Dietary intake, nutritional status and energy metabolism in adolescents with severe obesity

Effects of gastric bypass surgery

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Be ready to put in the work that isn't seen.

Respect everyone and their contribution.

Veritas, Dedicas & Amicus

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ABSTRACT

Background and aims: Roux-en-Y gastric bypass is an effective obesity treatment in adults and is becoming established in adolescents. Information is scarce on long-term changes in dietary intake, nutritional status and energy metabolism in adolescents undergoing gastric bypass. The overall aim of this thesis is to study these phenomena, to help improve treatment protocols (which currently are based on adult patients). The aim is also to evaluate the accuracy of the dietary assessment method, diet history interview, against the gold standard method, doubly labeled water, in this population.

Methods: Eighty-five adolescents (67% girls, mean age 16.5 years, mean BMI 45.5 kg/m^2) were followed in a longitudinal cohort study and assessed pre-surgically and at one, two and five years after gastric bypass surgery (paper I, II, and III). They completed diet history interviews (paper I, II, and III), including a form on adherence to prescribed supplementation (paper II), in addition, assessments on body composition (paper I and III), biochemistry (paper II), and energy expenditure (paper III). Eighty-one matched adolescents receiving conventional medical nutrition therapy for obesity, served as a non-surgical control group, and were assessed at five years (paper I, II and III). The accuracy of the diet history interviews is evaluated in comparison to doubly labeled water (paper III).

Results: Weight was decreased by 28% at five years following surgery while controls had gained 13%. Energy intake decreased (from preoperative 2558 kcal/day) by 34, 22 and 10% after one, two and five years. Dietary energy density decreased initially (at one year) but was no longer different at two years. Adherence to prescribed supplementation ranged between 44-61% through five years. Adhering to supplements was associated with more favorable biochemistry. By five years biochemistry showed a decrease in ferritin and hemoglobin and 61% had iron deficiency. Among females with iron deficiency, most did not adhere to supplementation, and 59% of these had anemia. A high prevalence of vitamin D insufficiency at baseline lasted through five years, and 80% of adolescents' nonadherent to supplementation had insufficiency at five years. Assessment of muscle mass showed better preservation in males and a protein intake ≥60 g/day was associated with preserved muscle mass. At five years adolescents who had undergone surgery and non-surgical controls had similar fat-free mass, total energy expenditure and resting energy expenditure. There was no association between reported energy intake from the diet history interviews and total energy expenditure measured with doubly labeled water in all adolescents. There was, however, a positive correlation in the surgically treated adolescents.

Conclusion: Energy intake and dietary energy density might be important factors, in weight loss following gastric bypass surgery in adolescents. Adequate protein intake could possibly facilitate preservation of muscle mass following surgery. Results support current recommendations; on monitoring of micronutrient intake and biochemistry in all patients following gastric bypass surgery; higher (>800 IU/20 μg) preventive supplementation of vitamin D; and iron in both sexes. Despite large difference in weight and similar fat-free mass, five years after gastric bypass surgery or conventional medical nutrition therapy, total energy expenditure and resting energy expenditure was similar between the groups. The diet history interview did not capture total energy expenditure in young adults with obesity or severe obesity.

Keywords: Roux-en-Y gastric bypass, metabolic bariatric surgery, adolescents, dietary assessment, body composition, micronutrient intake, medication adherence, vitamin deficiencies, energy intake, energy expenditure, doubly labeled water

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SAMMANFATTNING PÅ SVENSKA

Bakgrund och syfte: Gastrisk bypass-kirurgi (GBP) är en effektiv fetmabehandling hos vuxna som även visats effektiv för ungdomar med fetma. Det finns ett stort behov av bättre kunskap om långsiktiga nutritionella och metabola effekter av GBP hos ungdomar. Syftet med denna avhandling var att studera dessa effekter för att förbättra nuvarande behandlingsrutiner som hittills varit baserade på kunskap om vuxna patienter som genomgått GBP. Syftet var också att utvärdera noggrannheten i den använda kostmetoden, kosthistorisk intervju, mot den metod som anses bäst i att fånga energiutgifter, dubbelmärkt vatten, i denna population.

Metod: Åttiofem tonåringar (67 % flickor, medelålder 16,5 år, medel BMI 45,5 kg/m^2) följdes och undersöktes preoperativt och vid ett, två och fem år efter GBP (arbete I, II och III). De intervjuades utifrån ett kosthistoriskt frågeformulär (arbete I, II och III) och följsamhet till rekommenderade kosttillskott (arbete II) samt genomgick undersökningar för kroppssammansättning (arbete I och III), vitamin och mineralnivåer (arbete II), och energiomsättning (arbete III). Åttioen ungdomar under konventionell fetmabehandling utgjorde en kontrollgrupp, dessa undersöktes endast vid fem år (arbete I, II och III). Kostmetoden utvärderades gentemot referens-metoden dubbelt märkt vatten (arbete III).

Resultat: Fem år efter behandlingsstart hade ungdomarna som genomgått GBP minskat 28 % i vikt och ungdomarna som genomgått konventionell fetmabehandling hade ökat 13 %. Jämfört med före operation hade energiintaget (2558 kcal/dag) minskat 34 % vid ett år, 22 % vid två år, och 10 % vid fem år. Energitätheten (kcal/g) i kosten minskade initialt (vid ett år) men skilde sig inte längre vid två- och fem år. Ungefär hälften av ungdomarna tog kosttillskott. Att ta sina kosttillskott var associerat med mer gynnsamma blodnivåer av vitaminer och mineraler. Efter fem år hade järnnivåer och hemoglobin sjunkit och 61 % hade järnbrist. Huvuddelen av flickor med järnbrist tog inte sina kosttillskott, av dem hade 59 % järnbristanemi. En hög förekomst av vitamin D-brist före GBP varade genom fem år, och 80 % av ungdomarna som inte tog sina tillskott hade vitamin D-brist vid fem år. Pojkarna bevarade sin muskelmassa bättre än flickor, och ett proteinintag ≥60 g/dag förknippades med bevarad muskelmassa. Fem år efter behandlingsstart hade ungdomarna som genomgått GBP och konventionell fetmabehandling lika mycket fettfri (muskel) massa,

förbrukade lika mycket energi, både totalt och även i viloämnesomsättning. Rapporterat energiintag från det kosthistoriska frågeformuläret visade ingen korrelation mot den totala energiomsättningen hos hela populationen. Däremot fanns en korrelation hos ungdomarna som genomgått GBP.

Konklusion: Energiintag och energitäthet i kosten kan vara viktiga faktorer för viktminskning efter gastrisk bypass-kirurgi hos ungdomar. Tillräckligt proteinintag kan möjligen bevara muskelmassa efter gastrisk bypass-kirurgi. Resultaten stödjer nuvarande rekommendationer, för vuxna patienter som genomgått gastrisk bypass-kirurgi; vikten av monitorering av vitamin- och mineralintag och blodnivåer; högre doser av D-vitamin tillskott än de 20 mikrogram (800 IE) per dag som rekommenderades i denna studie; samt järntillskott till båda könen. Trots stor viktskillnad och likartad muskelmassa fem år efter GBP eller konventionell fetmabehandling var energiförbrukningen likartad mellan grupperna. Den kosthistoriska intervjun lyckades inte att fånga energiutgifter jämfört med dubbelmärkt vatten hos unga vuxna med fetma och svår fetma.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Henfridsson P, Laurenius A, Wallengren O, Gronowitz E, Dahlgren J, Flodmark CE, Marcus C, Olbers T, Ellegård L. Five-year changes in dietary intake and body composition in adolescents with severe obesity undergoing laparoscopic Roux-en-Y gastric bypass surgery. Surg Obes Relat Dis 2019; 15: 51-58.

II. Henfridsson P, Laurenius A, Wallengren O, Beamish AJ, Dahlgren J, Flodmark CE, Marcus C, Olbers T, Gronowitz E, Ellegård L. Micronutrient intake and biochemistry in adolescents adherent or nonadherent to supplements 5 years after Roux-en-Y gastric bypass surgery. Surg Obes Relat Dis 2019; 15: 1494-1502.

III. Henfridsson P, Wallengren O, Laurenius A, Dahlgren J, Flodmark CE, Marcus C, Gronowitz E, Olbers T, Ellegård L. Energy Expenditure assessed with Doubly Labeled Water five years after gastric bypass surgery or non-surgical treatment in young adults, and evaluation of Diet History Interview. In manuscript.

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ABBREVIATIONS

AFRO	African Region
AMOS	Adolescent morbid obesity surgery
AMRO	Americas Region
ANOVA	Analysis of variances
BMI	Body mass index
BORIS	BarnObesitas Register I Sverige, Swedish Childhood Obesity Treatment Register
CDC	Centers for Disease Control and Prevention
CM	Centimeter
CT	Computerized tomography
DIT	Diet-induced thermogenesis
DXA	Dual-energy X-ray absorptiometry
E%	Percent of energy intake
EAT	Exercise activity thermogenesis
E.G.	"for example" in Latin *exempli gratia*
E.I.	"that is" in Latin *id est*
EI	Energy intake
EMRO	Eastern Mediterranean Region
EURO	European Region
FDA	Food and Drug Administration
GLP-1	Glucagon-like-peptide-1
HB	Hemoglobin
IOTF	International Obesity Task Force
IU	International unit
KCAL	Kilocalories
KG	Kilogram
M^2	Square meter
μg	Microgram
MC4R	Melanocortin-4-receptor gene
MDT	Multidisciplinary team
MG	Milligram
ML	Milliliter
MRI	Magnetic resonance imaging
N	Number/counts
NEAT	Non-exercise activity thermogenesis
Non-REE	Non-resting energy expenditure
PAEE	Physical activity energy expenditure
PHH	Postprandial hyperinsulinemic hypoglycemia
PTH	Parathyroid hormone

PYY	Peptide YY
REE	Resting energy expenditure
RMSE	Root mean square error
SD	Standard deviation
SDS	Standard Deviation Scores
SEARO	South-East Asia Region
SEK	Swedish Krona (Currency of Sweden)
TEE	Total energy expenditure
WHO	World Health Organization
WPRO	Western Pacific Region

1 INTRODUCTION

Childhood and adolescent obesity is a chronic disease that continues to rise worldwide and has reached epidemic proportions (1, 2). It is characterized by an excess of body fat and caused by an imbalance between energy intake and energy expenditure (3). If left untreated, adolescent severe obesity will continue to adult severe obesity with a greater likely-hood to develop comorbidities and chronic diseases like diabetes and cardiovascular diseases at a younger age (4).

Medical bariatric treatment options for children and adolescents with obesity include conventional medical nutrition therapy (i.e. behavioral lifestyle interventions with nutrition and exercise alterations), together with pharmacotherapy (3). Unfortunately, conventional medical nutrition therapy in adolescents suffering from severe obesity, show modest success in long-term weight loss and resolution of comorbidities (5-7). Therefore metabolic and bariatric surgery under strict control and management has been accepted in the adolescent population with severe obesity (8). However, to date, most of the nutritional recommendations for the adolescent metabolic and bariatric surgery patient have been hypothesized from research in adults (8-10). Adolescence is a period of rapid growth and development and compared to adults they are more immature in cognition and physical performance. Hence, the long-term nutritional effects of metabolic and bariatric surgery in adolescence have previously been sparsely studied, despite being crucial to the outcome of bariatric surgery in this population. Therefore, the studies in this thesis were initiated to fill an important knowledge gap where little existed before.

This thesis focuses on the nutritional impact of metabolic and bariatric surgery in adolescence. It is based on the Adolescent Morbid Obesity Surgery (AMOS) study, a Swedish nationwide 10-year prospective non-randomized intervention study on the feasibility and safety of laparoscopic Roux-en-Y gastric bypass in adolescents.

The overall aim of this thesis is to examine long-term dietary macro- and micronutrient intake, body composition, biochemistry, and adherence to supplementation regimen in adolescents, who have undergone gastric bypass surgery. A further aim is to assess energy expenditure in adolescents with obesity and severe obesity, and to evaluate the diet history interview for energy intake in this population.

