: DATA EXTRACTION

Research Methods

1. How were intervention group and control groups formed?

☐ 1. Random assignment ☐ 6

☐ 2. Consecutive assignment

☐ 3. Consecutive assignment versus historical control

☐ 4. Other (Specify ____)

☐ 5. Cannot tell

2. In case of randomization, specify design

☐	1. Simple/systematic randomization of individuals	☐	7
☐	2. Matched pairs		
☐	3. Other (Specify ____)		
☐	4. Cannot tell		
☐	5. Not applicable		

3. Who performed group assignment?

☐	1. Research staff	☐	8
☐	2. Medical / treatment staff		
☐	3. Other (Specify ____)		
☐	4. Cannot tell		

4. If randomized, how was randomization performed?

☐	1. Computer generated	☐	9
☐	2. Random numbers table		
☐	3. Coins or dice		
☐	4. Sealed envelope		
☐	5. Other (Specify ____)		
☐	6. Cannot tell		
☐	7. Not applicable		

5. How many separate sites were included?

☐	1. One	☐	10
☐	2. Two		
☐	3. Three or more		
☐	4. Cannot tell		

6. Were group assignment (whether randomized or not) performed in the same way at all sites?

☐	1. Yes	☐	11
☐	2. No (Explain ____)		
☐	3. Cannot tell		

7. How many intervention groups were there?

☐	1. One (Restricted energy diet)	☐	12
☐	2. Two (Specify intervention______________________________________)		
☐	3. More than two (Specify intervention ____________________________)		
☐	4. Cannot tell		

8. How many control groups were there?

☐	1. No control	☐	13
☐	2. One		
☐	3. More than one (Explain_______________________________________)		
☐	4. Cannot tell		

Sample characteristics

9. Sample size of intervention group 1

☐	1. Number of participants recruited	☐	☐	14-15
☐	2. Number of participants consented	☐	☐	16-17
☐	3. Number of participants who started treatment	☐	☐	18-19
☐	4. Number of participants that completed treatment	☐	☐	20-21
☐	5. Number of participants dropped out (_______________%)	☐	☐	22-23
☐	6. Number of participants included in post-treatment data	☐	☐	24-25
☐	7. Number of patients lost to follow-up (______________%)	☐	☐	26-27

10. Sample size of intervention group 2 (if applicable)

	1. Number of participants recruited			28-29
	2. Number of participants consented			30-31
	3. Number of participants who started treatment			32-33
	4. Number of participants that completed treatment			34-35
	5. Number of participants dropped out (__________________%)			36-37
	6. Number of participants included in post-treatment data			38-39
	7. Number of patients lost to follow-up (_________________%)			40-41

11. Sample size of control group 1 (if applicable)

	1. Number of participants recruited			42-43
	2. Number of participants consented			44-45
	3. Number of participants who started treatment			46-47
	4. Number of participants that completed treatment			48-49
	5. Number of participants dropped out (__________________%)			50-51
	6. Number of participants included in post-treatment data			52-53
	7. Number of patients lost to follow-up (_________________%)			54-55

12. Sample size of control group 2 (if applicable)

	1. Number of participants recruited			56-57
	2. Number of participants consented			58-59
	3. Number of participants who started treatment			60-61
	4. Number of participants that completed treatment			62-63
	5. Number of participants dropped out (__________________%)			64-65
	6. Number of participants included in post-treatment data			66-67
	7. Number of patients lost to follow-up (_________________%)			68-69

13. Sample characteristics of intervention group(s):

	intervention group 1	intervention group 2	
1. BMI range	to	to	70-77
2. Age	to	to	1-8
3. Gender: %male			9-14

14. Sample characteristics of control group(s):

	control group 1	control group 2	
1. BMI range	to	to	15-22
2. Age	to	to	23-30
3. Gender: %male			31-36

15. Were there significant differences between intervention and control groups? ☐ 37

☐ 1. Yes (Describe ____)

☐ 2. No

☐ 3. Cannot tell

16. Are differences accounted for in data analysis? ☐ 38

☐ 1. Yes (Describe ____)

☐ 2. No

☐ 3. Cannot tell

Intervention

17. Characteristics of restricted energy diet in intervention group(s)

	intervention group 1	intervention group 2	
1. Duration (weeks)	to	to	39-46
2. Energy (kcal min)			47-54
3. Energy (kcal max)			55-62

