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Long-term results after surgical treatment for severe obesity

Doctoral thesis

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Norwegian University of Science and Technology
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Sammendrag

Ny kunnskap om utvikling av alvorlig fedme har erstattet oppfatningen av at av fedme er en individuell selvforskyldt tilstand med en forståelse av at fedme er en kronisk progressiv sykdom med sammensatte årsaksfaktorer. Begrepet «fedmebasert kronisk sykdom» skiller mellom fettmassesykdom som medfører en økt fysisk belastning på kroppens organer, og sykt fettvev som medfører metabolsk og inflammatorisk skade på kroppen.

I 2004 ble de regionale helseforetakene pålagt å etablere et tilbud om kirurgisk behandling av alvorlig fedme. Dette ga for første gang personer med alvorlig fedme status som pasienter i spesialisthelsetjenesten, og mange pasienter har hatt stor nytte av denne behandlingen. Andre har i etterkant fått betydelige plager som kan ha sammenheng med fedmeoperasjonen.

Tilbudet om fedmekirurgi ble begrenset til et fåtall sykehus da det ble innført i 2004. Det ble utarbeidet nasjonale retningslinjer for pasientseleksjon og oppfølging, og det var stor interesse fra både helsemyndigheter, politisk hold og i media. For å overvåke kvaliteten på behandlingstilbudet ble det etablert lokale kvalitetsregistre ved de enkelte sykehus i påvente av det nasjonale kvalitetsregisteret for fedmekirurgi som ble opprettet først i 2015.

Denne avhandlingen bruker data fra det lokale kvalitetsregisteret for fedmekirurgi ved Ålesund sykehus som inneholder forløpsdata for 644 pasienter operert med laparoskopisk gastrisk bypass fra 2004 til 2013 og som har en observasjonstid på mer enn fem år.

I den første artikkelen som inngår i avhandlingen undersøkes forekomst av magesmerter som medfører billeddiagnostikk og mageoperasjoner etter gastrisk bypass operasjonen. Med en gjennomsnittlig observasjonstid på åtte år hadde 40% vært til CT-undersøkelse en eller flere ganger for utredning av magesmerter, og ytterligere 10% hadde vært til annen billeddiagnostikk for samme problematikk. Hele 9,3% ble operert for mistanke om tarmslyng og like mange ble operert for gallestein i observasjonsperioden.

I den andre artikkelen undersøkes hvor vidt selvrapportert helse, et mye brukt mål på helsestatus i folkehelseforskning, kan brukes som mål for generell endring i helsetilstanden etter fedmeoperasjoner, slik at selvrapportert helse kan brukes til å fange summen av positive og negative erfaringer etter behandling.

Av 233 pasienter som hadde fylt ut livskvalitetsskjemaet SF-36 i forkant av og fem år etter gastrisk bypass operasjonen opplevde to tredjedeler at den generelle helsen var bedre, en fjerdedel opplevde ingen endring og 8% opplevde helsen som dårligere.

Jernmangel med og uten anemi er et vanlig problem etter gastrisk bypass fordi opptaket av jern er redusert på grunn av omkoblingen av tarmen. I den tredje artikkelen undersøkes endring i jernlager og blodprosent i løpet av de fem første årene etter operasjonen, og også bruk av intravenøs jernbehandling på grunn av lave jernlagre. En tredjedel av pasientene fikk jern intravenøst i oppfølgingstiden. Blodprosenten holdt seg stabil over tid for gruppen sett under ett, men det var et betydelig fall i jernlagre både hos kvinner og menn. Siden jern er viktig for en rekke funksjoner i kroppen, kan jernmangel uten anemi også knyttes til opplevelse av redusert helse blant annet i form av trøtthet og muskelsmerter.

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I want to thank my surgical mentor and co-surgeon Gustav Robert Hareide for invaluable cooperation in the operating theatre and informative discussions outside.

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Thanks also to all colleagues at Centre for Obesity at St. Olav's Hospital, Trondheim University hospital for inspiring discussions.

Most importantly, thanks to all the patients who have willingly shared their experiences and thoughts on living with obesity and life after obesity surgery.

Not least, thanks also to my husband Trond and my four sons Arnstein, Vemund, Torgeir and Audun, who has contributed with enthusiastic support and extensive reading of manuscripts.

Abbreviations

BMI	Body mass index
CT	Computer tomography
Hgb	Haemoglobin
HUNT	Helseundersøkelsen I Nord Trøndelag/ The Nord-Trøndelag Health Study
IH	Internal herniation
RYGB	Roux-en-Y gastric bypass
SF-36	Short form 36 Quality of life questionnaire
SOREG	Scandinavian obesity surgery registry
SRH	Self-rated health
T2DM	Type 2 Diabetes mellitus
US	Ultrasound
WHO	The World Health Organization
%TWL	Percentage total weight loss
%EWL	Percentage excess weight loss

List of papers

1. Sandvik, J., Hole, T., Klöckner, C.A., Kulseng, B.E. and Wibe (2018), High-Frequency of Computer Tomography and Surgery for Abdominal Pain After Roux-en-Y Gastric Bypass. OBES SURG 28, 2609–2616

2. Sandvik, J., Hole, T., Klöckner, C.A., Kulseng, B.E. and Wibe, A. (2019), Assessment of self-rated health 5 years after Roux-en-Y gastric bypass for severe obesity. BJS Open, 3: 777-784. doi:10.1002/bjs5.50223

3. Sandvik, J., Hole, T., Klöckner, C.A., Kulseng, B.E. and Wibe, A (2020), Intravenous iron treatment in the prevention of iron deficiency and anaemia after Roux-en-Y gastric bypass. Obes Surg. 2020 Jan 18. doi: 10.1007/s11695-020-04396-5. [Epub ahead of print]

Abstract

Background: Severe obesity reduce individual health, as well as length and quality of life. Surgery is a powerful tool to induce weight loss by changing the anatomy and physiology of the gastrointestinal channel. Since laparoscopic Roux-en-Y gastric bypass was introduced in Norway in 2003 more than 30 000 Norwegians have undergone surgery with this method. Gastric bypass has proven to be safe, result in a considerable weight loss, and improve comorbidities and quality of life during the first years after surgery. However, some patients experience long-term complications and problems, including abdominal pain, nutritional deficiencies, secondary weight regain, and decreased quality of life.

Aims: The aims of this project have been to study the long-term consequences of gastric bypass surgery, first in terms of the frequency of abdominal pain in need for medical imaging and surgical treatment, second to explore whether self-rated health changed from baseline to five years after surgery, and whether this measurement, widely used in public health research, may be applicable as a sum-score for long-term health-change after obesity surgery. The third aim was to explore the change in iron stores, the frequency of anaemia after gastric bypass, and the need for intravenous iron treatment.

Methods: Baseline and follow-up data on 795 patients who underwent obesity surgery at Aalesund hospital from 2004 to 2015 was collected prospectively in a local quality registry. The patients were between 18 and 65 years, and had a baseline BMI > 40 kg/m^2, or BMI > 35 kg/m^2 with obesity related comorbidity. The first study included 569 patients with five-year observational period by August 2017. The second paper included 233 patients who underwent surgery between 2006 and 2011, who had filled in the SF-36 questionnaire, including self-rated health, at baseline and five years after surgery, in addition to the clinical follow-up. The third paper included 644 patients with a five-year follow-up by January 2019.

Data were analysed with the Pearson χ^2, independent and paired t-tests, non-parametric tests and Kaplan-Meier estimates, depending on the variables' characteristics. $P < 0.05$ was considered statistically significant for all analyses.

Results: The first study revealed that after a mean observational time of eight years, medical imaging due to abdominal pain was performed on half of the patients, as 40% had one or more CT-scan, and 28% had one or more ultrasound scans. Abdominal surgery due to suspected internal herniation was performed in 9.3%, equal to the number of patients who underwent cholecystectomy in the same period.

In the second study, improvement in self-rated health was reported by two thirds of the patients from baseline to five years, a quarter of the patients reported no change, and 8% reported a decrease in self-rated health. There were no differences found in age, sex, BMI, or weight loss between improvers and non-improvers, but the improvers had less secondary weight regain.

In the third study, while only a minor decrease in haemoglobin levels were found, there was a considerable decrease in iron stores from baseline to five years, even though intravenous iron treatment was offered to patients with empty iron stores regardless of haemoglobin levels, and one third of the patients received this treatment.

Discussion/conclusions: As documented by others, abdominal pain and iron deficiency in need for medical interventions, affect many patients after gastric bypass surgery. However, only a minority of patients experience a general health decrease five years after surgery when compared to their condition prior to surgery. There seems to be a need for life-long access to follow-up by specialized healthcare for people who have undergone obesity surgery, as complications in need of medical intervention may occur long time after the operation.

Introduction

Obesity

Adipose tissue is an essential part of the human body, ensuring the body's ability to store energy in periods with abundance of food, for utilisation in times of food shortage. The adipocytes can increase their capacity to store energy by increasing in size (hypertrophy) or in numbers (hyperplasia) (1). In an environment with easy and continuous access to food and limited need for strenuous physical activity, conditions for increasing the amount of adipose tissue are ideal. Many questions are still unanswered when it comes to why some people do not increase their fat stores, and instead keep a normal weight, while others do and develop obesity, given that they live in the same environment.

During the last decades, the biological functions of adipose tissue have increasingly been revealed. Contrary to former beliefs, the adipose tissue is a dynamic and metabolically active organ, secreting various hormones and cytokines involved in appetite regulation, energy metabolism and inflammation (2, 3).

Just as with other organs in the body, a healthy adipose tissue is necessary for good health. Too much adipose tissue, as well as sick adipose tissue, reduces health. Excess adipose tissue is a very visible trait expressed by the size of the body, and the discussions on where the border between a normal and an abnormal body size is drawn, often mixes medical knowledge with aesthetic and moral arguments. Obesity has been regarded as a self-inflicted condition that may easily be cured by life-style modifications; this attitude is still common among lay people as well as among health personnel and politicians (4, 5). A consequence of this situation is that people with obesity experience stigma, both as individuals and on a group level (6, 7).

Twenty years ago a report from the World health organization (WHO) described obesity as a global epidemic (8). WHO has since 1997 listed obesity as a disease condition in the International classification of disease (ICD), defined as "a disease in which excess fat is accumulated to an extent that health may be adversely affected" (9). In lack of better measurements for body composition, body mass index (BMI) is still the most common measure for obesity. BMI is the weight in kilograms divided by the square of the height in meters (kg/m^2). The WHO-definitions of obesity are: BMI 30 – 34.9 kg/m^2 is referred to as obesity class 1, BMI 35.0 – 39.9 kg/m^2 as obesity class 2, and BMI > 40kg/m^2 is obesity class 3. Obesity class 3 and obesity class 2 along with obesity related comorbidities are defined as severe obesity (8).

In order to reduce the use of stigmatizing language, the term *morbid obesity*, previously used to describe BMI > 40, is avoided, and health personnel are encouraged to use people-first language, talking about *people with obesity*, instead of obese people (6).

The European association of the study of obesity (EASO) as well as the American association of clinical endocrinologists and American college of endocrinology have introduced the term Adiposity-Based Chronic Disease (ABCD) in an attempt to cover the many aspects of the health-reducing effects of obesity, and thereby defining severe obesity as a chronic disease.

In the ABCD-concept, the adverse effects of excess adipose tissue have two main aspects, distinguishing between *fat mass* and *sick fat*. *Fat mass disease* defines the physical load of excess weight, implying altered and pathological mechanical forces leading to functional limitations and bodily overload. *Sick fat disease* defines the metabolic aspects of obesity, leading to deranged endocrine and immune responses (3, 10, 11). The conceptual framework of adiposity-based chronic disease also includes distribution, function and amount of adipose tissue, as well as cultural and physical context, and the clinical burden of dysfunctional fat over time (3).

The World Obesity Federation have declared obesity as a chronic progressive disease clearly distinct from being just a risk factor for other diseases (12). The rationale for defining obesity as a chronic disease is the distinct pathophysiology in people with obesity resulting in a powerful homeostatic mechanism hindering weight loss and promoting further weight gain (13).

Obesity increases the risk of diseases as type 2 diabetes mellitus (T2DM), obstructive sleep apnoea, hypertension and other cardiovascular diseases, fatty liver disease, infertility and several types of cancers. Obesity may also influence the effect of disease treatment, by increasing the risk of complications to treatments, or by leading to less effect of the treatment (14).

National and global trends

Obesity has increased worldwide during the last 50 years and WHO regards obesity as one of the main global health issues (8, 13). Moderate obesity increases the risk of morbidity and mortality. Severe obesity also affects work participation, family life, and participation in community activities. Global health reports on the prevalence of obesity use BMI > 30 kg/m² as threshold value for obesity. The increase in prevalence of more severe obesity (BMI >35 kg/m² and BMI> 40 kg/m²) follows the same pattern as the increase in BMI > 30 kg/m² (15).

According to an analysis of global trends in adult body-mass index in 200 countries, the global age-standardized mean BMI increased from 21.7 kg/m² to 24.2 kg/m² in men, and from 22.1 kg/m² to 24.4 kg/m² in women from 1975 to 2014. In this period, age-standardized global prevalence of underweight decreased from 13.8% to 8.8% in men and from 14.6% to 9.7% in women. In 2014 2.3% of the world's men and 5.0% of women had BMI > 35 kg/m². Globally the prevalence of severe obesity (BMI ≥40 kg/m²) is 0.64% in men and 1.6% in women. If

post-2000 trends continue, global obesity prevalence (BMI > 30 kg/m²) will reach 18% in men and 21% in women, and severe obesity (BMI > 35 kg/m²) will surpass 6% in men and 9% in women by 2025 (15). In the HUNT 3-study with data from 2006-2008, 5.0% of Norwegian women and 3.2% of men were reported at BMI 35-39.9 kg/m², and 1.5% of women and 0.5% of men at BMI > 40 kg/m² (16). In HUNT 4 (2018) mean BMI was 27.2 (± 4.7) kg/m², unchanged from HUNT 3 (17).

Recently, the problem of obesity has been linked to other global phenomena as part of a global syndemic of obesity, undernutrition, and climate change that are driven by the same underlying forces, and a collective political action addressing all three issues has been called for (18, 19).

Non-surgical treatment of obesity

Severe obesity is in theory a preventable disease, and in a public health perspective, obesity prevention has a huge potential for improving the health status in the population. In discussions on obesity, strategies for prevention and treatment are often mixed. Unlike other diseases, the measures documented to prevent obesity – healthy food and physical activity – are also advised as therapy for people with severe obesity.

In discussing prevention, it is helpful to distinguish between the primary prevention of initial development of a disease, secondary prevention, which includes early detection of an existing disease as well as reducing severity and complications, and tertiary prevention to reduce the impact of the disease (20).

The aim of disease treatment may also differ. In some cases the aim of the treatment is to cure a disease, in chronic diseases, the options are to reduce the symptoms of the disease and strive for remission rather than healing.

Discussions on obesity often end up in problems regarding how to define who should be offered treatment, and who is responsible for offering prevention and treatment. Overweight and moderate obesity are often regarded as a personal responsibility, and professional help is usually not offered until the obesity is severe. The access to specialized health care for obesity in Norway is limited to individuals with severe obesity corresponding to BMI >40 kg/m^2, or BMI> 35 kg/m^2 with obesity related comorbidities (21).