2 BACKGROUND

2.1 CHILDHOOD AND ADOLESCENT OBESITY

2.1.1 DEFINITION OF OBESITY

Overweight and obesity are defined as excess weight related to height, measured by body mass index (BMI), dividing a person's body weight in kilograms by the square of height in meters (kg/m^2) (11). Children's body composition varies as they age and varies between sexes, therefore the BMI cut-offs in childhood and adolescence overweight and obesity are age- and sex- dependent. Internationally, different cut-offs are used, the World health organization (WHO) classification (12), the U.S. Centers for Disease Control and Prevention (CDC) classification (13), and the International Obesity Task Force (IOTF) classification (14) (Table 1). In Sweden a modification of the IOTF classification with age- and sex-matched growth charts are used (15, 16) (Figure 1). These are based on a Swedish child and adolescent population with reference values for the change in BMI given as the change in BMI standard deviation scores (SDS). The measure corresponds to the adult criteria of a BMI of 25 for overweight and 30 for obesity.

BMI is an objective measurement but does not distinguish between a high BMI due to excess fat or large muscle mass, and does not measure body fatness, excess weight or fat distribution (11). Direct measurements of body fat (i.e. bioelectrical impedance analysis, hydro-densitometry, and dual energy x-ray absorptiometry) have shown good correlations with BMI in children with overweight and obesity, at group level (17-20).

Table 1. Childhood obesity definitions from World Health Organization (WHO), U.S. Centers for Disease Control and Prevention (CDC), and International Obesity Task Force (IOTF).

Organization	Definition of Childhood Obesity
World Health Organization	*WHO Child Growth Standards (birth to age 5)* (21) • **Obese:** BMI > 3 standard deviations above the WHO growth standard median • **Overweight:** BMI > 2 standard deviations above the WHO growth standard median • **Underweight:** BMI < 2 standard deviations below the WHO growth standard median *WHO Reference 2007 (ages 5 to 19) (12)* • **Obese:** BMI > 2 standard deviations above the WHO growth standard median • **Overweight:** BMI > 1 standard deviation above the WHO growth standard median • **Underweight:** BMI < 2 standard deviations below the WHO growth standard median
U.S. Centers for Disease Control and Prevention	*CDC Growth Charts (13)* In children ages 2 to 19, BMI is assessed by age- and sex-specific percentiles: • **Obese:** BMI ? 95th percentile • **Overweight:** BMI ? 85th and < 95th percentile • **Normal weight:** BMI ? 5th and < 85th percentile • **Underweight:** BMI < 5th percentile In children from birth to age 2, the CDC uses a modified version of the WHO criteria (22)
International Obesity Task Force	• Provides international BMI cut points by age and sex for overweight and obesity for children age 2 to 18 (14) • The cut points correspond to an adult BMI of 25 (overweight) or 30 (obesity)

Abbreviations: WHO, World Health Organization; BMI, body mass index; CDC, Centers for Disease Control and prevention. Produced from sources: (12-14, 21, 22) https://www.hsph.harvard.edu/obesity-prevention-source/obesity-definition/defining-childhood-obesity/ (accessed 02/05/20)

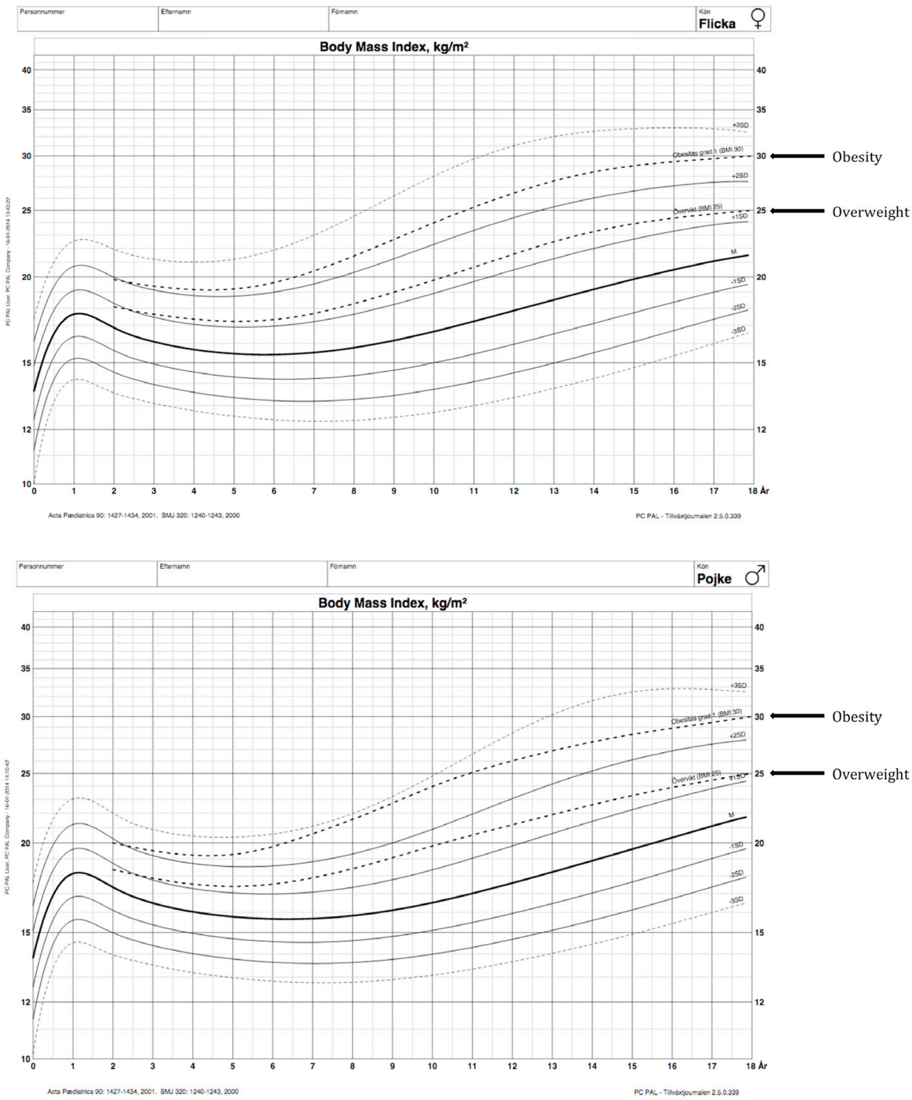

Figure 1. Body mass index reference values (mean and ± 1, 2 and 3 SD reference ranges) for Swedish children, population- based reference charts. Source: Karlberg J et al. (15, 16), with permission from Swedish Association for Pediatric Endocrinology and Diabetes.

2.1.2 ETIOLOGY

Obesity is a chronic disease, characterized by an excess of body fat, caused by an imbalance between energy intake and energy expenditure (3). Obesity is often multifactorial, caused by numerous contributing factors including: epigenetics and genetics of fetal programming and development; factors related to the obesogenic environment, such as lack of physical activity, increased sedentary behavior, sleep deprivation, and, unrestricted access to energy-rich foods (3, 23). Furthermore, behavioral and psychosocial issues and cultural and family norms matter.

2.1.3 PREVALENCE

During the last four decades the prevalence of overweight and obesity in children and adolescents has continuously increased with a greater rate than in adults, doubled in over a third of the world, with a remarkable increase in developed countries (1, 2). Overweight and obesity combined, rose from 16% to 23% in girls, and from 17% to 24% in boys in developed countries from 1980 to 2013 (2, 24). However, the most rapid rise has occurred in low-and middle-income countries (Figure 2) (25). Global prevalence of obesity, alone, in children and adolescents increased from 0.7% to 5.6% in girls, and from 0.9% to 7.8% in boys from 1975 to 2016 (25). Worldwide approximately 5% of children and adolescents are diagnosed with obesity (1). The prevalence of obesity increases with age from the age of 14, and the rates of increase in obesity are highest in early adulthood (>20 years of age). In Sweden 20-25% of children aged 6-9 years are overweight and approximately 10% are obese (25). Three percent of Swedish adolescents have obesity, and an estimated 1%, have severe obesity (26). Eighty per cent of children with obesity become adults with obesity, and almost all adolescents with severe obesity will continue to have severe obesity as adults (4).

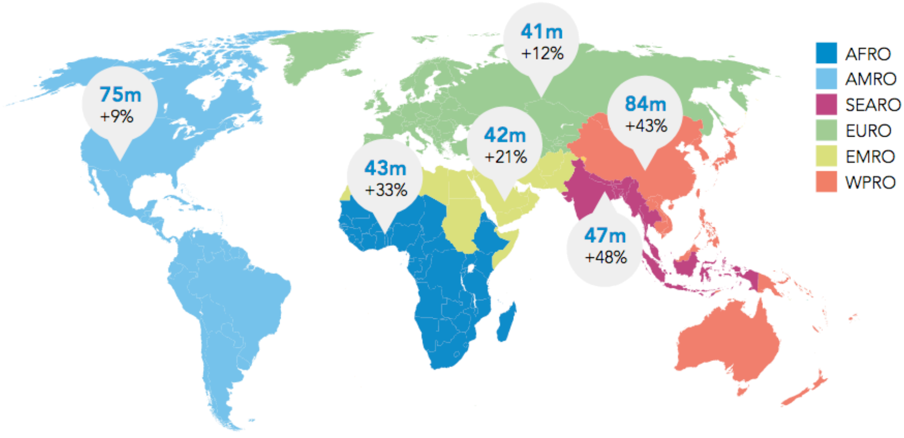

Figure 2. Number of children aged 5-19 living with overweight or obesity in 2016, and increase in prevalence from 2010 to 2016, by the World Health Organization (WHO) region. Abbreviations: AFRO, countries in the WHO African Region; AMRO, countries in the WHO Region of the Americas; SEARO, the WHO South-East Asia Region; EURO, countries in the WHO European Region; EMRO, countries in the WHO Eastern Mediterranean Region; WPRO, member states and areas in the Western Pacific Region. Source: WHO (25, 27), with permission from WHO.

2.1.4 COMORBIDITIES AND COMPLICATIONS

Obesity is a pro-inflammatory state that, if left untreated, increases the risk of several comorbidities and chronic diseases, which may present in childhood and adolescence (11, 24, 25) (Table 2). Adolescent obesity is a major risk factor for health problems that were once confined to adults. BMI increase during puberty has been associated with asthma, type 2 diabetes, risk of stroke, and colon cancer in adult men (28-31). Adolescents with obesity are more likely than adults, to have asymptomatic cardiovascular risk factors and pre-diabetes (32). Insulin resistance is more severe in adolescents than in adults and type 2 diabetes show a more rapid deterioration progress than in adults, with end organ injury occurring earlier in adolescents (8). The severe comorbidities and complications in adolescence are found to increase mortality rates in adulthood (33, 34). Adolescent obesity has been linked with mortality before the age of 55 (35), and with increased mortality from coronary heart disease before the age of 66 (36). Both overweight and obesity in adulthood is associated with increased risk of all-cause mortality, and the incidence of several co-morbidities (37-40) (Table 2).

Table 2. Common comorbidities and chronic diseases of overweight and obesity in adolescence and in adulthood.

Consequences of obesity (comorbidities and chronic diseases)	Adolescence	Adults
Asthma	✓	✓
Bodily pain and difficulty with physical functioning		✓
Cardiovascular disease		✓
Coronary heart disease		✓
Dyslipidemia	✓	✓
Gallbladder disease		✓
Gallstones	✓	✓
Gastroesophageal reflux disease	✓	✓
Hypertension	✓	✓
Idiopathic intracranial hypertension	✓	✓
Joint problems and musculoskeletal discomfort	✓	✓
Metabolic syndrome	✓	✓
Nonalcoholic- fatty liver disease, and steatohepatitis	✓	✓
Obstructive sleep apnea	✓	✓
Osteoarthritis		✓
Poor quality of life	✓	✓
Pre-diabetes	✓	✓
Psychosocial problems (such as anxiety and depression)	✓	✓
Stroke		✓
Systemic inflammation	✓	✓
Type 2 diabetes	✓	✓
Various cancers (including endometrial, esophageal, gastric, liver, kidney, pancreatic, colorectal)		✓

Produced from sources: Pratt et al. (8), and Centers for Disease Control and prevention (CDC) https://www.cdc.gov/obesity/adult/causes.html https://www.cdc.gov/obesity/childhood/causes.html (accessed 04/02/20)

2.1.5 HEALTH RELATED QUALITY OF LIFE

Children and adolescents with overweight and obesity often suffer from detrimental psychosocial stigmatization (41, 42). Adolescents report reduced health-related quality of life, compared to adolescents with a normal weight, and similar to those diagnosed with cancer (43). Children and adolescents with overweight or obesity may have poorer school-attendance levels, poorer academic achievements, and are risking poorer employments prospects and lower-paid jobs as adults (44). Severe obesity is associated with impaired mental health and depression in young adults and adults (45, 46).