18. Type of diet (intervention group 1) ☐ 63

☐ 1. Commercial (Describe ____)

☐ 2. Self-selection

☐ 3. Other (Specify ____)

19. Type of diet (intervention group 2) ☐ 64

☐ 1. Commercial (Describe ____)

☐ 2. Self-selection

☐ 3. Other (Specify ____)

20. Was there any information on diet compliance? ☐ 65

☐ 1. Yes (Explain ____)

☐ 2. No

☐ 3. Not sure

21. Main reason(s) for diet non-compliance?

☐ 1. Diet period too long ☐ 66

☐ 2. Taste

☐ 3. Not filling/satisfying enough

☐ 4. Personal reasons

☐ 5. Other (Specify ____)

22. Type of diet (control group 1)

☐ 1. No specific diet ☐ 67

☐ 2. Other (Specify ____)

23. Type of diet (intervention group 2)

	1. No specific diet		68
	2. Other (Specify ____)		

LEVEL 4: OUTCOME MEASURES

1. Who collected data?

	1. Research Staff		69
	2. Medical or treatment staff		
	3. Both		
	4. Cannot tell		
	5. Other (specify ____)		

2. Were data collected in same way for all intervention and control groups?

	1. Yes		70
	2. No (explain differences __________________________________)		
	3. Cannot tell		

3. Type of outcome data recorded. Mark all that apply (1=yes, 2=no)

	Liver volume		71
	Liver fat content		72
	Operating time		73
	Blood loss		74
	Surgical difficulty		75
	Occurrence of postoperative complications		76
	Compliance		77
	Conversion from laparoscopic to open procedure		1

APPENDIX C

DRAFT SUMMARY TABLE for publications on the preoperative use of restricted energy diets to reduce liver volume and fat content; and improve postoperative outcome in obese patients scheduled for bariatric surgery

	Study Author and year	Study design	Total n	Intervention diet			Control diet (describe)
				LCD or VLCD	Type	Duration	
1							
2							
3							
4							
5							
6							
7							

	Study Author and year	Reported outcome measures						
		Liver volume	Liver fat	Operating time	Blood loss	Surgical difficulty	Post-op complications	Compliance
1								
2								
3								
4								
5								
6								
7								

APPENDIX D

Modified Quality Assessment Form

Author(s):	
Publication date (year):	

Reporting:	yes	no	unclear
Is the hypothesis/aim/objective of the study clearly described?			
Are the main outcomes to be measured clearly described in the introduction or methods section?			
Are characteristics of patient included in the study clearly described?			
Are the intervention(s) clearly described?			
Are the distributions of principle confounders in each group to be compared, clearly described?			
Are the main findings clearly described?			
Does the study provide estimates of random variability in the data for the main outcome?			
Have characteristics of patients lost to follow-up been described?			

External validity:	yes	no	unclear
Were the subjects who were asked to participate representative of the entire population from which they were recruited?			
Were the subjects who agreed to participate representative of the entire population from which they were recruited?			
Were the staff, places and facilities where patients were treated representative of treatment majority of the patients receive?			

Internal validity:	yes	no	unclear
Was an attempt made to blind those who measured the main outcomes?			
Was compliance with intervention(s) reliable?			
Were the main outcome measures used accurate?			
Were lost-to-follow-up patients taken into account?			

Interpretation:

☐ Low risk of bias: all criteria met

☐ Moderate risk of bias: one or more criteria unclear

☐ High risk of bias: one or more criteria not met

APPENDIX E

Obesity Surgery: Instructions for Authors

OBESITY SURGERY
INSTRUCTIONS FOR AUTHORS

1. ABOUT OBSU

Obesity Surgery is published by Springer Science+Business Media LLC and is the official journal of the International Federation for the Surgery of Obesity and metabolic disorders (IFSO). Obesity Surgery publishes concise articles on Original Contributions, New Concepts, "How I Do It," Review Articles, Brief Communications, Letters to the Editor and dedicated Video Submissions. Requirements are in accordance with the "Uniform Requirements for Manuscripts submitted to Biomedical Journals," www.icmje.org.

Articles that are accepted for publication are done so with the understanding that they, or their substantive contents, have not been and will not be submitted to any other publication.