The first choice of obesity treatment has been lifestyle modifications to initiate weight reduction. Most patients with severe obesity have a long history of personal initiatives with the goal of losing weight, either by diets or by physical activity, with repeated experiences of weight loss success, and failure of weight loss maintenance. The long-term results of life style interventions on weight maintenance are however disappointing (22). Severe energy-restricted diets, (meal-replacement diets or very low-calorie diets) may produce a clinically relevant weight loss of more than 10% of initial weight in individuals with severe obesity when used for 6 weeks or more, but long-term outcomes are lacking (23). Weight cycling might have adverse effects and recommending treatment for obesity not proven to have long-term benefits requires ethical considerations (24, 25).

The long-term results of cognitive therapy, lifestyle intervention groups, or individual counselling by health personnel on weight reduction for individuals with severe obesity are also lacking (26). However, improvements in general health and a healthier lifestyle might be beneficial for the patients even if the weight reduction is limited.

Until recently, medical treatment as adjunct to lifestyle changes to achieve weight reduction in people with severe obesity has played a minor role. A handful of drugs have been on the Norwegian market the last fifteen years, but some of them have been withdrawn due to adverse effects. Orlistat (Xenical) which act by reducing fat absorption has been available for the last fifteen years, but is not widely used.

By now, two drugs, Bupropion-Naltrexone (Mysimba) and Lirglutide (Saxenda), are approved in Norway for treatment of obesity. Bupropion-Naltrexone targets the hedonic reward system in the brain, thereby reducing appetite and food consumption. Liraglutide is a glucagon-like peptide-1(GLP-1) receptor agonist that has been used in the treatment of type 2 diabetes for several years. Due to its beneficial effect on weight, it has also been approved for weight reduction (27, 28). In different ways these medications mimic the metabolic effects of gastric bypass surgery. Until January 2020 Norwegian patients had to pay for these drugs themselves, but they are now covered for patients with severe obesity.

The knowledge on the complex mechanisms behind the metabolic effects of obesity surgery may contribute to well-designed non-surgical treatment programs for severe obesity by combining several approaches. The idea of a *medical gastric bypass* that copies the various effects of gastric bypass surgery with medication has been proposed, but there is still work to be done to develop this concept (29, 30).

Obesity surgery

"*The surgery for massive obesity is a major challenge. The effort begins when the patient and the surgeon commit themselves to the performance of bariatric surgery, and eventuates in a lifelong commitment.*"(31) That was the opening words in the editorial of the first issue of the journal *Obesity Surgery* in 1991.

Surgery is about saving lives when acute situations or life-threatening diseases occur. It is also about improving the health and quality of life of patients when bodily functions or organs fail. Controversies arise when surgery is applied to modulate apparent normal bodies (32).

The clinical observation that removing parts of the gastrointestinal organs implies weight loss led to the development of operations where the primary goal was weight reduction (33). The

first reported surgical procedure for weight loss was a resection of small intestine performed by Viktor Henrikson in Gøteborg, and presented in Nordisk Medicin in 1952 (34). The weight loss after one year was minor, but the patient was satisfied and experienced improved health.

A magnitude of methods have been tried, often with high rates of morbidity and mortality, and a low rate of success (35). Improvements in surgical technique, a process of selection of methods that proved to be beneficial and documentation of results led to improvements in survival as well as in weight loss. The methods that aimed to reduce weight proved to have additional beneficial metabolic effects, improving T2DM, hyperlipidaemia and other weight related comorbidities, and the term metabolic surgery describes the additional effects of obesity surgery. Metabolic surgery is defined as "*the operative manipulation of a normal organ system to achieve a biological result for a potential health gain*"(35).

Gastrointestinal surgery for severe obesity has been performed since the 1950s, and the main recommendations from the 1991 NIH Consensus Conference on gastrointestinal surgery for severe obesity are still valid (36). These guidelines have later been updated to include new surgical techniques, as well as metabolic surgery (9, 37). Obesity surgery, often called bariatric surgery, and metabolic surgery cover a wide range of surgical methods to treat obesity and obesity related comorbidities.

Obesity surgery procedures are traditionally described as malabsorptive methods reducing the nutritional uptake from food in the gut, or restrictive methods limiting food intake. Some methods have been described as combinations of restriction and malabsorption (33). Increased knowledge on the metabolic effects of the procedures on gut hormones and gut-brain communication has changed the interpretation of the mechanisms behind the effects of anatomical change. The long-term effects of these surgical methods are probably more related to the wide physiological consequences of changing the passage route for food from the mouth to the intestines, than to malabsorption and restriction.

Surgical methods for weight reduction

The first paper on jejunoileal bypass with ileocolostomy or ileojejunostomy was published in 1954 as the first malabsorpive surgical treatment of severe obesity. Standardized versions of the method was published in 1969 and 1971(35). By creating a short bowel syndrome, the treatment was effective, but the method was, due to severe complications, abandoned when newer surgical methods with less complications were introduced (38, 39).

Gastric bypass was first performed in 1966 by Mason and Ito (40). The gastric bypass with Roux-en-Y gastrojejunostomy became the gold standard for surgical treatment of severe obesity and obesity-related metabolic disorders for several decades (35, 40, 41). The remission of T2DM after gastric bypass was almost discovered "by accident" (42). The popularity of gastric bypass increased when technical development and improvements in surgical skills made it possible to perform the procedure by laparoscopy (43, 44).

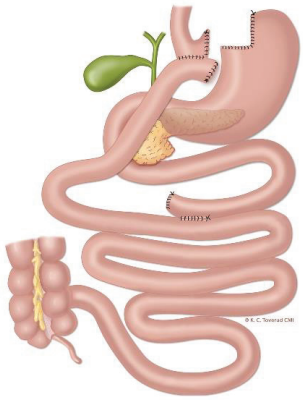
Gastroplasty was introduced in 1973, and the vertical banded gastroplasty (VBG) was described by Mason in 1982 as a less invasive procedure than gastric bypass. VBG became almost as popular as gastric bypass, but due to secondary weight regain, introduction of laparoscopic techniques and the introduction of the adjustable gastric band, its popularity declined (45).

Biliopancreatic diversion (BPD) was introduced by Scopinario in Italy in 1979, and this procedure combines a distal gastrectomy with a long intestinal bypass (46). In the American counterpart to BPD, the distal gastrectomy was replaced by a sleeve gastrectomy and pylorus preservation, called biliopancreatic diversion with duodenal switch (BPD-DS) (47). These methods imply more malabsorption than in gastric bypass, and they are also the most effective treatment for T2DM. Due to the high frequency of long-term nutritional deficiencies, these methods are by now only used in select cases.

Gastric banding, a method meant to restrict food intake by applying a band of Gore-Tex or other permanent material around the upper part of the stomach was introduced in 1978 (48). Gastric banding became a common procedure in the Nordic countries in the 1980ies, also being performed at several hospitals in Norway (49, 50). The weight loss was moderate, and many had the band removed due to adverse effects. The method was however improved with an adjustable silicone band in the late 1980s, and introduction of laparoscopic access in the beginning of the 1990s, and adjustable gastric banding (AGB) is still a popular method in many countries due to a low rate of complications (51-53).

Sleeve gastrectomy was originally the first part of the BPD-DS procedure, performed as a first step in patients with too high risk to tolerate a full BPD-DS. The sleeve gastrectomy proved to be effective as a stand-alone procedure, and is by now the most commonly performed obesity surgery procedure worldwide (54, 55) . The five years-results after gastric sleeve are in many aspects on the same level as following gastric bypass, but the results vary more among treatment sites as well as among the patients at the same hospital (56).

In a continuous search for surgical methods with better weight reduction and metabolic effects, less complications and better patient satisfaction, new surgical and endoluminal methods are regularly introduced (57). However, it is costly and time consuming to document the long-term results on new methods, and the majority of obesity surgical procedures are performed in health care systems without possibility for long-term follow-up and documentation.



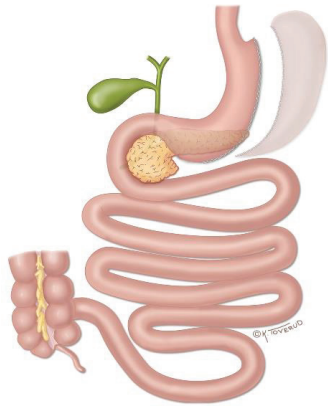


Figure 1. Gastric bypass **Figure 2.** Sleeve gastrectomy
Figures by Kari C. Toverud. Reproduced with permission.

Metabolic effects of obesity surgery

The different surgical methods for weight reduction have health improving effects in addition to weight loss. Some of these effects, like improvement in T2DM, occur before the patients have lost weight. Depending on the severity and duration of T2DM before surgery, remission of T2DM vary between sixty and seventy percent five years after gastric bypass and sleeve gastrectomy (58, 59). Obesity surgery is therefore approved as treatment for T2DM with BMI 30-35 kg/m^2 in several countries, including Norway.

In addition to T2DM, hypercholesterolemia, obstructive sleep apnoea, hypertension, general inflammation, polycystic ovarian syndrome (PCOS), and cognitive function are improved after obesity surgery (60). The diverse mechanisms behind the effects of gastric bypass, sleeve gastrectomy and other surgical procedures to induce weight loss, are still only partly understood. Changes in the communications between gut and brain, change in microbiota, and change in the hormonal responses to food intake are among the mechanisms which might be important for the additional beneficial outcomes (61).

Obesity surgery in Norway after 2000

In the era of open surgery, obesity surgery was associated with high postoperative morbidity and mortality, and the Norwegian Health Authorities and the Norwegian Surgical Association abandoned these treatments around 1990.

BPD-DS was introduced in Norway by Villy Våge at Førde hospital in 2001, and even if this method is rarely used now, the long-term follow-up of patients operated at Førde hospital are well documented in studies on weight reduction and comorbidities, quality of life and work participation (62-64).

Laparoscopic surgical technique contributed to safer surgery for obese patients by reducing surgical trauma and allowing early postoperative ambulation. At the same time, there was an increasing number of patients with severe obesity asking for this treatment. Therefore, the Norwegian Ministry of Health instructed all regional health authorities to offer surgical treatment for severe obesity in Norway in 2004.

St. Olav's hospital was the first and Aalesund Hospital was the second of seven public hospitals which established a program for obesity surgery in April 2004. Supported by regional health authorities, the surgeons established a local quality registry for obesity surgery to survey the activity and outcomes. Until the Norwegian quality registry for obesity surgery (SOREG-N) was recognized as a national quality registry in June 2015, data on all obesity surgical procedures at Aalesund hospital were registered in the local registry. By June 2015, data on the treatment outcomes of 697 gastric bypass procedures and 98 gastric sleeve procedures were recorded. Similar local quality registries and research data collections were established at other hospitals, establishing sources for several scientific papers and PhD-projects (65-68). Long-term results following surgical treatment for severe obesity have been requested by health authorities as well as patients (69).

In 2018, obesity surgery was performed at 15 public and 7 private hospitals in Norway, and nearly 3000 surgical procedures for weight loss are performed per year (70). It can be estimated that approximately 30 000 Norwegian patients have undergone gastric bypass surgery since 2004, and worldwide somewhere between one and three million people have had this treatment since the procedure was first performed in 1966 (71). Still there is a lack of studies on mid- and long-term results involving close follow-up of patients (72).

Obesity surgery research

The first documentation of the effects of obesity surgery was published in the form of case reports or case series reports on newly developed methods, (34, 40, 44).

As a follow-up after the 1991 National Institute of Health (NIH) Consensus Conference on surgical treatment of severe obesity, a multidisciplinary workshop was convened in USA in May 2013 by the National Institute of Diabetes and Digestive and Kidney Diseases and the National Heart, Lung, and Blood Institute. The aim of the workshop was to summarize the current state of knowledge about obesity surgery, review research findings on the long-term outcomes and establish priorities for future research (73).

At the workshop several knowledge gaps were identified, among them the incidence of surgical complications, the predictors of surgical outcomes, T2DM remission-rates, cardiovascular events, mental health outcomes, as well ass cost and health care use.

Randomized controlled trial (RCT) studies are challenging to perform in obesity surgery. It is particularly difficult to randomize between surgical and non-surgical treatment with long observation times, for ethical reasons. When two or more surgical methods are expected to be equal, randomization is possible, but it is often difficult to recruit patients because they have preferences for one method. Most RCTs have a limited number of participants, like the

Finnish Sleeve-pass study (N=240), the Swiss SM-BOSS (N=217), or the Norwegian Oseberg study (N=109) (58, 74, 75).

An alternative to RCTs is well designed observational studies with matched control groups. The longest running observational study following patients after obesity surgery is the Swedish Obesity Study (the SOS study), which follows patients undergoing obesity surgery compared to patients with severe obesity receiving care as usual (76-79). The SOS study is a matched, prospective trial including 4047 participants, where 2010 participants underwent obesity surgery (13% gastric bypass, 19% gastric banding and 68% vertical banded gastroplasty), and 2037 participants received standard care. After a mean follow-up of 15 years, weight loss and improvement in comorbidities was better, and the number of cardiovascular deaths were significantly lower in the surgery group (76, 78). The study is still collection data on 20 years follow-up.

The Utah-study is an observational study involving Roux-en-Y gastric bypass and two control groups, one with patients applying for obesity surgery, but without insurance coverage to get the treatment, and one with patients with severe obesity who did not opt for surgery. So far, six and twelve year's observational data have been published from the Utah study (80-83). The mean %TWL was 35% after two years, 28% after six years, and 27% after twelve years. Remission of T2DM was 75% after two years, 62% after six years and 51% after twelve years. There was nearly no change in weight in the non-surgical group. In addition to remission of T2DM, the surgery group had lower incidence of hypertension and dyslipidaemia than the non-surgical group (80).

Long-term observational studies comparing obesity surgery with non-surgical treatment are expensive and have organizational challenges in a clinical setting, particularly in healthcare systems where long-term follow-up is not covered. Therefore, many of the published studies on obesity surgery are either observational studies with historical or no controls, studies using

data collected for administrative purposes or studies with low numbers of participants. Studies using data from local or national quality registries, patient surveys, and studies using qualitative methods add important knowledge on the effects of obesity surgery, even if the scientific framework is not optimal.

To be able to compare results from studies performed in diverse setting, guidelines for standardized reporting of outcomes after metabolic surgery and obesity surgery are established (84).

Ethical aspects of obesity surgery

The medical ethos "Do no harm" is the ideal guide for all medical treatment. However, all treatments have adverse effects, and in clinical practice, it is often more about doing as little harm as necessary to gain as much benefit as possible. Surgery on healthy organs is controversial, even if the intention is good (32).

The ethical aspects of surgical treatment for severe obesity have been discussed among surgeons as well as from a more philosophical point of view. A health technology assessment from Finland by Saarni et al from 2011, concluded:

> "*Several ethical issues were considered important when organizing and performing surgical treatments for obesity. Patient autonomy, especially informing the patient, was thought to require special attention for several reasons: The operations are not immediately lifesaving; its success depends greatly on the patient understanding and adhering to life-long changes in eating habits; there may be commercial interests and societal prejudices that influence the autonomy of patients. Finally, given that obesity is more prevalent in socioeconomically disadvantaged populations and the obese are widely discriminated against, as well as the supply of obesity surgery not meeting the*

need in many places despite being cost-effective, a special emphasis on justice in access to surgical treatments of obesity is probably warranted."(4)

A decision to use surgery to treat severe obesity requires assessment of the risk-benefit ratio in each case (36). It also implies a commitment from the institution which offers the treatment to have a program for long-term follow-up of the patients, in order to prevent, discover and treat potential adverse long-term consequences of the surgical treatment (85).