2.1.6 GLOBAL ECONOMIC IMPACT

The increasing prevalence of obesity and growing needs for medical treatment of obesity-related comorbidities, will lead to a rising burden on health services (44). The global economic (or metabolic) impact of adult overweight and obesity (direct costs, indirect costs, and intangible costs) estimates 2 trillion dollars annually (47). In Sweden annual costs of adult overweight and obesity estimates 70 billion SEK ($7.5 billion) (48). Global economic impact of childhood and adolescent obesity has not been calculated. However, in US, investing $2 billion annually in childhood obesity prevention, estimates suggests interventions being cost-effective if obesity was reduced by one percentage point, in children aged 12 years (49). Hence, if treatment of childhood obesity was intensified the expected benefits would not only be on individual health, but also on societal economy.

2.1.7 INTERVENTIONS

Bariatrics specifies the medical treatment of obesity referring to the causes, assessment, prevention and treatment of obesity (9). The worldwide rapid evolvement, in both extent and prevalence, of adolescent obesity has made an urge for successful and sustainable strategies of management. If prevention strategies are failing, a life-long multidisciplinary staged treatment approach for managing adolescent severe obesity has been suggested as the best approach to combat the disease. This approach includes combinations of interventions: (i) non-surgical interventions, such as conventional medical nutrition therapy (i.e. behavioral lifestyle interventions with nutrition and exercise alterations); together with (ii) pharmacotherapy, and (iii) surgical interventions (metabolic and bariatric surgery) (Figure 3) (3, 8).

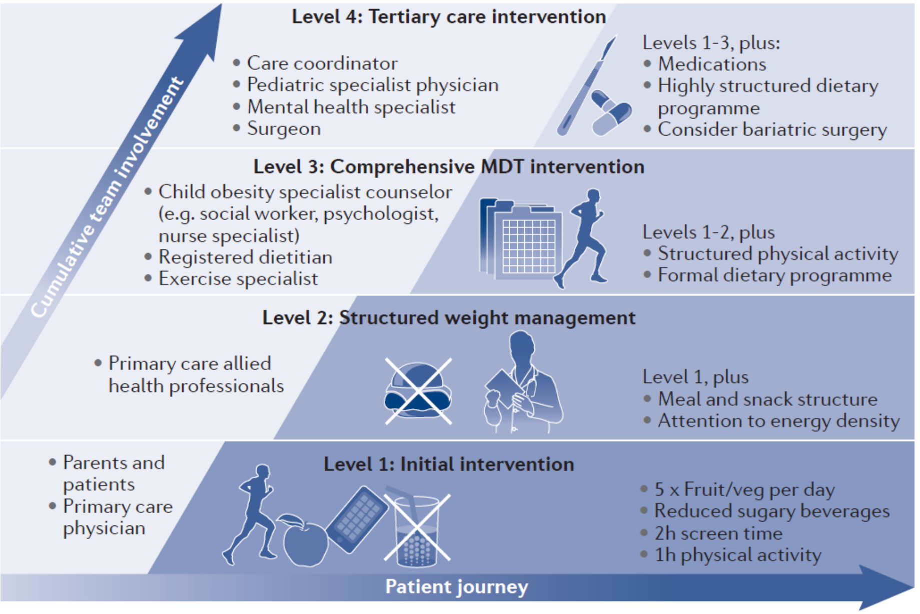

Figure 3. Patient pathway in childhood obesity. Abbreviations: MDT, multidisciplinary team. Source: Beamish AJ et al. (50), with permission from Springer Nature.

2.1.7.1 NON-SURGICAL INTERVENTIONS

First-line obesity treatment in adolescents is medical nutrition therapy (5, 51). In Sweden medical nutrition therapy for obesity is provided by a registered dietitian, and performed within a multidisciplinary team also including physician, physiotherapist, and/or psychologist (52). The therapy includes behavioral lifestyle interventions, with dietary changes (to decrease energy intake) and exercise alterations (to increase physical activity and decrease sedentary behavior) using cognitive behavioral therapy, and/or motivational interviewing (3, 53). Medical nutrition therapy can reduce BMI (-1.25 kg/m^2), and improve blood lipids, fasting insulin and glucose, and blood pressure in adolescents, at least in the short term (54-59). Medium-to-high intensity medical nutrition therapy, as a single-strategy, has shown modest effects in the short-term reduction of BMI (-1.9 to -3.3 kg/m^2) in adolescents with overweight or obesity (60), with few side effects (51), but less effective for adolescents with severe obesity (7). Unfortunately, long-term results of nutrition medical therapy in adolescents with obesity are modest and insufficient for long-term improvements of comorbidities and chronic diseases associated (6). As it is difficult to evaluate the long-term effectiveness of medical nutrition therapy, partly because of different treatment combinations used and follow-up regimens, there is only limited evidence on which to base treatment strategies (6). Medical nutrition therapy has shown better results if the treatment starts in childhood, with poorer results in adolescents (Figure 4) (5).

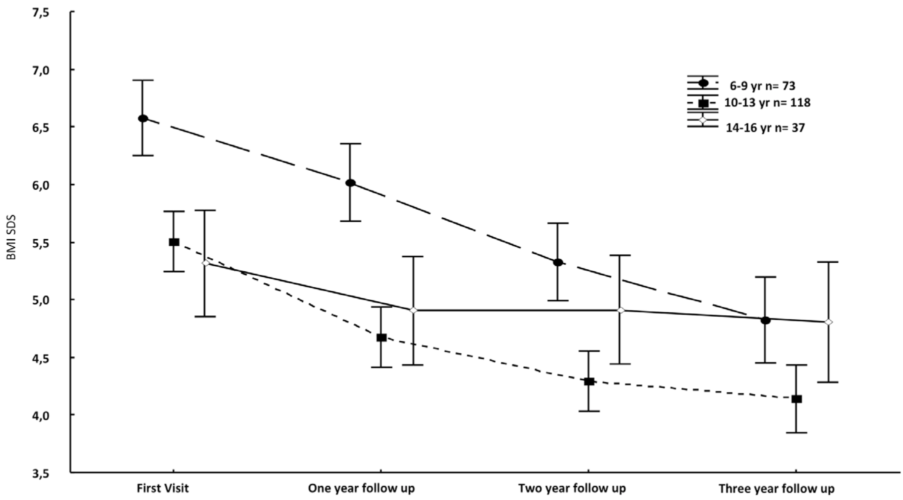

Figure 4. BMI-SDS changes during conventional medical nutrition therapy from first visit to year 3 by age group. Source: Danielsson P et al. (61), with permission from Karger Publishers.

Pharmacological drugs used as an adjunct therapy in medical nutrition therapy in the treatment of adolescent obesity has shown positive effects by reducing BMI (-0.85 to -2.6 kg/m^2) and bodyweight (60, 62). Drugs such as orlistat, which reduces uptake of fat in the intestine, and phentermine, which suppresses appetite, have been approved by the Food and Drug Administration (FDA) in the U.S., for prescription in adolescents (23). In Sweden orlistat is the only registered anti-obesity pharmacotherapy in adolescents and is only allowed in clinical trials (48), but is rarely used due to the gastrointestinal-related side effects. In both the U.S. and Sweden the anti-diabetic medication metformin, which decreases the glucose production in the liver, has been used in adolescents to improve insulin sensitivity (63), and has shown to be effective in reducing bodyweight in adolescents (64). Both orlistat and metformin come with gastrointestinal-related side effects including diarrhea, fecal urgency, and mild abdominal pain (60, 65).

2.1.7.2 SURGICAL INTERVENTIONS / METABOLIC AND BARIATRIC SURGERY

In adults with severe obesity metabolic and bariatric surgery is associated with over 20 years weight loss with -18% body weight, long-term improvements in or reversal of obesity-related comorbidity, improved long-term quality of life, decreased overall morbidity and mortality (32, 37, 66-70). The reduced morbidity leads to more life years gained by reducing the risk of end-organ damage (67). Because of the success in treating adult obesity there has been a growing interest in the use of metabolic and bariatric surgery in adolescents (71). Evidence emerges for metabolic and bariatric surgery in adolescents suffering from severe obesity (Table 3). Guidelines support metabolic and bariatric surgery to be considered for carefully selected adolescents, as standard treatment in the multidisciplinary care of adolescent severe obesity BMI ≥ 35 kg/m^2 and obesity-related comorbidity, or severe obesity BMI ≥ 40 kg/m^2 (8).

2.2 GASTRIC BYPASS SURGERY

The laparoscopic Roux-en-Y gastric bypass surgery (gastric bypass) is the most commonly performed metabolic and bariatric surgery procedure in Sweden, with estimated 5200 operations in adults in 2018 (72). Gastric bypass surgery is also one of the most commonly performed adolescent bariatric surgery procedures worldwide, and is associated with a more effective comorbidity treatment with a greater likelihood of remission of type 2 diabetes and hypertension, than in adults who had been obese since adolescence (73, 74) (Table 3).

In Sweden, 5 years after gastric bypass surgery adolescents had a reduced BMI (-13.1 kg/m^2) compared with a rise in BMI (+3.3 kg/m^2) in adolescent controls on conventional medical nutrition therapy, whereas the BMI change in adult controls, after gastric bypass, was similar to that in adolescent surgical patients (-12.3 kg/m^2) (75). In a study from the US, adolescents reduced BMI (-17.1 kg/m^2) at a mean of 8 years (76).

Gastric bypass procedures are generally safe and effective, but as with any major surgery, it poses potential risk of both short- and long-term surgical complications (Table 3) (77). Complications can also be endocrine such as micronutrient deficiencies, anemia, decreased bone density (discussed later in the chapter), and postprandial hyperinsulinemic hypoglycemia (PHH) (Table 3). PHH is a hypoglycemic response to hyperinsulinemia causing autonomic and neuroglycopenic symptoms, it occurs within 1-3 hours after consumption of undigested carbohydrates and does usually not appear before 1 year after gastric bypass surgery (78). PHH is a serious complication that may cause a deficiency of glucose in the central nervous system, i.e. neuroglycopenia. The mechanisms of PHH in gastric bypass are not yet fully understood.

Due to better surgical experience the prevalence of patients with complications following gastric bypass surgery have been reduced (79). The proportions of patients suffering from complications from metabolic and bariatric surgery in Sweden has decreased over a number of years and has now leveled out, about 3% suffered from severe complications in 2018 (72). Rarely, complications of gastric bypass can be fatal (80). Death within 30 days of the surgery in Sweden was 0.03% in 2018 (72). Heavier weight (BMI ≥50 kg/m^2), older age (≥50 years), male gender, and known risk factors for pulmonary embolism, are risk factors for surgery-related death (81).

Table 3. Benefits, in adolescents, and risks associated with gastric bypass surgery in adolescents and adults.