2. IMPORTANT SUBMISSION INFORMATION

2a. SYSTEM REQUIREMENTS

Authors will need the following items in order to use Editorial Manager:

- Internet access
- A current Adobe Acrobat browser plug-in
- Electronic files of all required documents for upload.

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Authors entering the journal's Editorial Manager site for the first time can create a new account at http://www.edmgr.com/obsu/ by clicking "Login" at the top of the screen, and "Register Now" at the next screen, and then following the online prompts in order to create your account and submit a manuscript. NOTE: If you have previously logged into the system, you should *always use your existing account* for ALL subsequent submissions. If you have forgotten your Username or Password, you may use the "Send Username/Password" link at the OBSU Log In Page.

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Note: Always keep copies of your word-processing, graphics, video and COI files. You may want to revise the manuscript text, figures or forms after the review process and you will need the original files if your manuscript requires revisions.

Please make sure that all required online fields are completed before attempting to submit. If you cannot finish your submission in one visit, you can save a draft and later re-enter the process at the same step by clicking on the "Incomplete Submissions" link in your Author Main Menu.

3. MANUSCRIPT PREPARATION

3a. MANUSCRIPT SECTIONS AND FILE ITEMS

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Please use the following format guidelines.

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- Double-space the text, and set page borders at one inch.
- Use italics for emphasis.
- Use the automatic page numbering function to number the pages.
- Do not use field functions.
- Use tab stops or other commands for indents; do not use the space bar for indents.

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In the "Attach Files" step (final step) of your submission, the file item "Manuscript" should include a Title Page, the Main Text (which should include a Conflict of Interest Disclosure Statement), References, and Figure Legends (if any). Tables may also be included at the end of this document, or submitted separately under the File Item, "Table."

Title Page. This should include:

- The title of the article.
- The manuscript type.
- The complete names and academic degrees for each contributing author (first name, middle initial[s], surname, degree[s]).
- The departmental and institutional affiliations with complete street or mailing addresses and email addresses for each contributing author. Include the city, state or province, and country where the work was performed.
- "Correspondence to" followed by the name and contact information for the corresponding author.
- A shortened title for use as a running head (not to exceed 30 characters in length, including spaces between words).
- At the bottom of the page, any detailed grant information, and an acknowledgment of grant support.
- Acknowledgments: Individuals, other than authors, who were of direct help in the reported work should be acknowledged by a brief statement. Each acknowledged person should give their written consent to be named in the manuscript.

Main Text. The main text document for most submissions should include:

- Abstract (not required for Letters)
- Introduction/Purpose
- Materials and Methods
- Results
- Conclusion
- Conflict of Interest Disclosure Statement (see details below)
- References (see details below)
- If separate figures are provided, then a Figure Legend should be included in the main text document after the References.
- Any Tables that you provide should be included at the end of the text.

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Conflict of Interest Disclosure Statement (in Text).
A Conflict of Interest disclosure statement is required to be included for each author within the manuscript text, and should be located just before the list of References. For each author, the statement must declare the potential conflict of interest, or "no conflict of interest."

Note: The details provided in the COI Disclosure Statement within the manuscript text must correspond with the information provided in the required author ICMJE COI forms.

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2. Consultancies in the last 3 years (please list)
3. Honoraria in the last 3 years (please list)
4. Stock ownership/ options other than mutual funds (current; please list)
5. Expert testimony in the last 3 years (please list)
6. Grants received in the last 3 years (please list)
7. Grants pending (please list)
8. Patents received
9. Patents pending
10. Royalties (describe)
11. Other relationships (please specify)

References
For the references, please:

- Use Medline®/Pubmed® Style.

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- Cite all references within the text or tables.
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- Number all tables using Arabic numerals.
- Always cite tables in the text in consecutive, numerical order.
- For each table, please supply a table heading. The table title should explain clearly and concisely the components of the table.
- Identify any previously published material by giving the original source in the form of a reference at the end of the table heading.
- Footnotes to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data) and included beneath the table body.
- All tables should be supplied on a separate page at the end of the main document and have callouts in the text.

ii. File Item: "Official Conflict of Interest Form(s)" – (required)

Every contributing author must complete the official ICMJE Conflict of Interest (COI) form, which is available by clicking the "Conflict of Interest Form" link in the "For Authors and Editors" section of the Springer page at www.springer.com/11695, or by directly visiting http://www.icmje.org/coi_disclosure.pdf. No hand-written information is required in this form. A completed, submitted form from each author is required for our records. The form(s) will not appear as part of the manuscript for review.