Theoretical framework for the thesis

Treatment goals in obesity surgery

From a medical point of view the treatment goal in obesity surgery is health improvement by reducing the fat mass by weight reduction, and to reduce the long term consequences of metabolic or sick fat disease (81, 86, 87). The growing understanding of obesity as a multifactorial, progressive chronic disease should also change the aim of obesity surgery from "curative" to "disease modifying" and moreover, maximal weight loss as success criteria may be replaced by optimal physical and mental function of the patient after surgery.

Reduction of the percentage of body fat mass is more strongly correlated to metabolic improvement after obesity surgery than weight reduction (88). However, easily applied, standardized methods for measuring fat mass are lacking.

From the patient's point of view, improvement of obesity related comorbidity ranks higher than weight loss among expectations prior to surgery (89, 90). Improved physical activity, pain reduction and increased life expectancy follows on the list of expectations. In addition to health improvement, patients also have a desire to change the appearance of their body (91).

Impaired quality of life is common among patients seeking obesity surgery, and they expect improved physical as well as mental health following weight loss. Improvement in health-related quality of life after obesity surgery is mainly documented in relation to improvement of physical function (92).

Although weight loss and resolution of obesity-related comorbidity are the main aims when considering obesity surgery, surgical complications and new morbidities are a possible downside, both for the patient and society.

The framework of this study has been to evaluate the long-term consequences of laparoscopic gastric bypass as it was documented in the local quality registry for obesity surgery from a single centre, supplemented with clinical information from the hospital's electronic patient records. Changes on individual and group level were explored, including the long-term consequences for the healthcare services.

Adverse effects following surgical treatment, generating a further need for medical treatment, is a cost for the hospital and a negative experience for the patient. Abdominal pain is a commonly reported problem after gastric bypass surgery, but it is a challenge to measure the degree of intensity and the duration of such pain. By analysing data on how this problem induces use of medical examinations and surgical treatment, the most severe consequences of abdominal pain may be measured.

Self-rated health

Self-rated health (SRH) has been the most widely used public health indicator since the 1950s, and has proved to be a more valid and powerful predictor of morbidity, mortality and future healthcare use than more comprehensive self-reporting instruments and objective biometric measures for predicting future health (93). Self-rated health is related to

inflammation, genetics, allostatic load, physical function, socio-economic, and psychological factors (94-97).

Self-rated health is measured as a person's subjective evaluation of his or her general health, expressed as the answer to the question "In general, would you say your health is 1) excellent? 2) very good? 3) good? 4) fair? 5) poor?" This is the first question on the Short form 36 (SF-36); a widely used quality of life questionnaire, but in public health surveys SRH is most often used as a single question.

Self-rated health may on one hand be interpreted as a person's spontaneous assessment of health status, or on the other hand as an aspect of one's enduring self-concept (98). Interpreted as a spontaneous assessment of an individual's health status it should be regarded as the most precise measure of actual experienced health. Interpreted as an enduring self-concept it expresses a person's attitude to own health and health challenges (99).

Measuring the effect of obesity surgery

The success of obesity surgery is usually measured as the degree of weight loss, either as % total weight loss, % excess weight loss, % excess BMI-loss or change in BMI. From an individual perspective, the more you lose the better off you are. On a group level the higher number of patients reaching a certain level of weight loss, the better is the surgical procedure.

The most obvious aim for obesity surgery is weight loss, but weight loss is only the means to achieve the goal of improved health, better quality of life and a longer life (100). The optimal measure of weight loss is debated, as all commonly used measures depend on initial weight. Total weight loss in kilograms, the percentage of total weight loss (%TWL) and change in body mass index (BMI) do not discriminate between loss of excess weight or reduction in normal weight. When excess weight is defined as weight above the upper limit of normal

weight of BMI 25 kg/m^2, the percentage of excess weight loss (%EWL) and percentage of excess BMI-loss (%EBMIL), have been recommended as suitable when reporting outcomes of obesity surgery (84). However, attempts have been made to find an even more clinically relevant measurement of postoperative weight loss based on clinically observed data, creating an algorithm for weight loss that considers preoperative BMI, gender and age (101, 102). In non-surgical studies %TWL is routinely used to assess weight loss, and this measure has lately been recommended used in surgical studies as well, as %TWL results in less variability when stratified by various preoperative patient characteristics. It is suggested that %TWL ≥ 20% should be considered as a good response to obesity surgery (103).

Maximum postoperative weight loss (Nadir BMI) is achieved 12-24 months after surgery, and most patients experience some weight regain in the following years. Whether this regain is a progression of the underlying obesity disease, or a treatment failure, can be debated. The measure of secondary weight regain that correlates best with clinical outcomes, is reported to be weight regain as percentage of maximal postoperative weight loss (104).

Resolution of comorbidities is another measurable outcome after obesity/metabolic surgery. It is important to standardize the preoperative definition and postoperative criteria for remission or resolution of T2DM and other comorbidities in order to compare results between different surgical methods (84).

Background for the three papers

Obesity surgery has a broad spectre of effects, both on the individual level, on the cellular level, as well as for the healthcare services. The topics chosen for the three papers were selected in discussion with my supervisors, and based on the data available in the registry, in

respect of the integrity of the patients and in recognition of the present knowledge gaps in the field.

This thesis used the local quality registry for obesity surgery at Aalesund hospital to explore the results of gastric bypass surgery after more than five years following surgery. The registry has been updated on an annual basis, and the number of primary gastric bypass procedures with five or more year's postoperative follow-up were 644 by the last update in January 2019.

Laparoscopic Roux-en-Y gastric bypass was the sole method used at Aalesund hospital from 2004 to 2009, and the major procedure until 2015. As the number of patients having undergone sleeve gastrectomy with more than five years postoperative observation in the registry was low when this project started, only gastric bypass patients were included in the studies in this thesis.

Abdominal pain is common after gastric bypass surgery, but sometimes this symptom is the signal of a life-threatening condition, leading the patient to undergo medical investigations and surgical treatment.

The first paper explored the need for medical imaging and surgical treatment for abdominal pain among patients observed more than five years after surgery.

The second paper addressed how to measure the global outcome for the patients after obesity surgery. At the intersection between weight loss, remission of comorbidities, change in quality of life, postoperative complications and life events, finding a measure that capture the sum of beneficial and adverse effects has been requested (100). This paper explored whether change in self-rated health was applicable as a sum-score for the global effect of obesity surgery.

As the food bypasses the main sites of absorption of many important nutritional elements following gastric bypass, nutritional deficiencies are prone to develop during the years after

treatment. The patients are advised to use supplements of vitamins and minerals, and to have blood tests taken on a regular basis (105). In the third paper the change in iron stores and the need for intravenous iron treatment were explored.

The aims of this thesis

Obesity surgery procedures are commonly performed on a worldwide basis. The short-term effects, like weight reduction and improvement in comorbidities and quality of health, are well documented. However, the patients undergoing obesity surgery are often in the middle of their lives, and knowledge about the long-term effects of obesity surgery, for the patients and the health care services, are lacking. By using observational data from a single centre cohort of patients with postoperative follow-up of more than five years after Roux-en-Y gastric bypass, the aims of this project have been to study the long-term effects of the gastric bypass surgery. More specifically to explore:

1. The frequency of acute, intermittent or chronic abdominal pain after gastric bypass surgery in need of medical investigation (imaging) and surgical treatment.

2. Changes in self-perceived general health five years after gastric bypass surgery compared to before the procedure.

3. The long-term changes in iron stores and anaemia after gastric bypass surgery, and the need for intravenous iron treatment for iron deficiency.

Materials and Methods

This thesis used data from a quality registry covering all patients who underwent obesity surgery at Aalesund hospital from April 2004 to June 2015. The registry was created on

request from Central Norway Regional Health Authorities, to monitor the activity and outcomes of obesity surgery, until a national registry for this treatment was created. Inclusion of new patients was closed when SOREG-Norway was recognized as a national quality registry for obesity surgery in June 2015.

The quality registry was established and approved by the Data Protection Officer for research in Helse Møre and Romsdal according to section 26 of the Health Personnel Act. The registry has been stored electronically as an Access file at the research server in Helse Møre and Romsdal, with access limited to persons involved in updating the registry.

This project was evaluated by the Regional Committee for medical and health research ethics (REK) in April 2016 as a quality assurance project that falls outside the scope of the Health Research Act, and it could be implemented without approval of REK (REK Sør-øst A 2016/331 Fedmekirurgi ved Ålesund sjukehus 2004-2015, langtidsresultater). The project was approved by the Data Protection Officer for research in Helse Møre and Romsdal.

This local quality registry contains preoperative, perioperative and follow-up data in terms of anthropometric data, comorbidities, complications and medical events that could be related to the surgical procedure, on a total of 697 patients who underwent gastric bypass from April 2004 until March 2015, as well as 98 patients who underwent sleeve gastrectomy from November 2009 until April 2015. The data was collected prospectively and updated with information from the common electronic medical record system for Central Norway Regional Health Authority on an annual basis, through January 2019. For each of the papers, only patients with follow-up of more than five years were included. The first sleeve gastrectomy was recorded in the registry in 2009. The number of sleeve gastrectomy patients who had a follow-up of more than five years was low when the study started, and therefore they were not included in any of the papers.

Baseline and perioperative data were entered into the registry after the operation, and the follow-up data was entered after the planned out-patients visits, or after unplanned events. For completeness of data, the registry was updated annually with data from the common electronic patient records containing information from the all hospitals under the Central Norway Regional Health Authority.

Surgical intervention and follow-up

The patients were selected for obesity surgery at the out-patient clinic based on the national guidelines for obesity surgery and individual evaluation (21). A standardized set of blood tests were taken at baseline and all patients had to participate in a preparation program including a patient education day in groups, an individual guidance on diet, evaluation of lung function and sleep apnoea. All patients had a preoperative upper endoscopy including a test for Helicobacter pylori, and preoperative eradication was given if the test was positive. Waiting time from the first visit at the obesity outpatient clinic to surgery was on average one year.

The gastric bypass surgery procedures were performed with laparoscopic antecolic, antegastric technique, with a biliopancreatic limb of 40-60 cm and an alimentary limb of 100 cm or 150 cm, depending on BMI below or above 50 kg/m^2. The gastrojejunostomy was constructed with a 45mm linear stapler and hand-sewn closure (43). The jejunojejunostomy was made with a triple-stapling technique as described by Madan for the first 438 patients (77%), whereas for the last 131 patients (23%), the jejunojejunostomy was made with one 60 mm linear stapling magazine and hand-sewn closure (106). The mesenteric defects were not closed at the primary procedure in this period. The rate of conversion to open technique was 0.2%. Planned postoperative hospital stay was in the first years three days, later reduced to two days. Lifestyle recommendations were given by dietician and physiotherapist before the patients left the hospital.

Recommended supplements after surgery were multivitamin-mineral tablets, Vitamin B12 as intramuscular injections every 2nd month and Calcium with vitamin D. In addition, per oral iron supplement were given, depending on ferritin level, to keep ferritin > 50µg/L.

Ursodiol to reduce gallstone formation in the weight loss period was not used. There was no routine use of proton pump inhibitor postoperatively, only if indicated.

After the procedure, a standardized set of lab-tests were taken when the patients met at the out-patient clinic for follow-up at 2, 6, 12, 18, 24, 36, 48 and 60 months after the operation. The individual follow-up visits included weight measurement, evaluation of blood tests and advice on nutritional supplements and medical issues related to the operation. The patients were also invited to participate in a follow-up program in groups involving 10-12 meetings over two years, and a two-week program at a rehabilitation center during the first year after the procedure.

Intravenous iron treatment was given at the obesity outpatient clinic if iron stores were empty, mainly as ferric carboxymaltose 1g in one visit, and less often as iron sucrose 200 mg over five visits. Indication for intravenous iron treatment was ferritin < 15µg/L, independent of haemoglobin level.

Material for the first paper

Data collection for the first paper ended in August 2017, at that point there were observational data exceeding five years on 569 patients who underwent gastric bypass surgery between April 2004 and June 2012. All medical imaging due to abdominal pain, including X-ray, ultrasound, Computer tomography and MRI, and all abdominal surgical procedures performed at hospitals in Central Norway Regional Health Trust, were registered. Medical imaging on other indications, and gynecological procedures were not included. The use of private

hospitals was minimal in this area, and no surgical emergency consultations were performed on the patients outside of public hospitals in the region in this period of time.

Material for the second paper

The registry was updated prior to the second paper in February 2018, increasing the sample to 601 patients with a follow-up period of more than five years. From September 2006 to June 2015 all patients were asked to complete the Short form 36 questionnaire (SF-36) at the end of the preoperative education day, approximately one month prior to the procedure (107). The responses to the questionnaire had no influence on the decision on whether the patients would have the procedure or not. From 2010 to 2016, the patients were asked to complete the same questionnaire at the five-year follow-up visit. The questionnaires were filled in on paper, and the results entered into the quality registry at a later stage. In total, the number of preoperative SF-36 questionnaires was 477, and at five years the number was 272.

The population of study for the second paper included the 233 patients with both preoperative and five-year SF-36 questionnaires, who underwent procedure between September 2006 and February 2011. In this period a total of 359 patients underwent surgery, and 322 (90%) attended the five-year follow-up appointment. The 233 with complete datasets represented 65% of the patients who underwent surgery during the period.

Material for the third paper

In the third paper, all patients with a follow-up period of more than five years by January 2019 were included. From April 2004 to December 2013, 644 patient underwent primary gastric bypass at Aalesund hospital. The additional 8 patients who underwent gastric bypass as a secondary surgical procedure for obesity in the same period were not included in the

study. Results from laboratory tests related to the five-year standardized outpatient follow-up program were added to the quality registry by collecting data directly from the hospital's laboratory data system. Only laboratory test results linked to visits at the outpatient clinic were included. Laboratory results were available in the registry for 544 (84%) patients at baseline, and 428 (66%) after five years. Missing laboratory data at baseline might be due to the lab-tests being analyzed at another hospital, or the physician requesting the tests not being affiliated to the surgical unit. Missing laboratory data in the follow-up period were mainly due to patients dropping out from the planned appointments.

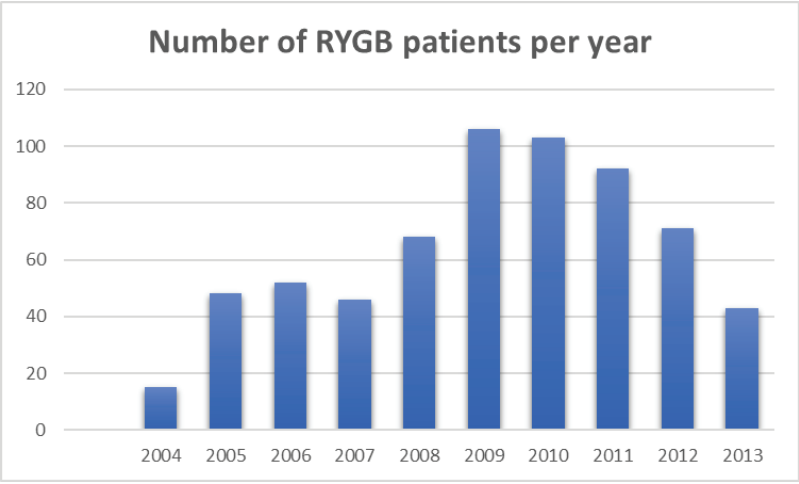


Figure 3. The number of patients who had gastric bypass surgery at Aalesund hospital per year in the study period.