Benefits associated with gastric bypass surgery in adolescents	**Risks associated with gastric bypass surgery in adolescents and adults**
Long-term weight loss and BMI reduction (75, 76, 82) Long-term improvements in, or reversal of obesity-related comorbidity (8, 75, 76, 83-85): • Type 2 diabetes • Hypertension • Dyslipidemia • Cardiovascular risk factors • Obstructive sleep apnea • Gastroesophageal reflux disease • Musculoskeletal problems Improved idiopathic intracranial hypertension (8) Improved quality of life (8, 84) Improvement and resolution of nonalcoholic fatty liver disease (75) Improvements in inflammation and metabolic status (75, 86) Improved functional capacity (87)	Short-term risks (up to 30 days), risks associated with surgery and anesthesia in general (77, 79): • Bleeding • Infection • Thrombus/embolus *Risks associated with gastric bypass surgery* (9, 72, 77, 79, 88, 89): • Wound rupture • Leakage • Bowel obstruction • Spleen or other organ injury • Anastomotic stenosis/stricture/narrowing anastomotic leakage/fistula • Thiamine deficiency *Long-term risks and complications associated with gastric bypass surgery (over 31 days)* (9, 77, 79, 90-97): • Gallstones (risk increases with rapid or substantial weight loss) • Gastric ulcer with perforation of stomach or intestines • Bowel obstructions and abdominal hernias • Small intestine bacterial overgrowth • Postprandial hyperinsulinemic hypoglycemia (PHH) • Excess skin • Micronutrient deficiencies • Anemia • Loss of bone density

2.2.1 SURGERY TECHNIQUE

The surgical technique of the gastric bypass surgery consists of a small (15-30 ml) gastric pouch, divided from the body of the stomach (i.e. gastric remnant), the bypassed duodenum and first part of the small intestine (i.e. biliopancreatic limb) of approximately 50-75 cm (Figure 5). The new small size gastric pouch is then anastomosed to the small intestine, where the initial, 100-150 cm is the alimentary limb (i.e. Roux limb) and the rest of the small intestine constitutes the common limb (98).

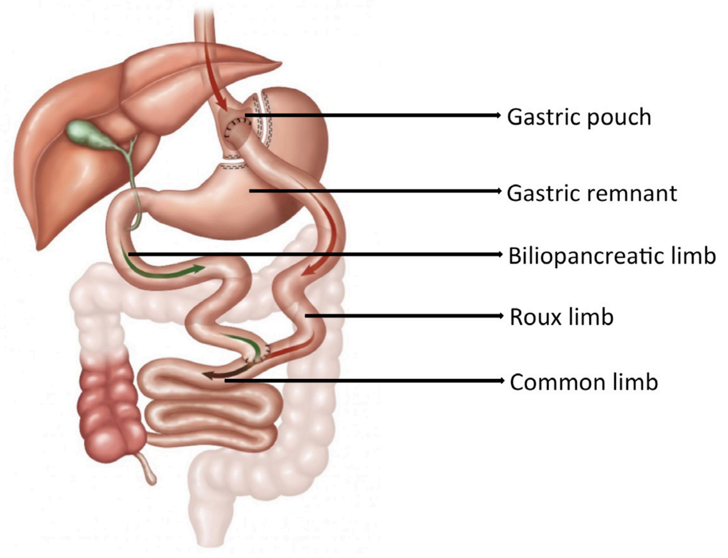

Figure 5. Roux-en-Y gastric bypass surgery. Source: Johnson & Johnson, with permission from Ethicon, Johnson & Johnson.

2.2.2 MECHANISMS AND PHYSIOLOGY

Gastric bypass induce altered physiological and physical mechanisms and responses to food, helps to reduce body weight by decreasing hunger, increase satiation during meals, and increase energy expenditure (79, 99). The mechanisms by which the gastric bypass surgery works are not yet fully understood. The procedure was initially believed to be both restrictive and malabsorptive. The size of the gastric pouch and the stoma diameter were thought to slow down the food to the Roux limb, whereas the bypassed biliopancreatic limb was thought to result in energy-malabsorption (79). However, functional capacity and ability to hold greater volume of food, in the Roux limb, increases over time (79). Even though some fat-malabsorption has been documented, it is not big enough to contribute substantially to the weight loss following surgery (100-102).

Instead research has shown that what determines caloric intake is the rapid transit of food to the small intestine which generates a multiple, satiety-gut hormone response; including glucagon-like-peptide-1 (GLP-1), peptide YY (PYY) and ghrelin; mediating increased satiety after a meal (79). This is associated with reduced overall energy intake leading to more weight loss, and sustained weight loss after gastric bypass

Gastric bypass appears to reduce the neural hedonic response (reward value) to high dietary energy dense foods, thus altering the amount of energy consumed (103). Anatomical changes after gastric bypass results in undiluted bile in the small intestine, raising serum bile acids concentrations, which in turn is associated with increased energy expenditure (103, 104). Improvements in weight, inflammation and metabolic status after gastric bypass have been associated with increased variety in gut microbiota (105).

When food enters the Roux limb quickly, without being digested, it triggers a variety of gastrointestinal hormones and rapid fluid shifts into the intestine, causing gastrointestinal and vasomotor symptoms, i.e. dumping syndrome or "early" dumping (78). The symptoms occur within 60 minutes after consumption of energy dense foods (rich in calories), and usually appear shortly after gastric bypass surgery (106, 107). To prevent dumping, patients need to make dietary modifications such as eating smaller meals, restricting drinking liquids with meals, and limiting intake of high-fat- and high-sugar foods (energy dense foods), e.g. ice cream, fast foods, cakes, candies and chocolate (78). Although, dumping is considered a complication to gastric bypass (78) it may help develop healthier food choices after surgery (108), and many patients consider it as a useful physiological mechanism to help them into conditioned food avoidance (109). In a study assessing dumping symptoms in both adults and adolescents after gastric bypass surgery, a plateaued effect of symptoms was seen two years after surgery in both groups (110). The authors speculate that most of the patients successfully learnt how to modify dietary intake and eating behavior in order to prevent symptoms of dumping after gastric bypass.

Because dumping share the triggering mechanism of rapid entering of undigested nutrients to the Roux limb, with a more severe complication PHH (Table 3, page 13) (78), they are both put under the "umbrella" of dumping syndrome, "early and late", based on the time of onset after a meal. However, underlying pathophysiology and symptoms of dumping and PHH differ distinctively (78). PHH is not a mechanism, but a complication and should be treated with diet, possibly in combination with drugs and in severe cases with surgical re-inventions.

2.2.3 MICRONUTRIENT DEFICIENCIES

Abnormalities in biochemistry (particularly iron, vitamin D, and vitamin B_{12}) are highly prevalent among adolescents with obesity (111, 112). Ten percent of adolescents presented for metabolic and bariatric surgery had two or more nutrient deficiencies prior to surgery (111). Guidelines recommend screening for micronutrient deficiencies prior to all metabolic and bariatric surgery treatments (8, 10). Risk factors for deficiencies include type of surgery, female sex, dark pigmentation, supplementation adherence, weight regain, and pregnancy (111). Micronutrient deficiencies are particularly at risk if patient adherence to recommended micronutrient supplementation is low (112, 113). Preventative treatment for all micronutrient deficiencies after gastric bypass surgery is required with daily supplementation (Table 4) (114). Currently, no specific guidelines with dosage recommendations have been developed for the adolescent gastric bypass patient, probably due to the lack of evidence. The existing nutrition recommendations are based on best-practice guidelines and adult research (8, 10, 114).

Table 4. Nordic guidelines for recommended daily supplement regimen after gastric bypass in adults (114).

Micronutrient	Recommended daily supplement regimen
Vitamin B 1	1.4 mg
Vitamin B12	1 mg/1000 µg
Folic acid	400 µg
Iron	100 mg
Vitamin D	1600 IU
Calcium	1000 mg
Zink	14 mg

Source: Laurenius et al. with permission from Läkartidningen.

The anatomical changes after gastric bypass surgery (described earlier on page 14 and Figure 5) result in physiologic effects that may decrease uptake of specific nutrients and may contribute to, or exacerbate pre-existing, nutritional deficiencies (107, 112):

- The bypassing of the gastric remnant reduces mechanical digestion as well as bypassing the gastric glands and the parietal (or epithelial) cells, as they are located in the stomach. Parietal cells produce hydrochloric acid (which is the main constituent of gastric acid) and intrinsic factor. The highly acidic environment in the stomach then activates pepsinogen into the enzyme pepsin (which is one of the main digestive enzymes in the digestive system, cleaving the proteins into amino acids, or proteolysis). Hence, gastric bypass alter these digestive processes and may prevent absorption of micronutrients.

- Bypassing the biliopancreatic limb diverts the bile and pancreatic juices to mix with the food in this part and in the Roux limb, which may prevent absorption of fats, carbohydrates and proteins.
- Both macro- and micronutrients will only be absorbed in the common limb, distal to the connection of the biliopancreatic and the Roux limb.

2.2.3.1 VITAMIN B1 - THIAMINE

Thiamine deficiency is the most serious micronutrient deficiency after metabolic and bariatric surgery and has been reported in < 1 to 49% in adult gastric bypass patients (9, 10) and has also been described in adolescents after gastric bypass surgery (8, 89). Thiamine is primarily absorbed in the duodenum and in the first part of the small intestine (107). The liver reserves are small and exhaustion may occur in less than 20 days (115). Hence, the highest risk of thiamine deficiency is during the first weeks after surgery, especially if poor intake and vomiting occur.

2.2.3.2 VITAMIN B12 - COBALAMIN

B_{12} deficiency has been found in 2-18% of adults with obesity *prior* to metabolic and bariatric surgery. After gastric bypass, B_{12} deficiency prevalence is approximately 20% in adults (9), and 12% in adolescents (111). In a recent study comparing adults and adolescents prior to and two years after gastric bypass surgery, vitamin B_{12} levels were found normal in the majority (99%) of both adults and adolescents before surgery, but by two years deficiencies were observed in approximately 4%, with no differences between the groups (73). Vitamin B_{12} is released from the food by gastric acids and absorbed in the distal part of the small intestine promoted by intrinsic factor (79, 112).

2.2.3.3 FOLATE - FOLIC ACID

Folate deficiency has been found in 45% of adult patients *prior* to metabolic and bariatric surgery and in up to 65% after surgery (9), but has not been seen in adolescents (111). Folate is primarily absorbed in the duodenum and in the first part of the small intestine, promoted by gastric acid and vitamin B_{12} (112).

2.2.3.4 IRON

Low serum concentrations of iron is common in both adults and adolescents with obesity, progressing with increasing BMI (116). The severity of iron deficiency increases with increasing fat mass and is twice as high in overweight adolescents compared to normal weight adolescents. Iron deficiency is the most common nutritional deficiency after gastric bypass with a prevalence of 20 to 55% in adults (9, 79, 107) and has been reported in 71% adolescents (111). In a recent study comparing adults and adolescents prior to and two years after gastric bypass surgery, all participants (98%) had normal preoperative ferritin levels, but by two years low ferritin levels were found in 48% of adolescents and in one-third (29%) of the of adults (73). In a resent study comparing biochemistry through five years after gastric bypass, or another metabolic and bariatric surgery technique in adolescents, low ferritin levels affected nearly twice as many gastric bypass recipients (111). Iron is primarily absorbed in the duodenum and in the first part of the small intestine, promoted by gastric acid (107).

Anemia was reported in 11% of adult patients with obesity prior to metabolic and bariatric surgery (9). Post-operative anemia was reported in 45% of patients up to 4 years after gastric bypass surgery (117). Anemia is associated with deficiency in iron (especially in females), folate, and B_{12} (8, 9).

2.2.3.5 VITAMIN D AND CALCIUM

Low vitamin D concentration is common in both adults and adolescents with obesity, progressing with increasing BMI. Prevalence of vitamin D deficiency has been found to be 37% higher in children and adolescents with obesity, compared with those with a normal weight (118). Preoperative prevalence of vitamin D deficiency ranges between 60 to 80% in adults (10) and has been reported in 38% in adolescents (111, 119). After gastric bypass surgery, deficiency has been reported in approximately 50% in both adults and adolescents (79, 111). In a recent study comparing adults and adolescents prior to and two years after gastric bypass surgery, low preoperative levels of vitamin D were present in 25% of adolescents and in more than 36% of adults, and increased to 38% by two years among the adolescents but decreased to 24% in adults (73). The primary site for both vitamin D and calcium absorption is in the first part of the small intestine (112). Vitamin D is also synthesized in the skin on exposure to sunlight (118). The body stores vitamin D in the fat tissue.