The corresponding/submitting author is responsible for collecting ALL participating authors' completed ICMJE COI forms and uploading them with the manuscript submission. It is recommended that each ICMJE COI form be saved and renamed as the author's name. If any contributing author's COI form is incomplete or missing from the submission, the submission will be returned to the author for correction prior to review. Each author must complete the form even if no conflict of interest exists.

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For vector graphics, the preferred format is EPS; for halftones, TIFF format is preferred. Very large figure files should be compressed as much as possible before uploading figures to the website. If the figures will be printed in black and white, do not refer to color in the captions. All figures are to be numbered using Arabic numerals. Figure parts should be denoted by lowercase letters. Figures should always be cited in text in consecutive numerical order. For each figure, include the figure legends at the end of the manuscript text. Make sure to identify all elements found in the figure in the caption.

Photographs of patients in which the subject is identifiable must either have the face masked out, or be accompanied by written permission from the individual in the photograph for publication.

Image Size

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- Height: No higher than 234 mm.
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    - Image Magick - www.imagemagick.org
    - Xn Convert - www.xnconvert.com

For detailed submission guidelines regarding Line Art, Halftone Art, Combination Art, Color Art, and other artwork details, please click here: ARTWORK INSTRUCTIONS

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Upon submission of articles that include supplementary video, the author(s) will be required to submit the video according to the following specifications:

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- If applicable, provide references (as detailed above) at the end of the Abstract.

3b. MANUSCRIPT TYPES AND FORMATS

The manuscript types for submission include Review Articles, Brief Communications, New Concepts, How I Do It, Original Contributions, Letters, and Video Submissions. Each of these manuscript types requires a specific format. You may submit your manuscript in either Format I or Format II, as detailed below. Please type all manuscript text (including references) double-spaced with one-inch wide margins. Number the pages consecutively and organize the manuscript in the order indicated below.

i. Manuscript Format I (Full Articles)

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- **New Concept**
- **How I Do It**

Format: The main body text in Original Contributions, New Concepts, and "How I Do It" submissions, is limited to eight double-spaced, typewritten pages (2,400 words, excluding references, figure legends and Abstract), and up to six figures/images. The following format should be followed:

Title Page

Manuscript Text For Review

- Abstract - The Abstract in full manuscripts must not exceed 250 words, and should consist of five (5) structured paragraphs: Introduction/Purpose, Materials and Methods, Results, and Conclusion.
- Key Words
- Introduction/Purpose - Should convey the background and purpose of the report.

- Materials and Methods, Results, and Discussion - Should follow the Introduction. When required by the nature of the report, manuscripts that do not follow this specific format may be accepted. Please include a statement in the Methods section indicating approval (or exemption) by your Institutional Review Board for the conduct of your research.
- Conflict of Interest Disclosure Statement – Is required to be included within the manuscript text for each author, and should be located just before the list of References.
- References (not included in word count)
- Tables (not included in word count)

Figures (Illustrations) - Submitted separately from the main text.

Official ICMJE Conflict of Interest forms - Must be completed and submitted from each contributing author, and are not viewable to reviewers.

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- **Brief Communication**
- **Letter**

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BRIEF COMMUNICATIONS

Format: The main body text in a Brief Communication is limited to six double-spaced, typewritten pages (1,800 words, excluding references and figure legends), and up to two figures/images. Aim to limit the total number of references in Brief Communications to a maximum of twenty (20). Brief Communications are descriptions of focused studies with important, but very straightforward results. An Abstract is optional; if included, it should not exceed 150 words. The order of presentation is Background, Methods, Results and Conclusion, followed by references, tables, and legends.