Methods

Anthropometric data were collected by nurses at the outpatient clinic, and scales designed for people up to 300 kg were used in the entire period. The patients were weighed with light clothes, without shoes. Height was measured at the first visit and after two and five years. BMI was calculated by weight in kg over (height in meter)^2.

Weight development from the point of gastric bypass surgery through five years following surgery was reported by the four standard measures, percentage excess weight loss (%EWL), percentage excess BMI loss (%EBMIL), percentage total weight loss (%TWL), and change in BMI (84). Weight regain from nadir weight occurring between one and two years postoperatively to five years following surgery was reported as change in BMI and percentage of maximum weight loss (104).

Categorical variables were reported in numbers and percentages, and continuous variables were presented as means ± standard deviation (SD), or median and interquartile range (IQR) if the variables were not normally distributed. For comparison of categorical variables, the Pearson χ^2 was performed, and for comparison of continuous variables, independent and paired t-tests were performed. Non-parametric tests were used for non-normally distributed variables. In the first paper, Kaplan-Meier estimates were used for continuous variables. $P < 0.05$ was considered statistically significant for all analyses. Statistical analyses were performed using IBM SPSS version 23 (SPSS Inc., Chicago, IL, USA) software and STATA 14 (StataCorp).

In the second paper, the difference between baseline SRH-scores and SRH-scores after five years was calculated, and the change in SRH was categorized as *improvement*, *no change*, or *decrease*. The no change and decrease categories was further merged to *non-improvers*, since the number with decreased SRH was low. Baseline and postoperative SF-36 answers were analyzed as sum-scores for the eight domains in the SF-36 questionnaire.

In the third paper, iron stores were graded as depleted (ferritin ≤15µg/L), low (ferritin 16-50 µg/L), moderate (ferritin 51-100 µg/L), and replete (ferritin > 100 µg/L).

Results

General results

Baseline and follow-up data on age, sex, weight, BMI and preoperative comorbidities are presented as patient's characteristics in all papers. As the number of patients included in the three papers differed, a summary of the data from the quality registry are presented here.

Mean ±SD age for the 644 patients with five years postoperative follow-up by January 2019, was 39.8 ± 9.7 years, and 483 (75%) of the patients were women. In the observation period of 5 to 14 years, mean 112 ± 29.3 months, fifteen (2.3%) patients have died, two of them in the early postoperative period.

Body mass index (BMI) was 45.2 ± 5.3 kg/m^2 when the patients first met at the outpatient clinic, and 43.9 ± 5.1 kg/m^2 when they underwent surgery. BMI at one year was 29.1± 4.3 kg/m^2, and BMI after five years was 31.6 ± 5.3 kg/m^2.

The mean weight at the time of surgery was 128 ± 20.4 kg, after one year 85 ± 16 kg, and 92 ± 19 kg after five years. Mean percentage total weight loss (%TWL) was 33.4 ± 6.9 % one year after surgery, and 27.6 ± 10.1 % after five years. Percentage Excess weight loss (%EWL) was 79.8 ± 18 % one year after surgery, and 65.8 ± 24 % after five years.

Of the 106 (16.5%) patients who were on medication for type 2 diabetes mellitus (T2DM) before the operation, eight used per oral medication and fifteen used insulin at five years. In addition, a total of 168 (26.1%) patients were on medication for hypertension, and 83 (12.9%) were on medication for hyperlipidaemia before the operation. When it comes to sleep apnoea 155 (25.2%) were diagnosed before the operation, and 125 (19.4%) used CPAP.

Seventy-four out of 483 women (15.3%) gave birth to 106 children in the follow-up period.

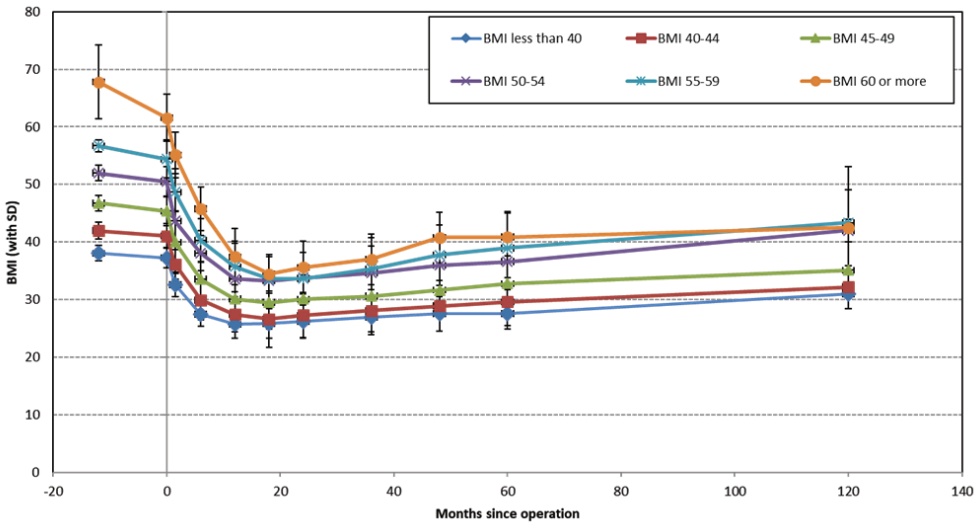


Figure 4. Change in mean BMI from baseline until 10 years after gastric bypass surgery.

The results are very much in line with results published by others on five-year follow-up after gastric bypass surgery, which is the reason for not publishing these data in a separate paper.

Summary of the results in the published papers

Paper 1

The first study explored the frequency of medical imaging and abdominal surgery for acute, intermittent and chronic abdominal pain in 569 patients who had Roux-en-Y gastric bypass at Aalesund hospital between 2004 and 2012. In this period the mesenteric defects were not closed. Patients with a follow-up of five years or more were included, and with a mean follow-up of eight years after gastric bypass surgery, half of the patients underwent medical imaging for abdominal pain. Forty percent had one or more CT-scans, and 28% had one or more ultrasound scans.

In the observation period, 127 (22%) patients underwent abdominal surgery, gynaecological procedures excluded, and 34 (6%) had two or more procedures Mean time from gastric bypass surgery to the first and second operation was 38 ± 28 months and 60 ± 27 months, respectively. The need of abdominal surgery for women was 25.6% compared to 12.5% for men ($p<0.001$).

The need for surgery treating suspected internal hernia and cholecystectomy was equal, at 9.3% for both procedures, but the mean time from gastric bypass surgery to operation was shorter for cholecystectomies. Half of the surgeries for suspected internal herniation were acute. Fifteen patients (2.6%), all women, underwent both surgeries. There were no gender differences in frequency of surgery for suspected internal hernia, but cholecystectomies were more frequent among women.

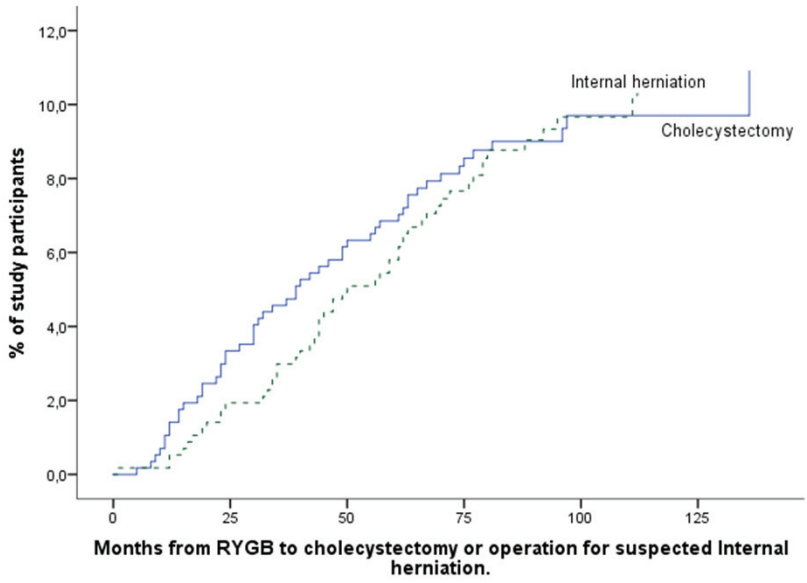


Figure 5 Time from gastric bypass surgery to cholecystectomy and surgery for suspected internal herniation.

Paper 2

The second study explored whether Self-rated health (SRH), a patient reported, simple and robust instrument from public health research, is applicable as an outcome measure in obesity surgery. The primary aim of the study was to evaluate change in SRH from before to five years after surgery.

The patients reported their health as worse than the general population before the operation, but at five years the results were similar to those reported by the general population in public health surveys performed in Norway (108). The proportion of patients reporting fair or poor SRH at baseline was 54.5% (127 of 233), compared to 18.5% (43 of 233) at five years.

Comparing baseline and five year follow-up, 154 (66.1 %) patients had a better SRH-score at five years, 60 (25.8 %) had no change and 19 (8.2 %) had a decrease in SRH score at five years. There were no differences in age, gender, weight related comorbidity, baseline weight and BMI, difference in %TWL or BMI at five years, for improvers compared to non-improvers, but the improvers had lower weight-regain from nadir to five years than non-improvers. Improvement in SRH corresponded to improvement in all domains in the SF-36 questionnaire.

SRH, expressed by the answer to one single question, seems relevant and valid as an outcome measure for obesity surgery.

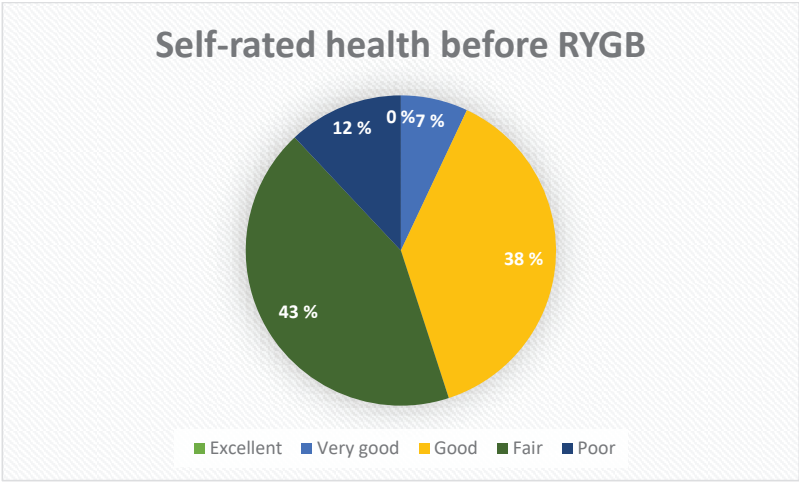


Figure 6 Self-rated health one month before gastric bypass surgery.

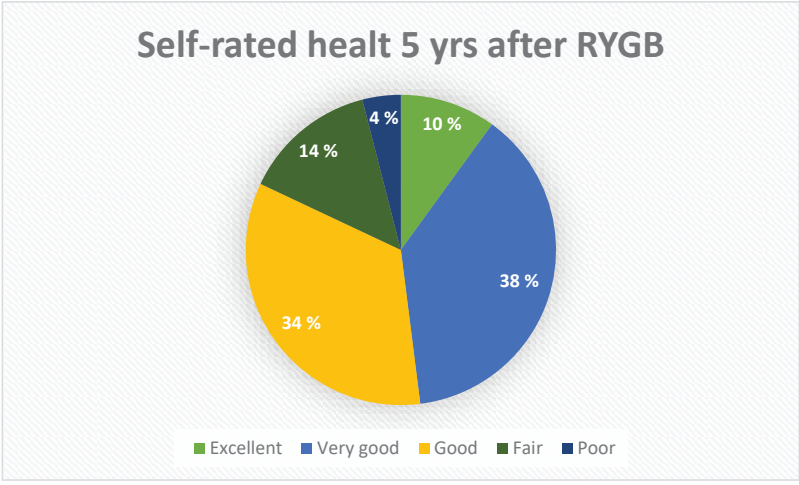


Figure 7 Self-rated health five years after gastric bypass surgery

Paper 3

Iron absorption is disturbed after gastric bypass and iron deficiency, with or without anaemia, are reported in almost half of the patients. Intravenous iron is an option when per oral iron is insufficient or not tolerated. The third study explored whether routinely offering intravenous

iron treatment when iron stores were depleted might prevent anaemia and iron deficiency after gastric bypass surgery.

Clinical information was available at baseline for 644 patients undergoing gastric bypass surgery between 2004 and 2013, and for 553/644 patients at five years, and laboratory results were available for 540/644 patients at baseline and 411/644 patients after five years. Overall, 187/483 (38.7%) women, and 9/161 (5.6%) men were given intravenous iron treatment in the observation period. From baseline to five years, mean haemoglobin decreased by 0.3 g/dL in both men and women. Anaemia occurred in 18/311 (5.8%) women and 9/100 (9%) men at five years. Depleted iron stores (ferritin ≤15µg/L) were observed among 44/323(13.6%) women and 3/102 (2.9%) men, and low iron stores (ferritin 16-50µg/L) occurred in 144/326 (44.6%) women and 38/102 (37.3%) men five years after gastric bypass surgery.

By routinely offering intravenous iron treatment to patients with depleted iron stores after gastric bypass surgery, haemoglobin levels were preserved, but half of the patients experienced low or depleted iron stores after five years.

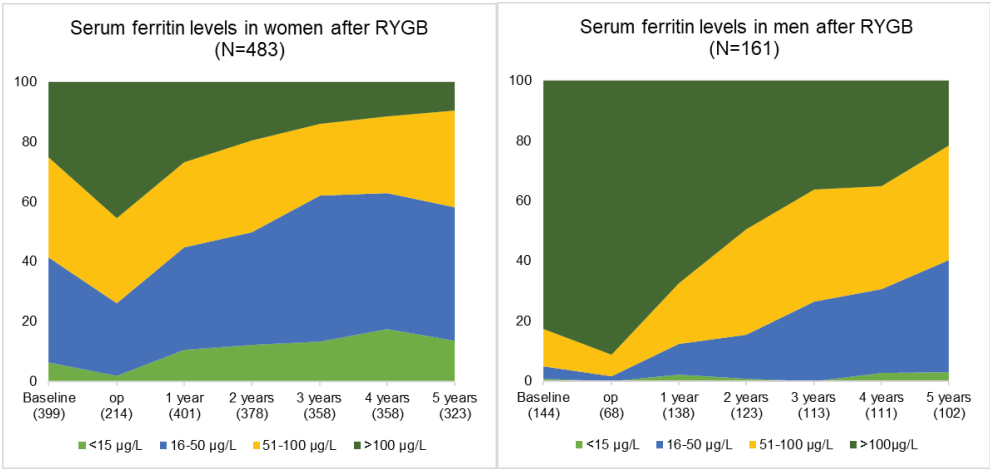


Figure 8 Serum ferritin levels from baseline to five years after gastric bypass surgery

Discussion

Obesity surgery as treatment for severe obesity and obesity-related metabolic diseases was re-introduced in Norway in 2004. The initiative came from the Ministry of Health, and the Regional Health authorities organized it as a centralized, high volume, multidisciplinary treatment with National guidelines and focus on research and long-time follow-up (21). After a rapid increase in the number of surgical procedures the first years, the number of operations has stabilized at around 3000 procedures per year from 2009. The number of hospitals performing obesity surgery has increased from seven in 2005 to 22 in 2018 (15 public and 7 private), and one third of the patients undergo surgery at private hospitals as self-paying patients (70). The number of patients admitted to non-surgical treatment for severe obesity is unknown.