Hypocalcaemia has been reported in 10% in adults after gastric bypass (79). Gastric bypass decreases calcium absorption, induces secondary hyperparathyroidism (increased parathyroid hormone (PTH) levels, which will then release calcium from the bone), and reduces vitamin D absorption, further complicating calcium malabsorption, as vitamin D is necessary for efficient calcium absorption and homeostasis (118, 120, 121). Hypocalcaemia may also be due to intolerance to calcium-rich foods after gastric bypass (79). Insufficient calcium absorption may eventually lead to demineralization of the skeleton, and cause loss of bone mineral density i.e. osteopenia and ultimately loss of bone mineral content i.e. osteoporosis, which increases the risk of bone fractures (107).

In adolescence over 50% of adult total bone mass is developed (8). Obesity during childhood and adolescence is associated with above-normal bone mineral density and bone mineral content (122). There seems to be an increased risk for bone fractures in adults with severe obesity (123). Gastric bypass in adults show a decrease in bone mineral density (124), and an increased risk of fracture (125, 126). Gastric bypass in adolescents has shown a decrease in bone mineral density and bone mineral content, although to age-appropriate levels (127). Fracture risk in adolescents after gastric bypass is unknown.

2.2.3.6 FAT-SOLUBLE VITAMINS AND MINERALS

Long term deficiencies of fat-soluble vitamin A has been reported in 70% in adult gastric bypass patients, while deficiencies in vitamins E and K are uncommon (8, 9). Deficiencies in fat-soluble vitamins following gastric bypass surgery may be due to long-term fat-malabsorption and reduced food volume (8, 9).

Deficiencies in minerals may include zinc, reported in 20%, and copper, reported in 13%, after gastric bypass in adults. Deficiencies may be due to impaired absorption because they are primarily absorbed in the duodenum and in the first part of the small intestine, and in the bypassed gastric remnant.

2.2.4 DIETARY INTAKE

Dietary intake after gastric bypass has been estimated largely from adult cohorts. Adults treated by gastric bypass appear to reduce their energy intake and change their food choices in a healthier direction, with reduced intake of high-fat- and high-sugar foods, and increased intake of fruits and vegetables, more low-fat foods, and foods with low energy density (79, 128-131).

Adolescents treated by gastric bypass report avoiding energy-dense food and beverages; i.e. high-fat- and high-sugar foods, sweet beverages, milk-drinks and dairy products; while fiber-rich foods, whole meat, raw vegetables, and fruits are more frequently consumed (110). Changes in appetitive behavior following metabolic and bariatric surgery in adolescents resulted in a reduction in the reward value of a high-fat- and high-sugar candy (132).

The macronutrient distribution of fat and carbohydrates in the diet decreased during the first post-operative year in adults (79). Adolescents reduced energy intake, with satisfactory macronutrient distribution but a lower than desirable intake of calcium, fiber, and protein (133, 134). A drastically decreased energy intake, during the first semi-starvation phase has been reported in adults, but with increasing levels by 12 months, and with a sustained reduced energy intake for several years (79). Also protein intake was reduced, under the recommended levels in the short term (8), but returned to preoperative levels by 12 months, in adults (79). Reduced protein intake could be due to a temporary intolerance of high protein diet and dairy food, with reduced reported intake of meat and dairy products after gastric bypass surgery (79, 112). In adults the changes in dietary intake after gastric bypass could partly account for sustained weight loss following surgery (79, 135). Dietary intake following gastric bypass in adolescence is an area in need of deeper scientific understanding.

2.2.5 DIETARY REPORTING

Nutritional assessment is one of the most fundamental problems facing nutritional research with concerns about validity, particularly due to its dependency to self-reported memory based, or self-monitored food intake i.e. misreporting (136). All dietary assessment methods have some way of self-reporting or self-monitoring of food intake. There are two main categories of dietary assessment methods, prospective e.g. food records, and retrospective e.g. dietary history, food frequency questionnaire, and 24 hour- or 7-day dietary recalls (137).

In adolescents the retrospective diet history has shown to be the best method to capture energy intake, where interviewing rather than having them to fill out a questionnaire has shown to be more accurate (10, 138). Misreporting includes both under- and over-reporting of habitual food intake. In adolescents, as well as adults, underreporting, or low-energy reporting, is especially associated with overweight and obesity and may be due to socially desirable answering, forgetfulness, genuine under-eating for weight-loss, or genuine over-eating as a reflection of growth spurts (139). Adolescence is defined by unstructured eating patterns, changing food habits, and more out of the home eating, and is possibly characterized by less motivation and lack of adherence (140). Underreporting has also been associated with female sex, socio-economic status, health consciousness, cultural variations and psychological differences, in adolescence (140, 141).

Assessing the validity of dietary assessment methods demands an objective measure. The accuracy of self-reported dietary intake can be validated using the doubly labeled water technique for energy intake, nitrogen excretion in urine for protein, and potassium and sodium excretion in urine for potassium and sodium (136, 142). Increasingly more objective biomarkers (nutritional metabolomics) are being developed, but because only a few biomarkers are available to this day, they can only complement self-reported dietary assessment methods.

2.2.6 ADHERENCE TO SUPPLEMENTATION REGIMEN

Adherence to medical regimens in adolescents with chronic disease has been estimated around 50% (143). In adolescents after gastric bypass only 12% reported taking supplements as directed (144). Studies with long-term follow-up in adults show that 33% of patients had a “reliable intake” of supplementation, while 16% reported they “never took” the prescribed supplements (145). Adherence to supplementation regimen in adolescents is another area in need of deeper scientific understanding.

Patient adherence to medication or supplementation regimen can be tricky as there is no gold standard measurement and no biologic basis for determining optimal levels (138, 143, 146). There are different strategies to measure adherence of medication regimen; subjective strategies involve patient self-reported adherence; and objective strategies include e.g. counting remaining dosage units, checking pharmacy databases, and electronic monitoring devices recording medication container openings (72). However, obtaining the medicine does not ensure its use or capture patterns of missed dosages, and patients may use more than one pharmacy, or could buy over-the-counter. Guidelines recommend screening for micronutrient deficiencies prior to all metabolic and bariatric surgery treatments (8, 10). The ideal is to monitor serum levels of vitamins and minerals in order to prevent potential deficiency risk.

2.2.7 BODY COMPOSITION

Overweight and obese individuals have excess total body mass compared to normal weight individuals, both in fat- and fat-free mass (147). Fat-free mass (muscle mass) is larger because it takes more strength to carry more weight. In all methods of successful weight loss, total body mass will decrease, inevitably also fat-free mass. Preserving fat-free mass while losing fat mass is the ultimate goal in all weight loss managements, as loss of fat-free mass may be detrimental because it will unavoidably decrease resting metabolism and may result in weight maintenance difficulties (148, 149).

Adult patients after gastric bypass experience larger weight loss, larger fat mass reduction, and a relative fat-free mass preservation compared to other techniques (129). Males seem more likely to preserve muscle mass post-operatively compared to females in both adults and adolescents (127, 129). The mechanism behind this sex disparity is not clear. The rapid weight loss after gastric bypass surgery in the first post-operative year (i.e. the semi-starvation phase) is in most part fat mass but also includes fat-free mass (150). Depletion of fat-free mass has been a concern in metabolic and bariatric surgery due to its elemental role in vital organ and skeletal muscle functioning and in resting energy expenditure (REE) (147). However, rapid weight loss following both non-surgical and surgical procedures result in a higher percentage loss of fat-free mas (148). In fact, compared with non-surgical, weight- and age matched, controls metabolic and bariatric surgery patients had similar or greater than expected fat-free mass within their BMI category, approaching normalized levels (151, 152). Body composition following gastric bypass in adolescence is thus another area in need of deeper scientific understanding.

2.2.8 ASSESSING BODY COMPOSITION

The measurement methods of body composition range from simple to advanced, where the more complex techniques are only available at laboratories and are more expensive (153). Together they measure fat mass, fat-free mass, bone mineral content, total body water, extracellular water, total adipose tissue (including visceral-, subcutaneous-, and intramuscular fat), and skeletal muscle mass. The techniques include bioelectrical impedance analysis, densitometry, dual-energy X-ray absorptiometry (DXA), computerized tomography (CT), magnetic resonance imaging (MRI) techniques, and anthropometry. Body composition techniques all have advantages and disadvantages, and no one is free of error.

Dual-energy X-ray absorptiometry is a whole-body-scan that estimates regional body composition of three main compartments and is often referred to as the gold standard method to assess body composition. It measures fat mass, fat-free mass, and bone mineral density (153). With validated equations derived from muscle mass from more accurate measurement methods (CT and MRI) in adolescents, skeletal muscle mass can be calculated from the DXA measurements (154). The DXA method is noninvasive, can be applied in all ages, has high precision and accuracy, and a low-radiation exposure compared to CT, but has an upper body-weight limit, and limits the whole-body field-of-view of very large persons (153).

2.2.9 ENERGY EXPENDITURE

Total energy expenditure (TEE) is the total amount of energy expended by the human body in order to stay alive and function (155). There are three main components of TEE (Figure 6):

1. Resting energy expenditure (REE), energy expended for homeostatic processes.

2. Diet-induced thermogenesis (DIT), energy expended to digest, absorb and convert food.

3. Physical activity energy expenditure (PAEE), energy expended during physical exercise. PAEE can be further divided into:

- Exercise activity thermogenesis (EAT), energy expended for sports-like exercise.
- Non-exercise activity thermogenesis (NEAT), energy expended for the movements we make that is not sports-like exercise (or resting, breathing, and eating) e.g. walking or riding a bicycle to school/work, standing up from a seated position, housework, shopping, and even small movements such as playing an instrument, typing, spontaneous muscle contraction or fidgeting.

Together DIT and PAEE are considered non-resting energy expenditure (non-REE) (Figure 6).

In a mainly sedentary individual REE accounts for approximately 60% of TEE (Figure 6). About 80% of the variance in REE is determined by body size. Fat-free mass is positively correlated with REE.

DIT accounts for 10-15% of TEE (Figure 6), and the variance has been associated with the nutrient composition and energy content of consumed foods. PAEE accounts for 15–30% of TEE, and (Figure 6).

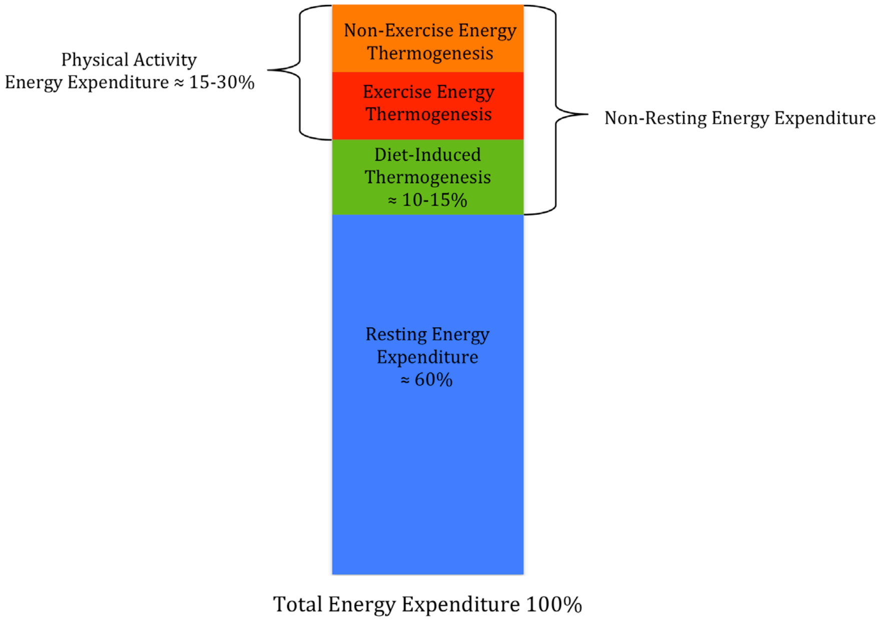

Figure 6. Total Energy Expenditure in a mainly sedentary individual.