LETTERS TO THE EDITOR

Format: Letters to the Editor should be no more than four double-spaced, typewritten pages (1,200 words), with up to three illustrations, and limited references. No Abstract is required. Letters are unstructured communications, in letter format. The editors reserve the right to accept, reject or excerpt letters without changing the views expressed by the author.

iii. Manuscript Format III

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vi. Statement of Informed Consent

Patients have a right to privacy that should not be infringed without informed consent. Identifying information, including patients' names, initials, or hospital numbers, should not be published in written descriptions, photographs, and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) gives written informed consent for publication. Informed consent for this purpose requires that a patient who is identifiable be shown the manuscript to be published. Authors should identify Individuals who provide writing assistance and disclose the funding source for this assistance. Identifying details should be omitted if they are not essential. Complete anonymity is difficult to achieve, however, and informed consent should be obtained if there is any doubt. For example, masking the eye region in photographs of patients is inadequate protection of anonymity. If identifying characteristics are altered to protect anonymity, such as in genetic pedigrees, authors should provide assurance that alterations do not distort scientific meaning and editors should so note.

vii. Other Required Forms

Copyright forms and color publication payment details are now handled online *after* an accepted article is accepted for publication. When proofs are ready for viewing, the author is contacted via e-mail by the typesetter, and sent a website address that will provide the author with forms/orders/proofs procedures.

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4. MANUSCRIPT SUBMISSION

4a. SUBMISSION STEPS

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Please view a copy of the SUBMISSION CHECKLIST here. We recommend that you have all items listed in the checklist complete and ready for upload before starting your online submission.

ii. Review Your Submission

After uploading the files for your submission, the system will convert the files to PDF. You will see the result of the conversion with the Acrobat plug-in in your browser. Make sure to review the PDF of your submission before you confirm your submission. Once you have reviewed your PDF document for completeness, click "Submit" and all contributing authors will receive an emailed confirmation.

After the manuscript is submitted, the Editors will inspect the submission before assigning reviewers. If any part of the manuscript is not complete, the manuscript will be unsubmitted and returned to your Submission Center, with an e-mail notification sent to the authors indicating the need for additional information and/or correction. Once a complete manuscript is correctly submitted, the OBSU editors will assign reviewers to your submission.

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If the manuscript is accepted pending minor revisions, or suggested for resubmission after major revisions, we emphasize the importance of authors providing their revisions as promptly as possible, and providing a point-by-point reply to all reviewer comments. The annotated version of the revised manuscript should identify all changes and include each reviewer point in parentheses, e.g., "(Reviewer 1, Comment 2)."

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If your article is accepted, you will receive a link to the special Springer web page with questions related to:

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The article will be published online after receipt of the corrected proofs. Online publication is the official first publication of the article, and citable with the DOI. After online publication, further changes can only be made in the form of an Erratum, which would be hyperlinked to the article. After release of the printed version, the paper can also be cited by issue and page numbers.

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Managing Editor, OBSU Editorial Office
Phone: +001 (562) 961-9928
E-mail: obsu.rodriguez@gmail.com

APPENDIX F

Title page prepared for journal submission

Title: The impact of preoperative restricted energy diets in reducing liver volume and improve operative outcome in obese patients scheduled for bariatric surgery: a systematic review

Manuscript type: Original research

Contributing authors:

Annelien Els. BSc (Dietetics)

Violet L van den Berg. PhD (Immunology), BSc (Dietetics)

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Shortened title for running head: Preoperative diet restriction

SUMMARY

Key terms: obesity, metabolic syndrome, non-alcoholic fatty liver disease, bariatric surgery, low calorie diet, restricted energy diet, liver volume, liver fat

Bariatric surgery is recognized as the most effective treatment modality for obesity. Since obesity levels are on the increase both locally and globally, it is expected that the number of procedures performed will increase in the future.

A practical limitation to performing bariatric surgery is the fact that operating space within the abdomen is limited by excessive layers of abdominal fat and the presence of a large, fatty liver. Fat deposition in the liver is common in obesity. Reducing the fatty deposits in the liver can reduce the size of the liver, thereby in theory it can also reduce the complexity of the surgical technique.

A number of individual trials have evaluated the potential of energy restriction for a period of two to 12 weeks before surgery to reduce the liver size and liver fat content. Data from these trials are promising, but individually does not provide sufficient evidence to justify evidence-based recommendation in favour of the use of restricted energy diets prior to surgery. This review combines the findings of individual trials in order to provide an evidence-base for such practice.

At the time of protocol development, no systematic review has been published to document the benefits of energy restricted diets in reducing liver size and fat content in obese patients who are undergoing bariatric surgery for weight loss.