Accepting severe obesity as a chronic disease implies accepting that it is a disease that can be treated but not cured. In this framework, the goal of obesity surgery should be to improve health and functionality, not primarily to bring the weight as close to normal level as possible (10). Qualitative studies have brought insights into life after obesity surgery, focusing on the negotiation between the positive and negative experiences living in a post-bariatric body (109, 110).

The positive effects of obesity surgery on weight reduction and improvement of comorbidities are well documented (81, 87, 111). It is also well known that abdominal pain, fatigue, iron deficiency, hypoglycemia and osteoporosis are among the problems that can arise in the wake of a successful postoperative weight loss (66, 112, 113). The present PhD-thesis explores the consequences of gastric bypass surgery beyond weight loss, by assessing the frequency of complications and other unexpected consequences after gastric bypass generating a need for medical investigation and treatment. Complications are a burden on patients, but also a cost to

the healthcare system and society. The thesis also explores how the diverse effects of obesity surgery influence patients' perception of their general health status.

Methodological considerations

This thesis is based on data from a single centre. Although national guidelines have been followed, local adaptations may have influenced patient selection, and also the indications for diagnostic imaging and surgical intervention in the years after surgery. The topics for the three papers were chosen after data collection, based on questions raised in clinical practice.

Observational data from clinical practice from an unselected population of patients seeking surgical treatment for severe obesity were used. The quality registry, constituting the main data source, was not created primarily for research purposes, but for surveillance of treatment quality in a well-structured clinical pathway, and included a standardized collection of data from baseline and follow-up visits. During the entire treatment period there was a stated ambition to collect data on a scientific level, and a limited number of trained personnel has been responsible for data collection.

The size of the population under study in the three papers are comparable to similar published observational studies in the field. In paper 1 and 3 all patients who underwent primary gastric bypass in the study period are included. In paper 2, the study population is limited to the patients who had completed SF-36 questionnaire prior to surgical procedure, as well as after five years. There were no differences in baseline characteristics and general outcomes when the study population in paper 2 was compared to the entire cohort.

A major strength in this study was that all patients who underwent obesity surgery in the period were included, and baseline and perioperative data were complete for all participants. The follow-up rate was high compared to other studies, and the follow-up regimen

standardized. Such an unselected study population is a firm basis for reporting results close to real world clinical practice.

In paper 3, results from laboratory tests were collected directly from the hospital laboratory data system. The number of laboratory test results was lower than the number of patients with clinical data at each point in time. No attempts were made to search for laboratory test results in the electronic patient record or in the paper patient record.

None of the papers had control groups. For all three papers, control groups of patients in non-surgical treatment for severe obesity, and patients undergoing sleeve gastrectomy, or another major abdominal surgery, would be of interest. Sleeve gastrectomy was introduced in 2009 at the Aalesund hospital, and in the beginning only performed when gastric bypass was contraindicated due to comorbidity. The number of patients undergoing sleeve gastrectomy with more than five years postoperative follow-up was less than fifty. To compensate for the lack of control groups, the results have been discussed against and compared with results in other comparable publications.

It is timely to raise the question of whether a surgeon who has been involved in patient selection, performing the surgical procedures, involved in the follow-up of patients after surgery, and also has been responsible for the quality registry, can be objective as investigator on the same material. To avoid bias and conflicts between the role as clinician and investigator, I have been out of clinical practice at Aalesund hospital in the period of the PhD project. I have had my workplace at the Regional centre for obesity research at St. Olav's hospital, Trondheim University hospital, in the research period, and all statistical analyses have been performed on anonymized datasets. All steps in the research process are transparent and can be documented, and all data registered in the quality registry can be checked against the hospital's electronic patient record.

Study design, setting and participants

The unique quality of this material is the completeness of data in the observational period, as data could be collected from all hospitals in the region, and possible adverse effects related to the treatment could be registered if relevant even if the treatment was performed at other hospitals in the region. The access to clinical data was however limited to somatic conditions, as the clinicians did not have access to documentation regarding psychiatric treatment given at the hospital. Information on psychiatric conditions were only available if reported in the somatic journal.

As inclusion in the registry was not based on written consent, only data assessed as necessary for quality surveillance and considered as being in the best interest for the patient have been used. Questions on mental health prior to and after the treatment is therefore not explored in this thesis.

Generalizability

Compared to other publications and reports from national quality registries on outcomes after gastric bypass surgery, the study population and results in the present dataset are surprisingly similar. Almost all study populations have a majority of female patients, except studies from American Veterans hospitals (114). A mean age of 40 years, preoperative BMI of 42-46 kg/m^2 seems to be typical. Differences in national healthcare systems and socio-economic factors related to the national economy and different welfare systems, may however be relevant when comparing the results in some studies with studies from other parts of the world.

Main findings

The main results of the papers included in this thesis were:

1) With a mean follow-up period of more than 8 years after gastric bypass surgery, 40% of patients suffered from abdominal pain, needing one or more CT scans. The need for surgery treating suspected internal hernia and cholecystectomy was equal, at 9.3% for both procedures, but the mean time from gastric bypass surgery to operation was shorter for cholecystectomies

2) Self-rated health five years after gastric bypass surgery was improved for two thirds of the patients, unchanged for one in four, and decreased for one in twelve of the patients, compared to before surgery.

3) One third of the patients were in need of intravenous iron treatment after gastric bypass surgery, which prevented anaemia, but did not prevent a major drop in iron stores during the first five years after surgery.

Discussions on the three papers

Gastric bypass and other metabolic and obesity surgical procedures are performed in nearly all countries in the world, under varying economic conditions and different healthcare systems. A considerable amount of the surgical procedures is performed outside the public healthcare services, in institutions not holding the responsibility for general acute surgical care. Knowledge on the long-term need for medical imaging and surgical treatment following obesity surgery is relevant to evaluate the long-term cost and the capacity for treating complications after surgery. A similar frequency of contact with the health care system and hospital admissions for gastrointestinal surgery due to abdominal pain after gastric bypass

found in this study are reported in studies from Denmark and Sweden (113, 115). Differences in the perception of pain and the threshold for seeking medical health among patients undergoing gastric bypass surgery have also been investigated (66).

The findings on use of medical imaging are in line with another study on this topic (116). However, the value of CT-scans in diagnosing internal herniation is under debate (116-120). A negative CT-scan can't exclude internal herniation in need of surgical treatment, and qualified clinical examinations are necessary in order to evaluate patients.

In this paper, all surgical procedures for suspected internal hernia were registered, not only the cases where internal herniation was found during the procedure. In half of the cases there was no internal herniation, but the cost and consequences of a surgical intervention are the same for the patient and the healthcare system. The level of internal herniation after gastric bypass surgery without closure of the mesenteric defects is reported to be at almost the same level in other studies with similar period of follow-up (121-124).

The jejunojejunostomy was made with a triple-stapling technique, as described by Madan and Frantzides, for the first 438 patients (77%), while for the last 131 patients (23%) the jejunojejunostomy was made with one stapling magazine and hand-sewn closure (106). Thirty-seven out of 438 (8.5%) patients who had a triple-stapled jejunojejunostomy (mean observation period 109 months) underwent a procedure for suspected internal hernia, compared to 15 out of 131 (11.5%) who had a single-stapled jejunojejunostomy (mean observation 70 months) ($p < 0.05$). This is an observation that has not been reported earlier, and to explore this observation further, a larger dataset is needed. Before it became routine to close the mesenteric defects, Madan recommended the triple-stapling technique to avoid internal herniation (125). The technique has been suggested as suitable in order to avoid kinking of the jejunojejunostomy when closing the mesenteric defects (126).

Regarding gallstone disease, it is well known that the rapid weight loss after obesity surgery increases the risk of gallstones. After gastric bypass, treating complicated gallstone disease is a challenge due to the altered anatomy in the patient. In the era of open surgery, cholecystectomy was often performed as part of the obesity surgery procedure. With laparoscopic techniques, concomitant cholecystectomy is more complicated, and is generally not advised (127). Treatment with Ursodiol in order to reduce gallstone formation during the first months after gastric bypass surgery has been advocated by some, but was not applied in this cohort.

The ASMBS guidelines, updated in 2019, recommend cholecystectomy after gastric bypass only for patients with symptomatic biliary disease, but prophylactic cholecystectomy may to be considered in asymptomatic patients to avoid choledocolithiasis (128). The updated guidelines also recommend routine use of Ursodiol after gastric bypass.

Measuring more than weight change, remission of comorbidities and frequency of complications is important in order to evaluate the true effect of obesity surgery for the patient. Valid measurements for improvement or decrease in general health is necessary when comparing the difference between surgical and non-surgical treatment for severe obesity, and also to compare the global effect of different surgical methods. General questionnaires like SF-36 are commonly used to explore change in quality of life after obesity surgery. The initial improvement in quality of life after one or two years measured by the SF-36 questionnaire, is often succeeded by a decrease after five years (129). This may be an effect of wear and tear after many years of physical as well as mental overload, owing to severe obesity prior to surgery. Disease-specific quality of life questionnaires for obesity and obesity surgery, like BAROS and the Impact of Weight on Quality of Life-Lite (IWQOL-Lite) are developed, but the use in clinical practice varies (130). Self-rated health, expressed by the answer to one single question, seems relevant and valid as an outcome measure for obesity surgery, and in

this observational study gastric bypass for severe obesity resulted in improved self-rated health in two-thirds of patients. In clinical use as well as in research, self-rated health might replace more comprehensive Quality of life tools, and self-rated health scores can be used to identify patients in need of closer follow-up after surgery. However, the present study on change in self-rated health after obesity surgery must be regarded as a pilot, and further research is needed to confirm whether this is a useful tool in follow-up after obesity surgery.

Despite the wide use of self-rated health in public health research, there is only a handful of studies on self-rated health in clinical settings. A study from Denmark found that self-rated health four weeks after coronary stenting was correlated to employment status after six months (131). In a study on knee-replacement, patients' self-rated health influenced pain and functionality after one year (132). However, a study on total hip and knee replacement surgery found no difference in average self-rated health after one year (133). SRH has also been explored in studies on follow-up after breast cancer treatment (134). There seems to be an unexplored potential for self-rated health as an easy-to-use tool for evaluating patients in clinical follow-up programs for several diseases. However, there is an ongoing discussion on how to understand what self-rated health really measures (135, 136)

Iron deficiency and iron deficiency anaemia are one of few nutritional deficiencies also being common in high income countries (137). Iron deficiency without anaemia is often overlooked as cause for diffuse symptoms of reduced health, such as fatigue, dizziness, reduced work capacity and so on. Iron is necessary for haematopoiesis, but also acts as an essential component of muscle myoglobin and mitochondrial activity (138). Iron is involved in energy production from glucose as well as fat, and it is of particular importance for muscles rich in red fibres, such as dorsal muscles, lower extremity extensors, the diaphragm, and intercostal muscles (139). Iron deficiency has been reported in up to half of patients following gastric bypass surgery, and it is caused by lower levels of gastric acid secretion, reduced intestinal

absorption surface, and dietary changes, with low tolerance to food being high in iron (140). The strict regulation of iron uptake from the gut by hepcidin might limit the ability to use per oral iron supplements to fill empty iron stores after obesity surgery, and thereby reduce the patients' quality of life and work capacity unnecessarily. To our knowledge, the present study on intravenous iron treatment after gastric bypass surgery is the first to document that routinely offering intravenous iron treatment to patients with empty iron stores might reduce the frequency of anaemia after gastric bypass surgery. A more active practice for per oral as well as intravenous iron treatment is probably needed to prevent empty iron stores after obesity surgery, and more studies are needed in order to explore the role of iron deficiency in relation to fatigue and muscular pain often reported in the long run following obesity surgery.

Clinical implications

The clinical implication of the findings in the first paper is that abdominal pain is a persistent problem long time after gastric bypass surgery. The frequency of internal herniation will probably be lower in patients undergoing surgery after the procedure of closing the mesenteric defects became standard, but the risk will not disappear. As some patients can have gallstones and internal hernia at the same time, relevant medical imaging should be performed prior to surgery in elective settings. Abdominal pain after gastric bypass may have other causes not calling for surgical intervention. Ulceration in the gastrointestinal anastomosis and bacterial overgrowth of the small intestines are conditions in need for medical treatment. Hospitals offering obesity surgery should as part of their follow-up program have a plan for medical examination and treatment for abdominal pain after surgery, to provide the patients with the best treatment, and also to gather experience on the consequences of the surgical techniques they use.

The clinical implication of the second paper is that a patient's self-rated health should be assessed before surgery, and be part of the shared decision making considering obesity surgery. Patients not perceiving their general health as reduced, should be informed about the possibility of experiencing an unchanged or decreased health after surgery, and may also be advised to wait until they experience reduced general health before they undergo a surgical procedure.

The clinical implication of the third paper is that intravenous iron treatment needs to be a treatment option in the follow-up after obesity surgery to prevent anaemia and iron deficiency. The optimal strategy for iron supplements to prevent iron deficiency after gastric bypass surgery must be explored, and life-long access to specialized care is necessary after obesity surgery. The clinical consequences of decreasing iron stores should be explored.

It should be considered to revise the threshold for intravenous iron treatment in the study population (ferritin < 15 µg/L) to prevent low iron stores and iron deficiency in the aftermath of obesity surgery.

The results from the third paper may be relevant for other groups of patients experiencing iron losses.

To conclude, a good life after obesity surgery depends on easy access to long-term follow-up by dedicated health personnel with sufficient knowledge about all sides of the consequences of the surgical procedures, who are able to diagnose possible complications at an early stage and give adequate treatment of surgical as well as non-surgical complications at the right time.

All types of symptoms after gastric bypass may be related to the surgical procedure, but they are most likely to be "just life", not in need for specific treatment. However, the patients are the experts – we have still a lot to learn.