Among adults, gastric bypass surgery contributes to decreased TEE and REE and increased DIT (150). Reduced REE following gastric bypass has also been reported both in adults (129, 156-162) and in adolescents (163). In adults, TEE decreases until 6 months after surgery and is still declined at 12 months but not different from that of at 6 months (150). REE on the other hand, continues to decline up to 12 month after gastric bypass. As there is no convincing evidence of increased physical activity following surgery (128, 129, 150, 159, 164, 165), the authors speculate that this could be explained by increased DIT (150). A greater long-term DIT has been reported in adult gastric bypass patients when compared to other metabolic and bariatric surgery procedures (99, 129). Increase in DIT after gastric bypass surgery may be explained by the anatomical changes and altered food digestion (Figure 5, and earlier discussed on pages 21-22 and page 25). Thus, metabolic changes might influence the central neuroendocrine signaling related to energy expenditure, together with increased variety in gut microbiota and increased number of cells in the intestinal mucosa, and possibly hypertrophy of the small intestine (105, 150).

Planned physical activity (EAT) does not seem to increase in adults after gastric bypass, however, the unplanned everyday exercise (NEAT) does (166-169).

The pronounced weight loss after gastric bypass surgery in the first post-operative year, is in most part fat mass which has a lower metabolic rate (4.5 kcal/kg/day) compared to fat-free mass (13 kcal/kg/day)(150). Hence, REE relative to fat-free mass decreases and REE relative to body weight increases after surgery. However, REE seems to decrease more than could be expected based on measured body weight and body composition changes. Changes in the components of energy expenditure may influence the long-term maintenance of weight loss after gastric bypass (164, 170). The mechanism of metabolic adaption following gastric bypass in both adults and adolescence is another area in need of deeper scientific understanding (149, 150, 163, 171).

2.2.10 ASSESSING ENERGY EXPENDITURE

Energy expenditure can be predicted by using mathematical regression equations, developed from more accurate methods, i.e. indirect calorimetry, which is used to measure REE. The accuracy in these equations depend on in which population they have been validated (i.e. age, gender, health status, malnourished, lean, overweight or obese) (172). The Molnar REE prediction equation has shown to be the most accurate equation to predict energy expenditure in adolescents with severe obesity (172). However, estimations through mathematically drawn equations are only predicting energy expenditure not actively measuring energy expenditure. Measuring energy expenditure in free-living individuals may be done by methods including: non-calorimetric techniques, e.g. accelerometer; calorimetry e.g. indirect calorimetry, and the doubly labeled water technique.

By using the Weir formula of total heat output; *(kcal) = 3.9 x oxygen used (L) + 1.11 x carbon dioxide produced (L)*; energy expenditure can be estimated by relatively simple measurements of oxygen consumption and carbon dioxide production during rest and under steady-state conditions (173). Indirect calorimetry measures respiratory gas exchange in whole-room respiratory chambers or using a metabolic cart that captures respiratory gas with a ventilated facemask, hood, canopy, or mouthpiece with nose-clips (174). Indirect calorimetry has a high accuracy and precision, but has limitations in free-living conditions as the respondent has a reduced mobility.

The doubly labeled water technique is often referred to as the gold standard method of longer-term energy expenditure in free-living conditions. It involves an individual drinking water containing isotopes of oxygen and hydrogen (doubly labeled). During a 1-3 weeks wash out period the amount of isotope is regularly measured in body water by sampling saliva, blood, or urine (174). The technique is highly expensive, due to the cost of isotope oxygen-18, and the technique and expertise is only available at metabolic research laboratories.

3 AIMS OF THE THESIS

The overall aim of this thesis is to evaluate long-term nutritional and biochemical effects in adolescents who have undergone gastric bypass surgery. The more specific goals are outlined below.

Paper I

To assess energy intake, dietary macronutrient distribution, dietary energy density, and body composition, pre-surgery, one, two, and five years after gastric bypass in adolescents.

To compare the five-year outcome of these factors to adolescents treated with medical nutrition therapy, as a contemporary control group.

Paper II

To assess self-reported adherence to prescribed dietary supplements in adolescents one, two, and five years after gastric bypass surgery.

To assess micronutrient intake and biochemistry, pre-surgery, one, two, and five years after gastric bypass in adolescents.

To compare prevalence of aberrant biochemistry in adherent and non-adherent adolescents, one, two, and five years after gastric bypass, and in adolescents treated with medical nutrition therapy at five years.

Paper III

To assess total energy expenditure and resting energy expenditure by reference methods (doubly labeled water and indirect calorimetry) in young adults five years after gastric bypass surgery and medical nutrition therapy.

To evaluate the accuracy of diet history questionnaire interviews used to estimate the energy intake of young adults with obesity or severe obesity in comparison to total energy expenditure measured by doubly labeled water.

4 METHODS

4.1 OVERVIEW OF STUDY DESIGN AND DESCRIPTION OF STUDY POPULATIONS

The manuscripts are part of the Adolescent Morbid Obesity Surgery (AMOS) study, a Swedish nationwide 10-year prospective non-randomized intervention study on the feasibility and safety of laparoscopic Roux-en-Y gastric bypass in adolescents. Study data time points include pre-surgery (baseline), one-, two-, and five years after surgery. Inclusion period was from February 2006 to June 2009 of all eligible adolescents seeking obesity treatment from three obesity centers in Sweden, Gothenburg, Malmö and Stockholm. Inclusion and exclusion see Table 5.

Table 5. Inclusion and exclusion criteria in the surgically- and non-surgically treated adolescents, in the Adolescent Morbid Obesity Surgery (AMOS) study.

Inclusion criteria
BMI ≥ 40 kg/m^2
BMI ≥ 35 kg/m^2 with comorbidities (including type 2 diabetes, obstructive sleep apnea, joint pain and dyslipidemia)
Age 13-18 years
Passed peak height growth velocity
Passed psychological assessment
One or more years of conventional medical treatment for obesity prior to inclusion
Puberty maturity of Tanner stage >3 (onset of puberty) (175)
Exclusion criteria
Mental retardation
Insufficiently treated on-going psychiatric disorder
On-going drug abuse
Specific obesity syndrome (Prader-Willi syndrome)
Brain injuries that may lead to obesity
Monogenic obesity (specific genetic defects, MC4R, leptin deficiency)

All adolescents in AMOS underwent gastric bypass surgery by the same surgical team, with two experienced bariatric surgeons performing all the surgery procedures, at Sahlgrenska University Hospital (Gothenburg, Sweden) according to protocol, described in detail previously (98). The operation was conducted with a small gastric pouch, and the same Roux limb length of 80 cm (thus minimizing the risk of variation on the absorptive capacity related to the surgery), and a short bilio-pancreatic limb. Mesenteric defects were not closed (98).

For weight change comparison the AMOS study had a control group with non-surgically treated adolescents on medical nutrition therapy, extracted from The Swedish Childhood Obesity Treatment Register (BORIS), a national healthcare quality register for childhood obesity (176). All pediatric clinics offering treatment for childhood and adolescent (up to the age of 18 years) obesity in Sweden are recommended to register patients in the BORIS register. Approval of registration from patients and guardians is documented in the patient's electronic medical file. Controls were matched for date for surgery, BMI, age, and sex, and the same inclusion and exclusion criteria were used (Table 5). They were followed up by registry data at baseline and for the five-year follow up the young adults were invited for assessment at the three obesity centers, Gothenburg, Malmö and Stockholm. At five years follow up, 25% of controls had undergone gastric bypass and could therefore not be included as controls at this time-point.

In Sweden, medical nutrition therapy for childhood and adolescent obesity, is comprised of evidence-based behavioral lifestyle modifications with dietary changes and exercise alterations, using cognitive behavioral therapy and/or motivational interviewing (48). Treatment aims are to: help adopt healthier eating habits; become more physically active; and reduce time spent in sedentary activities. The treatment is generally tailored towards the patients' needs and ability to adhere, and can be provided in groups and/or individually. Individualized treatment usually involves visits to a registered dietitian, a pediatric nurse, a pediatrician, and physiotherapist, and/or psychologist. With individualized treatment comes a varied frequency of follow-up visits and differences in the type of treatment offered. Thus, it is not uniform.

An experienced research team performed all the assessments, with the same few members conducting all follow-ups.

4.1.1. ADOLESCENT MORBID OBESITY SURGERY STUDY

Results from the AMOS study have demonstrated substantial long-term weight loss and improvements in metabolic risk factors, reduced low-grade inflammation, improved quality of life, better self-esteem, improved eating behavior, improvements in functional capacity and increased physical activity (75, 84, 86, 87, 177). A high prevalence of mental health problems before surgery (anxiety, depression, eating related problems, negative self-image and self-esteem) (84, 178) subsequently improved in the first 2 years after surgery (178-180).

While this may be true, mental health problems (psychiatric drug prescriptions and mental health disorder diagnoses) persisted 5 years after surgery (177), with a sub-group of adolescents with significant depressive symptoms and suicidal thoughts at two years (180). Adolescents reported having psychosocial problems with excess skin, feeling of having an unattractive body, and the majority wanted to have body-contouring surgery (181). Compared to the non-surgically treated controls, adolescent following surgery had higher health-care consumption (both for medical and mental issues) during the 5-year period (75, 177). Controls, however, experienced weight gain and 25% had metabolic and bariatric surgery when they reached 18 years of age (75). Twenty-five percent of the surgically treated adolescents had additional surgical procedures due to complications of surgery or rapid weight loss and 72% had nutritional deficiencies, and their bone mineral density and bone mineral content decreased to age-appropriate levels (75, 127). Five years after gastric bypass most of the AMOS adolescents (approximately 95%) expressed that they did not want their gastric bypass undone.

4.2 STUDY POPULATIONS

4.2.1 SURGICALLY TREATED ADOLESCENTS

Eighty-five consecutive adolescents from the AMOS study were included in the studies of this thesis.

4.2.2 NON-SURGICALLY TREATED ADOLESCENTS

Sixty-two non-surgically treated adolescents on medical nutrition therapy from the BORIS register were included for the five-year comparison in the studies of this thesis.

4.3 DIETARY ASSESSMENT – DIET HISTORY INTERVIEW

The dietary assessment used in this thesis included a structured diet history interview (Diet History Questionnaire). The validity of the questionnaire has been demonstrated to be satisfactory in adolescents with a normal weight (182). In addition, a form was used to explore supplementation adherence, documenting the name, dose, and frequency of prescribed supplements taken (Diet History Questionnaire).

The diet history questionnaire related to the participants' habitual food consumption and eating habits, including frequency and meal pattern, with emphasis on portion size using household measures and photos of different types of foods (Diet History Questionnaire) (182). Lunch and dinner was assessed with fixed questions in frequency charts including a list of different types of foods: meat, ground meat, stew, fish, vegetarian dishes, potatoes, rice, pasta, and vegetables. Additionally, the participants were shown photos of the different types of foods on plates with three different portion sizes (Diet History Questionnaire), to estimate the most commonly eaten for each type of dish. There was a possibility to combine two serving sizes. An open-ended question covered consumption outside the fixed questions. Breakfast and intake of drinks, alcohol, and bread to the main meals were assessed with questions containing frequency charts and specified amounts in household units. Amounts of snack foods and candies were quantified using sizes for pre-confectioned packages as sold in Sweden. Bread-type, thickness, and contents of sandwiches were described in detail. The amounts of food reported were converted into grams from which daily intake of energy and micronutrients were computed via a spreadsheet and thereafter calculated using the DIET32 software (Aivo, Stockholm, Sweden), with a nutrient database from the Swedish National Food Composition Tables (183), and micronutrient contents from the supplementation regimen were added.

The diet history interviews took 45-60 minutes each and were conducted by one out of eight trained dietitians. Prior to the diet history interview, an open dietary recall of the participants' habitual food consumption was conducted, where the participants' overall eating habits and food choices were covered, to gain additional information.

Participants were asked about entering the doubly labeled water study after the diet history interview, as this might enhance the accuracy of reporting by decreasing the risk of socially desirable reporting.

Most dietary data (approximately 95%) was processed by PH.