A systematic literature search was undertaken to identify studies published between 1980 and 2012 on the research topic. Studies were evaluated and eliminated based on inclusion

and exclusion criteria so that a total ofnine studies were included in the review. Study design and methodology were appraised, and results of individual trials compared and combined where appropriate in order to provide a comprehensive overview of current literature in the form of a narrative systematic review. A meta-analysis was not possible due to differences in reporting.

Results indicated that preoperative diet restriction effectively reduces liver volume by decreasing the liver fat content. It was however not clear if these changes can be directly linked to reduction in operative complexity, reduction in intra-operative blood loss, or reduction in duration of surgery. Randomized, blinded trials are needed to confirm if a relationship exists. One well-designed study indicated reduction in post-operative complications.

In conclusion, this review found that preoperative restricted energy diets used for an acute period before surgery can significantly reduce liver volume and fat content in obese patients, and may translate to improved patient outcome.

OPSOMMING

Sleutelterme: vetsug, metaboliese sindroom, nie-alkoholiese lewer vervetting, bariatriese chirurgie, lae energie dieet, beperkte energie dieet, lewer volume, lewervet.

Bariatriese chirurgie word beskou as die mees effektiewe manier om vetsug te behandel. Aangesien vetsug plaaslik en wêreldwyd aan die toeneem is, is die verwagting dat die hoeveelheid bariatriese chirurgie prosedures wat uitgevoer word, in die toekoms sal toeneem.

‘n Oormatige hoeveelheid buikvet tesame met ‘n vergrootte vet-geïnfiltreerde lewer beperk spasie in die buik van ‘n vetsugtige persoon, en skep ‘n praktiese probleem vir die chirurg wanneer bariatriese prosedure uitgevoer word. Die neerlegging van vet in lewer weefsel is algemeen in vetsugtige pasiënte. Deur vetneerleggings in die lewer te verminder kan die lewer se grootte verklein word, en teoreties kan dit dus help om die uitvoer van die prosedure te vergemaklik.

Om vermindering van vetneerlegging in die lewer te bewerkstellig, het verskeie individuele navorsers ondersoek ingestel na die effek van beperkte energie diëte wat vir ‘n periode van twee tot 12 weke voor chirurgie deur die pasiënt gevolg word. Alhoewel hierdie studies belowende resultate gelewer het, regverdig dit nie die insluiting van ‘n riglyn oor die gebruik van ‘n lae energie dieet in sogenaamde navorsing-gebasseerde riglyne nie. Hierdie oorsig kombineer die bevindings van individuele navorsingstudies met die doel om bewys te lewer van die voordele verbonde aan hierdie gebruik.

Ten tyde die ontwikkeling van 'n protokol vir hierdie studie, is geen sistematiese oorsig met betrekking tot die onderwerp gepubliseer nie.

'n Sistematiese soektog na literatuur is gedoen om alle studies, gepubliseer tussen 1980 en 2012 en wat met die onderwerp verband hou, te identifiseer. Hierna is studies geëvalueer volgens insluitings- en uitsluitingskriteria, en verskeie studies is uitgesluit met slegs nege publikasies wat in die finale oorsig ingesluit is. Die ontwerp en metodes van hierdie publikasies is nagegaan, resultate is vergelyk en gekombineer waar van toepassing, ten einde 'n omvattende oorsig te lewer van navorsing wat oor die onderwerp beskikbaar is. Weens verskille in data rapportering was dit nie moontlik om 'n meta-analise uit te voer nie.

Hierdie sistematiese oorsig het bevind dat energie beperking voor bariatriese chirurgie wel 'n effektiewe manier is om vetinhoud van die lewer, en sodoende lewer grootte, te verminder. Dit is egter nie duidelik of hierdie veranderinge direk lei tot vermindering in chirurgiese kompleksiteit, verminderde bloedverlies tydens chirurgie, of 'n korter tydsduur van chirurgie nie. Verdere inligting vanuit gerandomiseerde studies is nodig om 'n moontlike verwantskap te bevestig. Een studie met 'n goeie navorsingsontwerp het wel aangetoon dat post-operatiewe komplikasies verminder kan word.

In samevatting het hierdie sistematiese oorsig bevind dat lewer volume en –vetinhoud beduidend verminder kan word deur 'n beperkte energie dieet vir 'n kort tydperk voor chirurgie te volg, en dat dit ook moontlik pasiënt-uitkoms kan verbeter.