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Assessment of self-rated health 5 years after Roux-en-Y gastric bypass for severe obesity

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Background: **Patients' perceptions of health change after bariatric surgery are complex. The aim of this study was to explore whether self-rated health (SRH), a widely used tool in public health research, might be relevant as an outcome measure after Roux-en-Y gastric bypass (RYGB) for severe obesity.**

Methods: **This was a single-centre retrospective study of a local quality registry. SRH score was registered at baseline and 5 years after RYGB. SRH, one of the 36 items in the quality-of-life Short Form 36 (SF-36®) questionnaire, is the answer to this single question: 'In general, would you say your health is excellent (1), very good (2), good (3), fair (4) or poor (5)?' Change in SRH was analysed in relation to change in weight, co-morbidities and quality of life after 5 years.**

Results: **Of a total of 359 patients who underwent RYGB between September 2006 and February 2011, 233 (64·9 per cent) reported on SRH before and 5 years after surgery. Of these, 180 (77·3 per cent) were women, and the mean(s.d.) age was 40(9) years. Some 154 patients (66·1 per cent) reported an improvement in SRH, 60 (25·8 per cent) had no change, and SRH decreased in 19 patients (8·2 per cent). SRH in improvers was related to better scores in all SF-36® domains, whereas SRH in non-improvers was related to unchanged or worsened scores in all SF-36® domains except physical function.**

Conclusion: **Two-thirds of patients reported improved SRH 5 years after RYGB for severe obesity. In view of its simplicity, SRH may be an easy-to-use outcome measure in bariatric surgery.**

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Introduction

The patient's experience of improvement in general health is the ultimate goal for all medical treatment. The perception of health has several aspects, and the WHO defines health as 'a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity'[1]. As severe obesity and bariatric surgery affect all of these aspects, and the most important factors motivating patients to consider seeking bariatric surgery are physical health and longevity[2,3], measuring weight change alone seems insufficient to evaluate the global effect of this treatment.

Generic as well as disease-specific tools have been used to evaluate change in quality of life (QoL) after bariatric surgery[4]. Generally, these measures are comprehensive and time-consuming, and more useful in research than in clinical settings. An association between improvement in QoL and objective improvement in health has not been documented.

Self-rated health (SRH) is a person's subjective evaluation of their general health, expressed as the answer to the question: 'In general, would you say your health is excellent, very good, good, fair, or poor?'[5–8]. In public health surveys and sociological research, SRH has been the most widely used health indicator since the 1950s[9]. Owing to its simplicity, SRH has proved to be a more valid and powerful predictor of morbidity, mortality and healthcare use than more comprehensive self-reporting instruments and objective biometric measures predicting future health[10–12]. Interpreted as a spontaneous subjective assessment of a person's health status, SRH is regarded as

Table 1 Patient characteristics

	SRH improvers ($n = 154$)	SRH non-improvers ($n = 79$)	P†
Age (years)*	39·9(9·0)	39·5(9·1)	0·711
Sex ratio (F : M)	115 : 39	65 : 14	0·190‡
BMI (kg/m^2)*			
At baseline	43·2(5·1)	43·8(4·7)	0·374
Nadir	27·7(3·9)	27·7(4·0)	0·993
At 5 years	30·5(4·9)	31·8(5·2)	0·057
Weight (kg)*			
At baseline	124·9(18·7)	126·1(19·6)	0·634
Nadir	79·6(13·8)	79·3(15·8)	0·885
At 5 years	88·3(17·0)	92·0(20·7)	0·138
BMI ≤ 35 kg/m^2			
At 1 year	140 (90·9)	69 (87)	0·396‡
At 5 years	121 (78·6)	58 (73)	0·377‡
%EWL > 50% at 5 years	124 (80·5)	58 (73)	0·215‡
%EWL at 5 years*	71·0(23·9)	64·3(23·9)	0·044
%EBMIL at 5 years*	71·6(24·0)	65·0(24·5)	0·049
%TWL at 5 years*	29·2(9·6)	27·2(10·3)	0·132
Change in BMI at 5 years (kg/m^2)*	12·7(4·9)	12·0(5·0)	0·295
Change in BMI from nadir to 5 years (kg/m^2)*	2·8(2·5)	4·0(2·7)	0·001
Change in weight from nadir to 5 years (kg)*	8·7(7·0)	12·0(8·2)	0·002
Weight regain (% of maximum weight loss)*	20·0(18·4)	26·6(18·0)	0·010
Type 2 diabetes mellitus			
At baseline	28 (18·2)	10 (13)	0·280‡
Remission at 5 years	21	6	0·369
Hypertension at baseline	40 (26·0)	18 (23)	0·594‡
Hyperlipidaemia	22 (14·3)	7 (9)	0·235‡
Sleep apnoea at baseline	40 (26·0)	16 (20)	0·333‡
Musculoskeletal pain at baseline	118 (76·6)	61 (77)	0·786‡
Smoking at baseline	50 (32·5)	14 (18)	0·019‡
Abdominal operations after RYGB	39 (25·3)	18 (23)	0·669‡
Internal herniation after RYGB	22 (14·3)	4 (5)	0·034‡
Cholecystectomy after RYGB	12 (7·8)	7 (9)	0·778‡
Abdominal excess skin removal after RYGB	75 (48·7)	37 (47)	0·787‡
Births after RYGB	17 of 115 (14·8)	5 of 65 (8)	0·163‡
SRH score*			
At baseline	3·83(0·76)	3·14(0·76)	< 0·001
At 5 years	2·25(0·77)	3·43(0·89)	< 0·001

Values in parentheses are percentages unless indicated otherwise; *values are mean(s.d.). %EWL, percentage excess weight loss; %EBMIL, percentage excess BMI loss; %TWL, percentage total weight loss; RYGB, Roux-en-Y gastric bypass. †Paired t test, except ‡χ^2 test.

the most precise measure of actual experienced health[13]. Public health surveys from different countries and social contexts have documented a relationship between SRH and genetic factors, inflammation and allostatic load, indicating a connection between SRH and biological processes[14–19].

People suffering from severe obesity report lower SRH than the non-obese, even in the absence of chronic disease[20]. However, despite many advantages, bariatric surgery also has some adverse effects[21–24]. As a general measure of perceived health, SRH might express the sum of positive and negative aspects of life as experienced by patients in the aftermath of the surgical procedure[25]. Nevertheless, there appear to be no publications on change in SRH after bariatric surgery.

The present study explored whether SRH, a patient-reported, simple and robust instrument from public health research, is applicable as an outcome measure in bariatric surgery. The primary aim of the study was to evaluate change in SRH from before to 5 years after

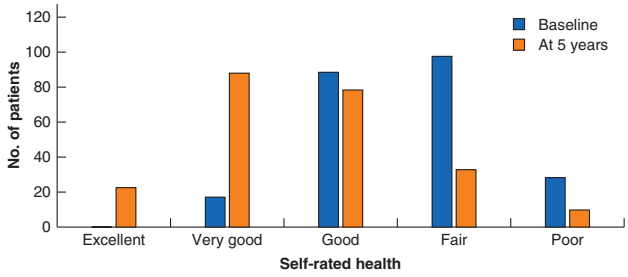
Fig. 1 Change in self-rated health from baseline to 5 years after Roux-en-Y gastric bypass for severe obesity

Improved SRH No change in SRH Decrease in SRH

Baseline	5 years					
	Excellent	Very good	Good	Fair	Poor	Total
Excellent	0	0	0	0	0	0
Very good	3	11	3	0	0	17
Good	9	36	30	10	4	89
Fair	7	37	37	15	2	98
Poor	4	4	9	8	4	29
Total	23	88	79	33	10	233

SRH, self-rated health.

Fig. 2 Self-rated health before and 5 years after Roux-en-Y gastric bypass



Roux-en-Y gastric bypass (RYGB) for severe obesity. The secondary aim was to explore the relationship between change in SRH to weight loss, co-morbidity and change in QoL.

Methods

This study is a retrospective analysis of patients who had RYGB at Aalesund Hospital, a public, non-academic, secondary referral centre covering a population of 260 000 in Norway. The indication for RYGB was a BMI above 40 kg/m^2 or a BMI above 35 kg/m^2 with obesity-related co-morbidity in an adult population. The SRH response was collected as part of the Short Form 36 (SF-36®; QualityMetric, Lincoln, Rhode Island, USA) questionnaire about 1 month before the operation, at the end of a preoperative education day[26]. Answers had no influence on the decision regarding whether the patient would have the operation or not.

SRH is the first question of the SF-36®, and the version used in this study was the Norwegian translation of the question and alternative answers: 'In general, would you say your health is (1) excellent, (2) very good, (3) good, (4) fair or (5) poor?'.

Data for all patients who had RYGB at Aalesund Hospital between September 2006 and February 2011 were collected prospectively in a local quality registry, and data from routine visits at 6 weeks and 6, 12, 18, 24, 36, 48 and 60 months after surgery were updated to January 2018. Participation in postoperative support groups, adverse events, plastic surgery and new symptoms related to the bariatric procedure were also registered.

The difference between baseline SRH scores and scores at 5 years was calculated, and the change in SRH was categorized as improvement, no change, or a decrease.

Weight development from baseline through 5 years was reported by standard measures: percentage excess weight loss (%EWL), percentage excess BMI loss (%EBMIL), percentage total weight loss (%TWL) and change in BMI[27]. Weight regain, from nadir weight occurring between 1 and 2 years after surgery to 5 years, was reported

Table 2 Change in SF-36® domain scores among improvers and non-improvers at baseline and 5 years after Roux-en-Y gastric bypass

	Baseline			5 years		
SF-36® domain	Improvers	Non-improvers	*P*†	Improvers	Non-improvers	*P*†
Physical function	57·4(20·1)	62·6(20·7)	0·065	93·4(13·0)	80·9(21·2)	< 0·001*
Role physical	41·0(35·3)	52·2(38·4)	0·026	84·2(31·8)	57·6(40·1)	< 0·001
Bodily pain	48·8(23·5)	54·5(28·9)	0·149	71·2(27·6)	49·7(27·7)	< 0·001
General health	44·5(20·1)	57·5(18·7)	< 0·001	81·8(17·3)	60·0(23·4)	< 0·001
Vitality	36·3(16·82	45·1(18·9)	< 0·001	57·1(21·5)	41·2(23·9)	< 0·001
Social function	67·0(25·9)	76·1(23·3)	0·007	86·4(20·7)	76·1(26·1)	0·003
Role emotional	71·2(36·1)	77·9(33·2)	0·137	82·6(33·3)	69·0(43·6)	0·019
Mental health	69·7(15·4)	75·2(14·7)	0·008	79·2(16·6)	70·6(19·2)	0·001

Values are mean(s.d.). *At 5 years, the scores for physical function were not normally distributed; the median (i.q.r.) score for improvers was 95 (95–100) and that for non-improvers 90 (75–95) ($P < 0·001$, Mann–Whitney *U* test). †Paired *t* test.

Table 3 Change in SF-36® domains from baseline to 5 years after Roux-en-Y gastric bypass in improvers and non-improvers

	Improvers			Non-improvers		
SF-36® domain	Baseline	5 years	*P**	Baseline	5 years	*P**
Physical function	57·4(20·1)	93·3(13·0)	< 0·001	62·6(20·7)	80·9(21·2)	< 0·001
Role physical	41·0(35·3)	84·2(31·8)	< 0·001	52·2(38·4)	57·6(40·1)	0·314
Bodily pain	48·8(23·6)	71·2(27·6)	< 0·001	54·5 (28·9)	49·7(27·7)	0·158
General health	44·5(20·2)	81·8(17·3)	< 0·001	57·5(18·8)	60·0(23·4)	0·271
Vitality	36·3(16·8)	57·1(21·5)	< 0·001	45·1(18·9)	41·2(23·9)	0·152
Social function	67·0(25·9)	86·4(20·7)	< 0·001	76·1(23·3)	76·1(26·1)	1·000
Role emotional	71·2(36·1)	82·6(33·3)	0·003	77·9(33·2)	69·1(43·6)	0·094
Mental health	69·7(15·4)	79·2(16·6)	< 0·001	75·2(14·7)	70·6(19·2)	0·017

Values are mean(s.d.). *Paired *t* test.

as change in BMI and percentage of maximum weight loss[28].

The study was approved by the Regional Ethics Committee (REK 2016/331) and by the local Data Protection Officer.

Statistical analysis

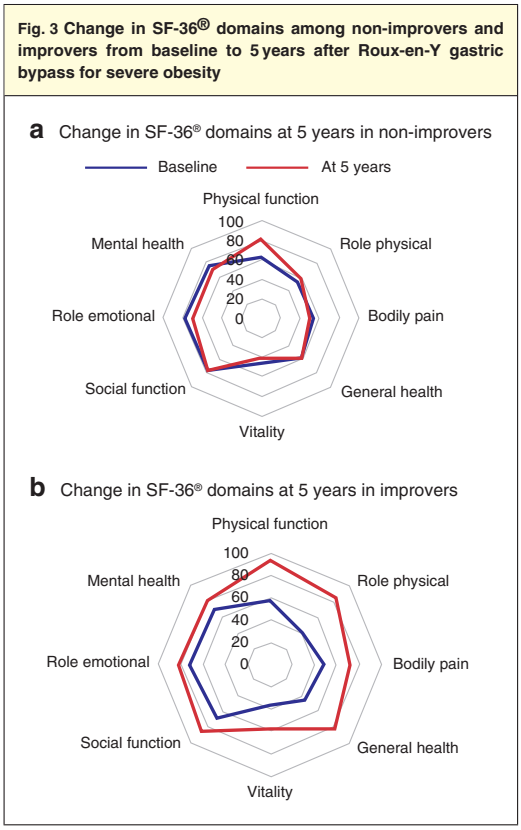
Categorical variables are given as proportions. All but one of the continuous variables (SF-36® physical function sum-score) were normally distributed and are given as mean(s.d.) values. SRH acts as a categorical as well as a continuous variable. Pearson's χ^2 test was performed for comparison of categorical variables, and independent and paired *t* tests were performed for comparison of continuous variables. Multiple logistic regression analysis was used to explore whether baseline variables could predict changes in SRH. $P < 0·050$ was considered statistically significant for all analyses. All analyses were performed using IBM SPSS® version 23 (IBM, Armonk, New York, USA).

Results

A total of 359 patients underwent laparoscopic RYGB as a primary bariatric procedure between September 2006 and February 2011. At baseline, 339 patients completed the SF-36® questionnaire. After the operation, 322 patients (89·7 per cent) attended the 5-year follow-up visit, of whom 242 completed an identical questionnaire. There were complete baseline and postoperative SF-36® data, as well as clinical information on weight, co-morbidity, complications and blood test results, for 233 patients, representing 64·9 per cent of patients undergoing RYGB at this hospital in the study period.

Of the 233 patients who formed the study cohort, 180 were women (77·3 per cent) and 53 were men (22·7 per cent). All participants were Norwegian/Caucasian by ethnicity. At baseline, their mean(s.d.) age was 40(9) years and BMI was 43·4(5) kg/m^2. Nadir BMI was 27·7(4) kg/m^2, and BMI at 5 years was 30·9(5) kg/m^2. Details of co-morbidity at baseline are shown in *Table 1*.

Fig. 3 Change in SF-36® domains among non-improvers and improvers from baseline to 5 years after Roux-en-Y gastric bypass for severe obesity



a Self-rated health (SRH) non-improvers and **b** SRH improvers.

Mean(s.d.) preoperative SRH was 3·6(0·8), corresponding to a level between 'good' and 'fair'. No patient reported excellent health at baseline, but 17 (7·3 per cent) reported very good SRH, 89 (38·2 per cent) good, 98 (42·1 per cent) fair and 29 (12·4 per cent) poor SRH (*Fig. 1*). At 5 years, mean(s.d.) SRH was 2·7(1·0), corresponding to a level between good and very good; 23 (9·9 per cent) reported excellent, 88 (37·8 per cent) very good, 79 (33·9 per cent) good, 33 (14·2 per cent) fair and ten (4·3 per cent) poor SRH (*Figs 1* and *2*). The proportion reporting fair or poor SRH at baseline was 54·5 per cent (127 of 233), compared with 18·5 per cent (43 of 233) at 5 years.