4.4 DIETARY CHARACTERISTICS

Energy intake (EI) is reported in absolute amounts (kcal/day) as well as in adjusted amounts (kcal/kg body weight/day). Macronutrient intake (carbohydrates, fat, protein, fiber, and alcohol) is reported as energy percentages (E%) and in absolute amounts (gram/day). Food weight is reported as weight from foods and beverages, excluding energy free drinks, still and carbonated water, and diet sodas (131). Dietary energy density was defined as food energy divided by food weight (kcal/grams) (131).

Protein intake (grams/day) in surgically treated adolescents is compared with the protein recommendations for adult gastric bypass patients, ≥60g/day (184).

Alcohol consumption is compared with hazardous consumption (defined as >36g/day of pure alcohol for female and >48g/day for male) and heavy episodic drinking (defined as ≥60g of pure alcohol at one single occasion at least monthly (185, 186).

Micronutrient intake refers to reported micronutrient intake from both diet and supplements (Table 1 and 3 in paper II).

4.5 SUPPLEMENTATION, ADHERENCE AND BIOCHEMISTRY

Surgically treated adolescents were prescribed daily oral vitamin and mineral supplementation of 1000 mg calcium, 800 IU/20 μg vitamin D, 1000 μg vitamin B_{12}, 400 μg folic acid, and 100 mg iron (females only) (Supplementary Table 1, paper II).

Participants' adherence status were categorized as either "adherent", if they reported to take the specific (five different) prescribed supplement three or more times weekly, or "non-adherent" if these supplements were taken less than three times weekly (paper II).

Laboratory biochemistry tests were taken in the morning after fasting overnight (from 22.00 hours), for analyses and cut-offs see Table 3, paper II. Analyses were performed at accredited biochemical laboratories.

4.6 ANTHROPOMETRY AND BODY COMPOSITION

Anthropometric measurements and the clinical examination of body composition in papers I-III were performed with the subjects dressed in light clothing, after an overnight fast. Research nurses conducted all the anthropometric and body composition assessments.

4.6.1 BODY WEIGHT, HEIGHT AND BMI

Body weight was measured to the nearest 0.1 kg on calibrated electronic scales, in bare feet and wearing light clothing. Body weight was assessed pre-surgery and at each follow-up. For paper III, to ensure the participants were in energy balance during the study period, body weight was assessed prior to the participant drank the doubly labeled water mixture, day 0, at the clinic. Weight was also measured by the participant after weighing on home-scales at the first day, day 0, and at the last day of the study, day 16, and reported back. They were instructed to weigh themselves in bare feet, wearing light clothing, and to measure their weight on the same scales at both time-points. Height was measured to the nearest 0.5 cm with the participant standing with the back to a calibrated wall-mounted stadiometer in bare feet. Height was assessed pre-surgery and at each follow-up.

BMI was calculated from the equation:

BMI = body weight (kg) ÷ height (m^2)

Total body weight change was calculated from the equation:

Total body weight change = [(preoperative body weight – current body weight) ÷ preoperative body weight] × 100

BMI change was calculated from the equation:

BMI change = [(preoperative BMI – current BMI) ÷ preoperative BMI] × 100

Excess BMI change was calculated from the equation:

Excess BMI change = [(preoperative BMI – current BMI) ÷ (preoperative BMI – 25)] × 100

4.6.2 BODY COMPOSITION – DUAL-ENERGY X-RAY ABSORPTIOMETRY

Body composition measurements were made with whole-body dual-energy X-ray absorptiometry (DXA) using a Lunar Prodigy scanner (GE Healthcare, Lunar Corp, Madison, WI, USA), with an in-house precision of 2.2% for fat mass and 0.8% for fat-free mass, calculated as the coefficient of variation in duplicate measurements. Bone mineral content, fat-mass, and lean tissue mass were analyzed by whole-body scans and for specific regions of the body (i.e. arms, legs, trunk) by the DXA three-compartment model. Fat-free mass was calculated using the sum of lean soft tissue and bone mineral content, and muscle mass was calculated, using the sum of appendicular lean soft tissue (187).

Muscle mass was calculated from the equation (187):

Muscle mass = 1.19 × (lean arms + lean legs) – 1.65

4.7 ENERGY EXPENDITURE

4.7.1 TOTAL ENERGY EXPENDITURE – DOUBLY LABELED WATER

For the measurement of total energy expenditure by doubly labeled water used in this thesis, see paper III.

4.7.2 RESTING ENERGY EXPENDITURE – INDIRECT CALORIMETRY

For the measurement of resting energy expenditure by indirect calorimetry used in this thesis, see paper III.

4.7.3 NON-RESTING ENERGY EXPENDITURE

For the calculation of non-resting energy expenditure used in this thesis, see paper III.

4.7.4 PHYSICAL ACTIVITY

For the calculation of physical activity level and step count, assessed by the multi-sensor arm-worn accelerometer SenseWear Armband Pro_2, see paper III.

4.8 VALIDATION OF ENERGY REPORTING

For the assessment of validity of energy reporting, see paper III.

4.9 DATA ANALYSIS

All data (papers I, II, and II) were analyzed using IBM SPSS statistics for MAC software program (version 23; Armonk, NY, U.S.). Data is expressed as mean ± standard deviation (SD) unless otherwise stated. P-value <0.05 was considered to be significant.

Shapiro-Wilk test of normality was used for all data, between-group comparisons of continuous variables were thereafter analyzed with Student's t-test, ANOVA and Mann Whitney U-test was used between group comparison, and within group comparisons was tested with paired samples t-test and Wilcoxon signed ranks test, as appropriate (papers I, II, and III).

Covariate adjusted general linear model, with adjustments for baseline body weight, weight loss, and body composition, was used to detect differences in body composition between sexes (Paper I).

Covariate adjusted general linear model, with adjustments for 5-year body weight, BMI and age, was used to detect differences in intake between surgically treated and non-surgically treated adolescents at five years (Paper I).

Covariate adjusted general linear model, with adjustments for gender, 5-year body weight, BMI and age, was used to detect differences in demographics, anthropometry, intake and biochemistry between groups (Paper II).

Covariate adjusted general linear model, with adjustments for body composition, was used to detect differences in REE between surgically treated and non-surgically treated adolescents at five years (paper III).

Non-parametric Cochrane's Q-test and post hoc McNemar chi-square test, by the method of Bonferroni was used to detect differences in proportions over time (paper I and II).

Pearson's chi-square test was used to detect relationships between categorical variables (paper II and III).

Pearson correlation was used to detect association between reported energy intake from the diet history interviews and total energy expenditure from the doubly labeled water method (paper III).

Root mean square error (RMSE) normalized for total energy expenditure was used to express mean energy intake reporting error (paper III).

For sufficient power in assessing differences in TEE and REE a power calculation was made, 20 subjects expected to be needed in each group (for 85% power at $P<0.05$ level (paper III).

4.10 ETHICS APPROVALS

Both verbal and written information about the studies were given to all adolescents and their caregivers before an informed written consent was obtained. Subjects were allowed to withdraw at any point without giving a reason.

The regional ethics committee of the Swedish ethical review authority approved the AMOS study protocol (523-04, paper I and II) with an addition of (T1011-11, Ad 523-04, paper III). The study was conducted according to the Declaration of Helsinki, registered at ClinicalTrials.gov (NCT00289705). The Swedish general healthcare system subsidized the surgical interventions, the non-surgical treatment, and other health care.

4.10.1 DESCRIPTION OF THE ETHICS OF THE AMOS STUDY, AND THE DOUBLY LABELED WATER STUDY

In 2005, gastric bypass surgery was considered the gold standard in metabolic and bariatric surgery with good long-term results in weight loss combined with a good eating quality in adult. Surgery for severe obesity in adolescents was sporadically performed worldwide. It was thus considered important to perform prospective controlled studies, to determine whether surgery was feasible also in adolescence.

Two publications form the basis of AMOS (188, 189):

1. A review of a 20-year database on metabolic and bariatric surgery in adolescents (n=33), where the majority (91%) was gastric bypass surgery (188). Metabolic and bariatric surgery in adolescents was considered safe and associated with significant long-term (>14 years) weight loss, resolution of obesity comorbidity, and improved self-image and socialization.
2. A review of medical records of all patients under the age of 20 years who had undergone metabolic and bariatric surgery (n=5), with a mean follow-up time of 17 months (189). Outcome variables included weight, BMI, length of hospital stay, comorbid conditions, and tolerance of a regular diet.

Primary scientific questions to be answered through the AMOS study were:

- Can the positive effects (quality of life, improved metabolic health, and reduced morbidity) seen in adults after laparoscopic gastric bypass surgery with severe obesity, similarly be obtained in adolescents?
- Are there any age specific problems?

The ethics committee approved adolescents to be admitted through the three childhood obesity centers (Gothenburg, Stockholm and Malmö), and all operations to be performed at Sahlgrenska University hospital in Gothenburg, with follow-up visits at the referring centers. The study was considered a case-control study were adolescents opting for surgery would be considered a "case". To each and all surgery patient, a matching (by age, sex, weight and BMI) of controls (who did not opt for surgery) would be made, and would instead be offered medical nutrition therapy, within the frame that the three different obesity centers were offering. Monitoring was to be pre-surgery, and follow-up visits after one, two, and five years following surgery, at Sahlgrenska University hospital, Gothenburg. Additional medical treatment, such as dietary advice and support was to be done through the admitting childhood obesity center. Study variables included anthropometry, BMI, eating patterns, iron metabolism and B_{12}, folic acid, and DXA measurements of fat mass, and fat-free mass. Power calculations were made on expected BMI and weight reduction, and on secondary endpoints (medical and metabolic risk factors, quality of life, and eating pattern), because these aspects were considered important to describe the patients overall situation, 70 participants were needed in each group for 80% power at $P<0.05$ level.

The risk of long-term late adverse events included "some risk" of iron and vitamin deficiency (but was considered to be able to be substituted). The adolescents were considered to have "good" long-term eating patterns, and they were expected to be able to eat "normally" after the first few months.

In the addendum (of T1011-11, Ad 523-04, paper III), concerning the sub-study with doubly labeled water, the aim was to compare total energy expenditure and resting energy expenditure in surgically and non-surgically treated adolescents from the AMOS-study at five years. Power calculation was made on the difference between groups in total energy expenditure and resting energy expenditure, 20 participants were needed in each group for 85% power at $P<0.05$ level.

5 MAIN RESULTS

The dietary assessment (paper I and II) was completed in 98% (n=83) of the surgically treated adolescents at baseline, 93% (n=79) at 1 year, 87% (n=74) at 2 years, and 75% (n=64) at 5 years.

For the five-year comparison with non-surgically treated adolescents on medical nutrition therapy 65% (n=40) completed the dietary assessment (paper I and II).

Body composition measurements (paper I) were obtained from 89% (n=76) at baseline, 97% (n=82) at 1 year, 94% (n=80) at 2 years, and 91% (n=77) at 5 years after gastric bypass, and from 63% (n=39) in non-surgically treated adolescents at 5 years.

For obtained prevalence of biochemistry measurements (paper II) of calcium, vitamin D, PTH, B_{12}, folate, ferritin and Hb, see table 6.

Table 6. Prevalence of biochemistry measurements obtained in adolescents at baseline, and 1-, 2- and 5 years after gastric bypass surgery (n=85), and in non-surgically treated adolescents at 5 years (n=62) (paper II).

	Surgically treated adolescents				Non-surgically treated adolescents
Micronutrient	Baseline (%)	1 year (%)	2 years (%)	5 years (%)	5years (%)
Calcium	92	94	92	85	63
Vitamin D	39	48	66	86	57
PTH	0	18	45	88	47
B_{12}	87	92	91	87	50
Folate	58	79	78	0	0
Ferritin	77	93	91	88	50
Hb	92	95	93	92	53

For the energy expenditure measurements (paper III), the Malmö and Gothenburg cohorts were asked to participate, of which a total of 86 subjects both surgically (n=44) and non-surgically (n=42) treated adolescents 49% (n=42) accepted, five subjects were disqualified because of flawed samples. Hence, energy expenditure measurements were obtained from 34% (n=15) surgically treated adolescents and 52% (n=22) non-surgically treated adolescents at five years. All of the subjects in paper III completed the dietary assessment.