In terms of individual changes in SRH, 154 patients (66·1 per cent) had a better SRH score at 5 years, 60 (25·8 per cent) had no change, and 19 (8·2 per cent) had a decrease in SRH score (*Fig. 1*). As the number with decreased SRH was low, the variable 'change in SRH' was dichotomized to improvers and non-improvers by merging the no change and decrease categories.

There were no differences between improvers and non-improvers in terms of age, sex, weight-related co-morbidity, or baseline weight and BMI (*Table 1*). At 5 years, mean(s.d.) %EWL was 71·0(23·9) per cent for improvers and 64·3(23·9) per cent for non-improvers ($P = 0·044$), and %EBMIL was 71·6(24·0) and 65·0(24·5) per cent respectively ($P = 0·049$). There was no significant difference in %TWL (29·2(9·6) per cent for improvers and 27·2(10·3) per cent for non-improvers; $P = 0·132$), or change in BMI (12·7(4·9) *versus* 12·0(5·0) kg/m^2 respectively; $P = 0·295$) (*Table 1*).

At 5 years, mean(s.d.) BMI was 30·5(4·9) kg/m^2 for improvers compared with 31·8(5·2) kg/m^2 for non-improvers ($P = 0·057$). Even though there was no significant difference in BMI at 5 years, the improvers had significantly lower weight regain from nadir to 5 years than non-improvers: 8·7(7·0) *versus* 12·0(8·2) kg respectively ($P = 0·002$), equivalent to a difference in BMI of 1·2 kg/m^2. Measured as weight regain in percentage of maximum weight loss, from their nadir weight improvers had a weight regain of 20·0(18·4) per cent and non-improvers 26·6(18·0) per cent ($P = 0·010$) (*Table 1*).

One of the success criteria for bariatric surgery is the achievement of a postoperative BMI of less than 35 kg/m^2. In total, 179 patients (76·8 per cent) had a BMI of 35 kg/m^2 or less at 5 years. There was no significant relationship between BMI below or above 35 kg/m^2 and change in SRH ($P = 0·377$).

Another criterion of success is %EWL of 50 per cent or more, which occurred in 124 (80·5 per cent) of improvers and 58 (73 per cent) of non-improvers at 5 years ($P = 0·215$). In multiple logistic regression analysis, none of the baseline variables predicted change in SRH (data not shown).

At baseline, improvers had worse sum-scores than non-improvers for all SF-36® domains. However, this difference was not significant for physical function ($P = 0·065$), bodily pain ($P = 0·149$) or role emotional ($P = 0·137$). At 5 years, the opposite relationship was found, as sum-scores for improvers were significantly better ($P < 0·050$) than those for non-improvers for all domains. For improvers, sum-scores at 5 years were better than baseline scores for all eight SF-36® domains ($P < 0·005$). Non-improvers had better scores for physical function ($P < 0·001$) and worse scores in mental health ($P = 0·017$) at 5 years compared with the baseline, but no change in the other domains. Details on the relationship between changes in SRH and the eight domains in SF-36® are given in *Tables 2* and *3*, and *Fig. 3*.

In terms of co-morbidity, none of the 19 patients with decreased SRH at 5 years had type 2 diabetes mellitus (T2DM) before surgery. Of the 60 with no change in SRH, ten (17 per cent) had T2DM at baseline and six of these patients did not require medication at 5 years. Of the 154 patients with improved SRH, 28 (18·2 per cent) had T2DM at baseline and 21 did not require medication at 5 years (*Table 1*).

Abdominal surgery for suspected internal herniation was more common among the improvers, but there was no difference between improvers and non-improvers for cholecystectomy, abdominal excess skin removal or births (*Table 1*).

Discussion

Before RYGB, patients with severe obesity in the present cohort reported SRH far below that in the general population[29], but after 5 years their scores were similar, with 81·5 per cent reporting SRH as good, very good or excellent.

QoL scores in SRH improvers were worse than those of non-improvers at baseline, but they were better at 5 years. Although improved SRH was related to better scores in all SF-36® domains, non-improvement was related to unchanged or worsened scores in all domains except physical function. None of the baseline characteristics predicted in which patients perceived health would improve. In a clinical context, these findings may indicate that patients with severe obesity who perceive their health as poor have more to gain from bariatric surgery than patients who perceive their health as good. Moreover, in the long run SRH can be interpreted as the result of the patients' continuous negotiation between the positive and negative effects of the RYGB procedure on all aspects of life.

It terms of the relationship of SRH with weight loss, the study found that the difference between SRH improvers and non-improvers depended partly on the formula used: %EWL and %EBMIL were better for improvers than for non-improvers, but %TWL and change in BMI were not different; and the proportion of patients attaining a BMI of 35 kg/m^2 or less, or %EWL above 50 per cent at 5 years, was similar for improvers and non-improvers. However, non-improvers regained 3·3 kg more than improvers from nadir to 5 years after RYGB, a significant difference. Whether this 'marginal' weight regain reduced SRH, or whether other health issues led to increased weight among non-improvers, could not be explored further from the available data.

Considering long-term outcomes, a meta-analysis[30] reported that health-related QoL improved in the first year after bariatric surgery, declined after 2 years and stabilized at a level below that in the general population at 5 years and, compared with control groups with obesity, improvement in both physical and mental health was reported more than 5 years after surgery[31]. Long-term observational studies[32–34] of adults with severe obesity have reported that, compared with usual care, bariatric surgery is associated with a reduced rate of cardiovascular events and deaths, but still with a higher mortality rate than in the general population. The sample size in the present study was too small and the observation time too short to explore whether improved SRH after RYGB had an effect on mortality and future morbidity.

The strengths of this study are the close follow-up and complete registration for many variables from baseline to 5 years after the RYGB, and that patients reported on SRH when they had long-term experience of the positive and negative effects of the surgery on their general health status. Among the limitations of the study are the small sample size, and that the SF-36® questionnaire was not given to all patients who attended the 5-year follow-up visit. In addition, the study did not consider socioeconomic factors or life events that may have affected SRH at baseline or during follow-up after the bariatric procedure.

SRH, expressed by the answer to one single question, seems relevant and valid as an outcome measure for bariatric surgery, and in this observational study RYGB for severe obesity resulted in improved SRH in two-thirds of the patients. Focusing not only on weight, but also on health in general, might reduce the stigma experienced by people with severe obesity considering or undergoing bariatric surgery. The increased knowledge on what to expect from bariatric surgery will be useful for patient education, their choice of treatment, and their view of life after treatment for severe obesity. In clinical use, SRH might replace more comprehensive QoL tools, and SRH scores can be used to identify patients in need of closer follow-up after surgery.

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ORIGINAL CONTRIBUTIONS

Intravenous Iron Treatment in the Prevention of Iron Deficiency and Anaemia After Roux-en-Y Gastric Bypass

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Abstract

Background Iron absorption is disturbed after Roux-en-Y gastric bypass (RYGB) and iron deficiency with or without anaemia affects almost half of all patients. Intravenous iron is an option when per oral iron is insufficient or not tolerated. This study explores whether routinely offering intravenous iron treatment when iron stores are empty can prevent anaemia and iron deficiency after RYGB.

Methods This is a study of prospectively registered data on clinical information, haematological tests and intravenous iron treatment from 644 RYGB patients who underwent surgery between 2004 and 2013, postoperatively followed more than 5 years. Intravenous iron treatment was offered to patients with ferritin ≤ 15 μg/L.

Results Clinical information was available for all patients at baseline and for 553/644 patients at 5 years; laboratory results were available for 540/644 patients at baseline and 411/644 patients after 5 years. The mean age was 39.8 (± 9.7) years. Overall, 187/483 (38.7%) women and 9/161 (5.6%) men were given intravenous iron treatment in the observation period. From baseline to 5 years, mean haemoglobin decreased by 0.3 g/dL in both men and women. Anaemia occurred in 18/311 (5.8%) women and 9/100 (9%) men at 5 years. Depleted iron stores (ferritin ≤ 15 μg/L) were seen among 44/323(13.6%) women and 3/102 (2.9%) men, and low iron stores (ferritin 16–50 μg/L) occurred in 144/326 (44.6%) women and 38/102 (37.3%) men 5 years after RYGB.

Conclusion By routinely offering intravenous iron treatment to patients with depleted iron stores after RYGB, haemoglobin levels were preserved. Half of the patients experienced low or depleted iron stores at 5 years.

Keywords Iron deficiency · Anaemia · Intravenous iron replacement · RYGB · Gastric bypass · Bariatric surgery · Iron deficiency anaemia · Iron deficiency without anaemia · Iron deficiency after RYGB

Introduction

Roux-en-Y gastric bypass (RYGB) has been a common bariatric procedure for more than 50 years [1], and more than 30% of the 635,000 patients worldwide undergoing a bariatric procedure each year get RYGB [2]. This procedure implies that the food bolus bypasses the main part of the stomach, the duodenum and the proximal jejunum, and instead passes

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through an alimentary limb of 1 m or more before the food blends with bile and pancreatic enzymes. The aim of this procedure is to reduce capacity for food intake and absorption of energy from the food. The downside is that the main sites for absorption of essential vitamins and minerals, like folate, vitamin B_{12}, calcium and iron, are also bypassed, and nutritional elements dependent on acidic environments are less likely to be absorbed [3]. Patients are advised to use supplements of micronutrients to compensate for the reduced absorption and regularly monitor their levels of micronutrients by blood tests [4, 5].

Anaemia has been reported in up to half of the patients 5 years after RYGB, and iron deficiency is even more frequent, due to a combination of lack of intake of iron-rich food and lack of iron absorption [6–8]. Most of the iron used by the cells is recycled, but a daily iron uptake of 1–2 mg is needed to replace the iron losses caused by shedding of epithelial cells from the skin and intestines, menstrual blood and sweat. Symptoms of anaemia are well known, but there is less awareness of symptoms of iron deficiency with normal haemoglobin levels [9].

In addition to haematopoiesis, iron is an essential component of myoglobin in the muscles, necessary for optimal function of neurons, and it is an important element of mitochondrial activity and energy production [10–13]. Iron deficiency without anaemia is a potential cause of fatigue, decreased exercise performance and cognitive impairment, symptoms which are frequently reported after bariatric surgery [14–20].

Iron homeostasis differs from other minerals by having a complex regulation of absorption, recycling and storage, but no mechanism for excretion of surplus iron, and iron overload is toxic [17, 21]. Iron is mainly absorbed by the enterocytes in the duodenum and proximal jejunum, areas that are bypassed after RYGB, but small amounts of iron can be absorbed by the more distal parts of the gastrointestinal tract [22]. The hepatic hormone hepcidin is central in regulating iron absorption from the intestinal lumen to the enterocytes, as well as the transfer of iron from the enterocytes to the blood [23, 24]. When hepcidin levels are high, iron absorption is low. High doses of per oral iron supplements can increase hepcidin and thereby block iron absorption [25, 26].

In clinical settings, iron stores are best assessed by serum ferritin levels [27]. Ferritin plays a major role in iron sequestration and transport, and low ferritin levels are diagnostic for iron deficiency [28]. However, ferritin levels are increased by inflammation, and iron deficiency can therefore coexist with high ferritin levels [29]. The cut-off level for depleted iron stores recommended by WHO is < 15 μg/L for adults [30]. However, higher and lower gender-specific thresholds for ferritin have been used. A ferritin level of 30 μg/L is the most sensitive (92%) and specific (98%) cut-off level for absolute iron deficiency [31]. Haemoglobin levels will remain normal until the iron stores are depleted, and normal haemoglobin levels do not exclude empty iron stores [32].

International guidelines recommend oral iron supplement to prevent iron deficiency and anaemia after bariatric surgery, and intravenous iron treatment if per oral treatment fails [4]. If the iron stores are emptied, it may take several months to restore them by per oral iron supplements [7]. Intravenous iron treatment is a safe procedure that restores iron stores in less time, but access to this treatment can be limited due to financial and organizational causes [9, 33, 34]. In studies published thus far, the indications for intravenous iron treatment after bariatric surgery have been anaemia or per oral iron treatment failure, and less than 10% of the patients have received this treatment after RYGB [6, 35, 36]. The same studies report anaemia in until 30% of the patients. The aim of this study was to explore whether routinely offering intravenous iron treatment to patients with depleted iron stores after RYGB, regardless of haemoglobin levels, preserved iron stores and prevented iron deficiency anaemia 5 years after surgery.

Material

This study is a retrospective analysis of prospectively collected data on 644 patients who underwent RYGB as a primary treatment for severe obesity at a public hospital from 2004 to 2013 with a postoperative follow-up of more than 5 years.

The RYGB procedure was performed with laparoscopic antecolic, antegastric technique, using a biliopancreatic limb of 40–60 cm and an alimentary limb of 100 cm or 150 cm, depending on BMI below or above 50 kg/m^2 [37].

The patients were enrolled in a local quality registry and followed a standardized clinical pathway according to international guidelines at the time [38]. A standardized set of lab tests was taken 1 year before the RYGB procedure and at 2, 6, 12, 18, 24, 36, 48 and 60 months after the operation.

Data on weight, comorbidity, complications and other relevant events in the postoperative period were registered. In addition to information from planned visits in the follow-up program of 5 years, information on intravenous iron treatment was recorded until 14 years after RYGB. Results from laboratory tests related to the 5-year outpatient follow-up program were added to the quality registry by collecting data directly from the hospital's laboratory data system. The registry was last updated January 2019. Laboratory results were available in the registry for 544 (84%) patients at baseline and 428 (66%) after 5 years.

The over-the-counter multivitamin-mineral product most commonly used in this cohort contained 15 mg iron (II) fumarate and 400 μg folate per unit. In general, the patients were advised to use additional per oral iron supplements with ascorbic acid for 1 month twice a year if ferritin was > 50 μg/L, or more often if the ferritin values were lower. Patients with

ferritin levels above the normal range were advised not to take iron supplements. The patients were also recommended supplemental vitamin B_{12} and calcium with vitamin D, and they were offered intravenous iron treatment if the iron stores were depleted, defined as ferritin ≤ 15 μg/L.

Methods

Continuous variables are given as means ± standard deviation (SD) if normally distributed, and median with interquartile range (IQR) in non-normally distributed variables. Categorical variables are reported in numbers and percentages. Independent *t* tests were performed for normally distributed variables, and non-parametric tests were used for non-normally distributed variables. χ^2 tests were performed for categorical variables. Differences were considered to be significant at $p < 0.05$.

Iron stores were graded as depleted (ferritin ≤ 15 μg/L), low (ferritin 16–50 μg/L), moderate (ferritin 51–100 μg/L), and replete (ferritin > 100 μg/L). Intravenous iron treatment was given mainly as ferric carboxymaltose 1 g in one visit and less often as iron sucrose 200 mg over five visits. Blood transfusions for iron deficiency anaemia were not given unless there was an acute medical situation, like haemorrhage after elective or acute surgery, in the observation period.

Statistical analyses were performed using IBM SPSS version 25 (SPSS Inc., Chicago, IL, USA) and STATA 14 (StataCorp).

Results

A total of 644 patients underwent RYGB as a primary bariatric surgery for severe obesity from 2004 to 2013. Mean (SD) age was 39.8 ± 9.7 years, and 75% of the patients were women. In the observation period of 5 to 14 years, mean 112 ± 29.3 months, fifteen (2.3%) patients have died, two of them in the early postoperative period. Baseline body mass index (BMI) was 43.9 ± 5.1 kg/m^2 and percentage total weight loss (%TWL) at 5 years was 27.6 ± 10.1 kg/m^2 (Table 1).

Median (IQR) ferritin changed from 61 (36–100) μg/L to 43 (23–69) μg/L in women, and from 173 (123–265) μg/L to 62 (40–93) μg/L in men before to 5 years after RYGB (Table 2).

The number of patients experiencing iron depletion increased from 25/399 (6.3%) before RYGB to 44/323 (13.6%) after 5 years among women and from 1/143 (0.7%) to 3/102 (2.9%) among men. The number of patients with low iron stores (ferritin 16–50 μg/L) was 141/399 (35.3%) before RYGB and 144/323 (44.6%) after 5 years among women and 5/143 (3.5%) before and 38/192 (37.3%) after 5 years among men (Figs. 1 and 2). The mean reduction in ferritin values in the 5 years after RYGB was 40 ± 85 μg/L in women and 105 ± 83 μg/L in men (Fig. 3).

In the Scandinavian population, anaemia has been defined as haemoglobin < 12.0 g/dL in women and haemoglobin < 13.7 g/dL in men [39]. According to these definitions, anaemia occurred in 13/451 (2.9%) of women and 7/158 (4.4%) of men at RYGB, in 36/382 (9.4%) of women and 16/122 (13.1%) of men after 2 years, and in 18/311 (5.8%) of women, and 9/100 (9.0%) of men 5 years after RYGB.

Mean haemoglobin levels changed from 13.7 ± 1.0 g/dL before to 13.4 ± 1.0 g/dL 5 years after RYGB in women ($p < 0.001$) and from 15.2 ± 0.95 g/dL to 14.9 ± 0.95 g/dL in men ($p < 0.001$) (Fig. 4). Annual values are given in Table 2.

With a mean observation time of 9.25 ± 2.4 years after RYGB, a total of 196/644 (30.4%) patients, 187/483 (38.7%) women and 9/161 (5.6%) men, had one or more intravenous iron treatments. Median (IQR) time from RYGB to first intravenous iron was 3 (2–4) years for women and 4 (2–7) years for men. Among the patients who were given intravenous iron treatment, 102 (16% of the study population) were given one treatment, 42 (6.6% of the study population) were given two treatments and 27 (4.2% of the study population) were given three treatments in the observation period. Thirty-two patients (5% of the study population) had their first intravenous iron treatment more than 5 years after RYGB.

Table 1 Patients' characteristics

	All, *N* = 644	Female, *n* = 483	Male, *n* = 161
Age*(years)	39.8 ± 9.7; 644	39.4 ± 9.6; 483	40.9 ± 10.1; 161
BMI baseline* (kg/m^2)	43.9 ± 5.1; 644	43.8 ± 4.8; 483	44.3 ± 5.7; 161
BMI nadir* (kg/m^2)	28.5 ± 4.3; 633	28.0 ± 4.1; 474	29.7 ± 4.3; 159
BMI 5 years* (kg/m^2)	31.6 ± 5.3; 553	31.2 ± 5.5; 418	32.6 ± 4.5; 135
%TWL nadir* (%)	35.3 ± 7.8; 633	36.1 ± 7.5; 474	32.8 ± 8.0; 159
%TWL 5 years* (%)	27.6 ± 10.1; 533	28.3 ± 10.2; 418	25.2 ± 9.3; 135
%EWL 5 years* (%)	65.8 ± 24.4; 533	67.8 ± 25.0; 418	59.9 ± 21.6; 135

*Mean ± SD, *BMI* body mass index, *%TWL* percentage total weight loss, *%EWL* percentage excess weight loss

Table 2 Haemoglobin (Hgb) and serum ferritin levels yearly from before to 5 years after RYGB

	Baseline	Operation	1 year	2 years	3 years	4 years	5 years
Hgb g/dL (mean ± SD); all patients	14.1 ± 1.2; 539/644	14.3 ± 1.2; 609/644	13.6 ± 1.1; 542/644	13.5 ± 1.2; 504/644	13.5 ± 1.2; 481/644	13.6 ± 1.2; 462/644	13.8 ± 1.2; 411/644
Hgb g/dL (mean ± SD); women	13.7 ± 1.0; 398/483	13.9 ± 1.0; 451/483	13.3 ± 1.0; 401/483	13.2 ± 1.0; 382/483	13.2 ± 1.0; 370/483	13.3 ± 1.0; 353/483	13.4 ± 1.0; 311/483
Hgb g/dL (mean ± SD); men	15.2 ± 0.9; 141/161	15.3 ± 1.0; 158/161	14.5 ± 1.0; 141/161	14.7 ± 1.0; 122/161	14.6 ± 0.9; 111/161	14.7 ± 1.0; 109/161	14.9 ± 0.9; 100/161
Ferritin μg/L; median (IQR); all patients	80 (42–141); 544/644	111 (60–211); 282/644	76 (33–133); 542/644	59 (31–105); 504/644	45 (22–84); 488/644	43 (23–81); 472/644	47 (25–75; 428/644
Ferritin μg/L; median (IQR); women	61 (36–100); 401/483	96 (49–149); 214/483	59 (27–104); 405/483	50 (26–89); 382/483	40 (21–74); 375/483	36 (21–70); 361/483	43 (23–69); 326/483
Ferritin μg/L; median (IQR); men	173 (123–265); 143/161	236 (161–319); 68/161	135 (91–205); 137/161	101 (68–174); 122/161	78 (48–122); 113/161	75 (42–120); 111/161	62 (40–93); 102/161

The levels of folate and vitamin B_{12} increased after RYGB, indicating that most patients were adherent to the recommended supplements.

Discussion

The main findings in this study are that during the first 5 years after RYGB; more than one out of four patients were given intravenous iron treatment when this treatment was routinely offered to iron depleted patients. There was a minor decrease in mean haemoglobin levels in the group, but a substantial increase in the proportion of patients with low or depleted iron stores 5 years after RYGB.

Compared with other studies, intravenous iron treatment was more widely applied in the present cohort and also given to patients without anaemia if ferritin levels were low [7, 35]. However, half of those who were in need of intravenous iron only had a single treatment over the average observation time of 9 years. This could be due to better compliance to per oral prophylactic treatment, improvement in iron absorption over time, food modifications or treatment for underlying disease after the first treatment with intravenous iron. It is also possible that iron deficiency was less likely to be diagnosed when the follow-up was handed over from the bariatric outpatient clinic to primary health care 5 years after RYGB.

In a systematic review on iron deficiency after RYGB and sleeve gastrectomy with an average follow-up time of 27.8 months, the overall incidence of iron deficiency anaemia were 14.8% post-RYGB, and iron deficiency occurred in 22.5% [40]. Only two of the studies included in the review reported on intravenous iron treatment.

In a retrospective study by Obinwanne, 53% of the RYGB patients were found to have ferritin < 50 μg/L at some point in the postoperative period [6]. In this study, only 6.7% of the patients were given intravenous iron treatment, and mean haemoglobin changed from 13.5 g/dL preoperatively to 11.6 g/dL more than 5 years after RYGB. Compared with the present study, the proportion of patients with ferritin < 50 μg/L is almost at the same level, but the fall in haemoglobin of 1.9 g/dL compared with 0.3 g/dl may be due to a lesser extent of intravenous iron treatment. In another retrospective study where no use of intravenous iron was reported, a quarter of the women were anaemic, and 42% had depleted iron stores 5 years after RYGB [41].

The number of post-bariatric patients is continually increasing, and the capacity at specialized centres for individualized follow-up is limited. However, lifelong follow-up is important to avoid vitamin and mineral deficiencies. For water-soluble vitamins and minerals, general

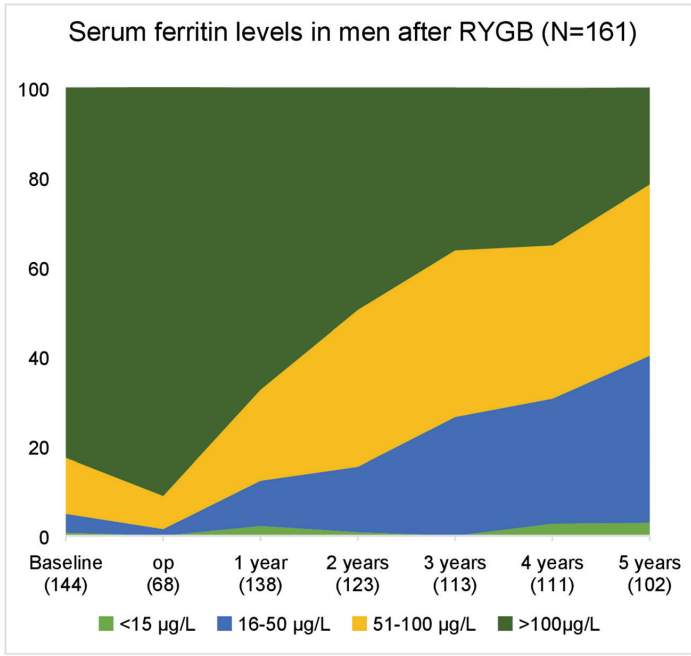

Fig. 1 Serum ferritin from before to 5 years after RYGB in men

recommendations are feasible. Iron supplement, however, needs to be individualized, and as the regulation of iron uptake is complex, there is a need for educating patients as well as primary health care providers on how to avoid

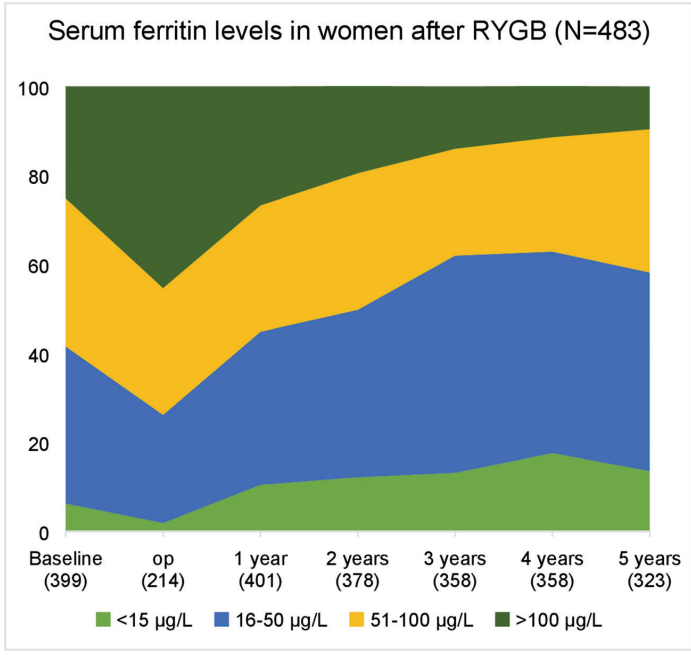

Fig. 2 Serum ferritin from baseline to 5 years after RYGB in women

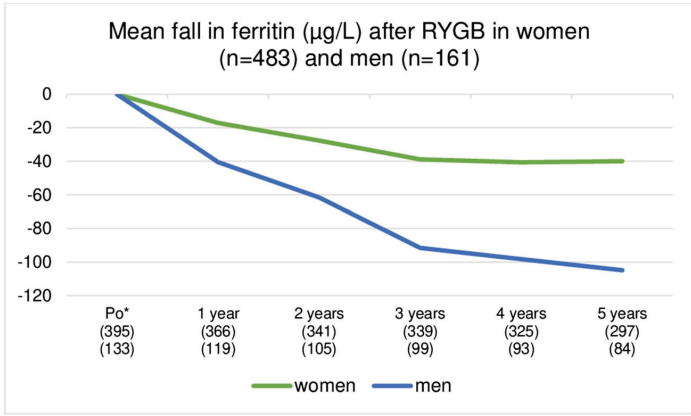

Fig. 3 Mean change in ferritin (µg/L) after RYGB. Asterisk means ferritin before RYGB might be increased due to obesity induced inflammation; the ferritin value 1–2 months after RYGB are used as reference

iron deficiency as well as overuse of iron supplements after bariatric surgery.

According to the findings in the present study, access to intravenous iron treatment when iron stores are empty prevents anaemia 5 years after RYGB in women, but not to the same degree in men. To prevent low or depleted iron stores after RYGB, an even more liberal indication for intravenous iron treatment might be necessary.

Iron deficiency even in the absence of anaemia has been related to fatigue and lower ability to respond to increases in mental and physical workload [42]. Fatigue is a major complaint among RYGB patients [19]. In non-anaemic iron-deficient adults, iron supplementation has been associated with reduced fatigue, although without any objective measurements of improved physical capacity [43, 44]. The present study did not contain systematic information on fatigue or other symptoms that could be related to iron deficiency, and any connection between fatigue and low iron stores could not be explored.

Strengths and Limitations

The strength of this study was the close follow-up of the patients in a standardized post-operative program with haematological results of more than 65% of the patients at each point in time. All treatments with intravenous iron were registered prospectively.

The limitations were the lack of systematic information on symptoms, ferritin and haemoglobin levels before and after each intravenous iron treatment, and that haematological results were not collected for more than 5 years after RYGB. Also, there was no information recorded on menstrual status or to what degree the patients followed the recommendations on per oral iron supplements.

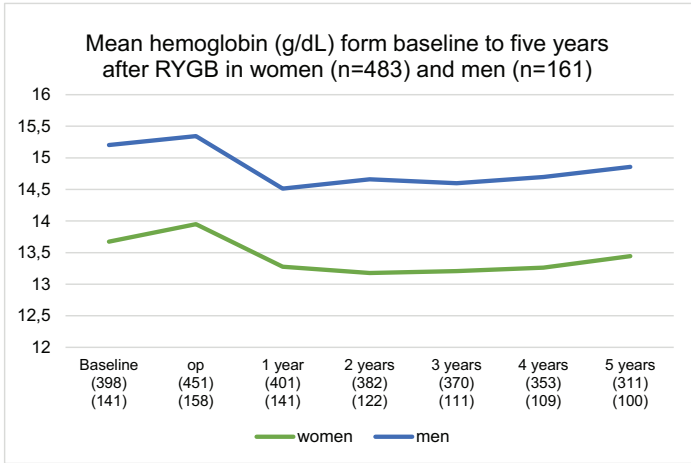

Fig. 4 Mean haemoglobin levels from baseline to 5 years after RYGB

Conclusion

Iron deficiency and anaemia are common in the long run after RYGB. Individualized advice on iron supplements and access to intravenous iron treatment when iron stores were depleted seemed to reduce the frequency of anaemia, but did not prevent iron deficiency in the present study. Major falls in iron stores appeared more than 2 years after surgery, when many patients are no longer followed in bariatric outpatient clinics. The primary health care providers might not be aware of the need for lifelong individualized iron supplements for RYGB patients. The clinical relevance of low iron stores after RYGB needs further investigation. If there is an association between iron deficiency and fatigue among these patients, better access to intravenous iron treatment can contribute to improve health after RYGB.

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Compliance with Ethical Standards

The study was evaluated by the Regional Ethics Committee (REK 2016/331) as a QUALITY improvement project and approved by the local Data Protection Officer. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

Conflict of Interest The authors declare that they have no conflict of interest.

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