5.1 PAPER I - DIETARY INTAKE AND BODY COMPOSITION IN ADOLESCENTS AFTER GASTRIC BYPASS SURGERY

Results below refer to data from table 1 and 2 in paper I.

5.1.1 BODY WEIGHT

Adolescents in the surgical group had a higher weight (133 vs. 117 kg), a higher BMI (45.5 vs. 40.2), and were older (16.5 vs. 15.6) at baseline compared to adolescents in the non-surgical group. Adolescents treated with gastric bypass lost weight and decreased in BMI from preoperative levels through all time-points. At five years surgically treated adolescents had lost 28% while non-surgically treated adolescents had gained 13%.

5.1.2 DIETARY INTAKE

Adolescents reported energy intake decreases from preoperative levels at all time-points, at five years it was 10% lower than preoperative energy intake, and 30% lower than the reported intake in the non-surgically treated adolescents.

Food weight decreased during the first two year but returned to preoperative at five years and was not different from the non-surgically treated adolescents food weight at five years.

Dietary energy density decreased during the first year in the surgically treated adolescents but remained similar to preoperative levels through two and five years. At five years dietary energy density was lower in the surgically treated adolescents compared to the non-surgically treated adolescents.

There were no changes in the proportions of protein, fat and carbohydrates intake from pre-surgery through two years, but at five years the proportions of protein and carbohydrate were lower.

Alcohol intake, both proportion of macronutrients and in absolute grams per day, increased compared to pre-surgery levels through all time-points. Compared to the non-surgically treated adolescents at five years, there was no difference in alcohol intake, hazardous consumption or heavy drinking.

5.1.3 BODY COMPOSITION

Fat- and fat-free mass decreased in the surgically treated adolescents through five years. Boys had a more pronounced weight loss in fat mass and preserved more muscle mass than girls. At five years total muscle mass was not different between the surgically and the non-surgically treated adolescents, but girls in the surgically treated group had lower muscle mass than girls in the non-surgically treated group.

5.1.4 BODY COMPOSITION AND PROTEIN INTAKE

Twenty-two percent of adolescents following gastric bypass did not reach up to the recommended intake of 60 grams protein per day. Mean protein intake was 20% lower than recommendations at five years. A better preservation of muscle- and fat-free mass was seen through two and five years in those who reached the protein intake goals.

5.2 PAPER II – MICRONUTRIENT INTAKE AND ADHERENCE TO SUPPLEMENTATION IN ADOLESCENTS AFTER GASTRIC BYPASS SURGERY

Results below refer to data from table 2 and 3 in paper II.

5.2.1 MICRONUTRIENT INTAKE

Micronutrient intake, from food and supplements together, increased from preoperative intake and was higher than the non-surgically treated micronutrient intake in all but calcium, which was similar. Adolescents' not taking supplementation had similar micronutrient intake as the non-surgically treated adolescents in all but calcium. Iron intake in males, from food only as they were not prescribed iron supplementation, sustained through five years after gastric bypass surgery and was not different from micronutrient intake in the non-surgically treated males.

5.2.2 ADHERENCE TO SUPPLEMENTATION

Half of the adolescents reported sufficient adherence to micronutrient supplementation trough five years after gastric bypass surgery. Adhering to supplements was associated with more favorable biochemistry of vitamin B_{12}, vitamin D, and also of ferritin (in females who were prescribed iron supplementation).

5.2.3 ABERRANT BIOCHEMISTRY

Adolescents had a high prevalence (49%) of vitamin D insufficiency prior to surgery, which remained through five years (63%) after surgery, which was not different from the non-surgically treated at five years (57%). PTH levels were higher in adolescent after gastric bypass regardless of adherence status compared with non-surgically treated adolescents at five years.

Preoperative prevalence of iron deficiency, in both female (10%) and male (13%) increased over time in adolescents treated surgically and the prevalence was higher than in the non-surgically treated adolescents at five years (61% vs. 12% in females, and 62% vs. 7% in males, respectively).

Female adolescents were prescribed iron supplementation following gastric bypass surgery and 46% (range 44-48%) reported that they followed instructions through five years. Adherence to iron supplementation showed lower in comparison to adherence to other supplements through five years after surgery. Not adhering to iron supplementation showed higher prevalence of iron deficiency five years after gastric bypass surgery (77% vs. 33% in female not adhering vs. female adhering, respectively). Fifty-nine percent of females with iron deficiency also had anemia at five years and the prevalence of anemia was higher than in the non-surgically treated females (41% vs. 6% respectively).

5.3 PAPER III – ENERGY EXPENDITURE AND EVALUATION OF ENERGY REPORTING IN ADOLESCENTS AFTER GASTRIC BYPASS SURGERY

Results below refer to data from table 1 and 2 in paper III.

5.3.1 BODY WEIGHT CHANGE AND BODY COMPOSITION

Adolescents in the surgical group had a higher weight (130 vs. 112 kg) and a higher BMI (44.7 vs. 38.0) at baseline compared to adolescents in the non-surgical group, respectively. At five years surgically treated adolescents had lost over 33 kg while non-surgically treated adolescents had gained over 14 kg. The surgically treated adolescents had a lower fat mass (40 vs. 62 kg) but there was no significant difference in fat-free mass (57 vs. 62 kg), compared to the non-surgically treated adolescents, respectively.

5.3.2 ENERGY EXPENDITURE

Total energy expenditure measured with the doubly labeled water technique over a 16 day period was not different between the adolescents treated with gastric bypass surgery or non-surgically treated adolescents at five years. Resting energy expenditure measured with indirect calorimetry was lower in the surgically treated adolescents but not when adjusted for body composition. There was no difference in the remaining, calculated, non-resting energy expenditure between the groups. However, when adjusted for weight and calculated physical activity level the non-resting energy expenditure was higher in the surgically treated adolescents. There were no significant differences in assessed step counts or calculated physical activity levels between the groups.

5.3.3 EVALUATION OF ENERGY REPORTING

There were no differences between the groups or sexes in self-reported energy intake. There was no association between reported energy intake from the diet history interviews and total energy expenditure measured with doubly labeled water in all adolescents (n=37). There was, however, a positive correlation in the surgically treated adolescents (n=15).

6 DISCUSSION

The long-term nutritional effects of gastric bypass surgery in adolescence have previously been sparsely studied, yet being crucial to the outcome of metabolic and bariatric surgery in this population. The studies in this thesis add important knowledge where little existed before in this emerging population. In what follows, I will discuss the methodological considerations and the findings of the study.

6.1 STUDY DESIGN, STUDY POPULATION AND PARTICIPATION RATES

The manuscripts are results of the Adolescent Morbid Obesity Surgery (AMOS) study, a prospective non-randomized case-control, intervention study with efficacy and safety of gastric bypass in adolescents as primary endpoints. During the recruitment period non-surgically treated controls were contemporary identified in The Swedish Childhood Obesity Treatment Register (BORIS). All adolescents were selected using the same inclusion and exclusion criteria (Table 5 page 28). All adolescents had received medical nutrition therapy for at least a year prior to inclusion, this treatment continued in the non-surgically controls. At five years non-surgically treated controls were invited to the clinic for an outpatient visit, hence the studies have data from the five-year visit, and baseline data on anthropometry.

The possibility of randomization to treatment was carefully considered in the AMOS study but it was considered impractical and unethical to randomize adolescents to such different treatment options. The ideal would have been a randomized study between surgical and non-surgical intervention in adolescents, with a standardized medical nutrition therapy in the non-surgically treated controls.

At five years, despite great efforts, it was hard to engage non-surgically treated adolescents for an outpatient visit. Thirty subjects (37%) were missing, 25% (n=21) had metabolic and bariatric surgery when they reached 18 years of age (75), thus decreasing the sample of non-surgically treated controls at five years for all papers (I, II, and III). It was decided to include 10 new young adults from the BORIS registry who had gone through medical nutrition therapy during the same period of inclusion to AMOS. The matching of age, gender and BMI in the non-surgically treated controls was only partially successful (see Table 1, in papers I, II and III). One reason for this being that the heaviest adolescents had opted for surgery during inclusion.

Two of three studies used the same subjects, followed longitudinally with repeated measurements from pre-surgery, through all time-points after surgery (paper I and II). Longitudinal design assesses changes over time but the number of subjects often decreases over time.

The dietary assessment did decrease over time (from 98% at baseline but was still 75% at five years). This decrease might reflect the fact that the diet history interviews were time consuming and most often were assessed after an enormous battery of assessments included in the follow-ups in the AMOS study. This is supported by attrition rates for body composition measurements being higher through five years (approximately 93%). Non-surgically treated adolescents, who where assessed at five years, had similar attrition rates for both dietary intake (63%) and body composition data (65%).

One study (paper III) was conducted at the five-year visit (with a sample of subjects from paper I and II), with an analytic, observational case-control study design, with no preoperative or baseline data in energy expenditure and body composition in either of the groups. To rigorously assess the differences in total energy expenditure and resting energy expenditure, 20 participants in each group would have been minimum. Unfortunately these numbers were not achieved for a number of reasons:

1. The eligible number of participants from both the surgically and non-surgically treated young adults at five years was limited.
2. The workload and adherence expected from the participants to the experimental part of the doubly labeled water study.
3. The sensitive age group of the participants.
4. The characteristics of the population in our cohorts with a high prevalence of mental health problems mentioned on page 29 and previously reported (84, 177, 178, 180). Psychological differences in adolescence may impair accuracy of reporting (140, 141), and five subjects were excluded due to flawed samples.

Given the many potential confounders between the cohorts (i.e., differences in treatment, dietary instructions, support, follow-up, and different sample sizes), these may affect the generalizability of the results.

6.2 METHODOLOGICAL CONSIDERATIONS

6.2.1 DIETARY ENERGY INTAKE ASSESSED WITH DIET HISTORY INTERVIEWS

The dietary assessment method, diet history interview, was chosen:

To:

1. Capture habitual intake.
2. Achieve a high participation rate.
3. Reduce the bias of self-reported dietary intake in this population by trained dietitians to collect data by interview.
4. Evaluate the method for energy intake in Swedish adolescents, with obesity and severe obesity.

Because:

5. Research has shown that diet history interviewing has proven to be the most accurate method to capture energy intake in adolescents, both normal weight, over weight and with obesity (10, 138, 190).
6. The method provides consumption at meal level, essential for the relation between diet and micronutrient status.
7. The diet history questionnaire used in the studies had previously been validated in Swedish adolescents, with normal weight (182).

6.2.1.1 HAZARDS WITH RELIABILITY OF SELF-REPORTED ENERGY INTAKE IN ADOLESCENTS WITH OBESITY OR SEVERE OBESITY

Even though nutritional assessment is one of the most crucial problems facing nutritional research, there is no golden standard method. The diet history interview relies heavily on the participants' ability to recall and estimate their habitual intake (140). This can be particularly difficult in adolescence because of unstructured eating patterns and changing food habits, with more eating outside home, high energy requirements, socially desirable answering, and body image, together with a possible lack of motivation and adherence that may impair reporting accuracy (139, 140).

Accuracy of dietary reporting has wide variation between studies and there is no consensus on criteria used to identify misreporting, making it hard to compare between studies and populations (137). Underreporting energy intake has been associated with characteristics including female sex, higher BMI, obesity, weight consciousness, frequent dieting, and psychological differences (137, 139, 140). These are characteristics often found in adolescents with severe obesity, and also in the cohorts in this thesis, making them a difficult population for dietary assessments.

An alternative would have been to remove misreporting from the analyses, but with risk of: (i) missing valuable information on dietary intake; and (ii) selection bias. Removing misreporting creates a problem with being able to identify them correctly e.g., removing participants reporting low energy intake risks missing participants with relatively high, energy intake but with even higher total energy expenditure.

Furthermore, underreporting of energy intake has been associated with higher reward value for expected tasty food and with lower reward value for receiving tasty food in adolescents (191). The authors speculate that these effects may lead to overeating and consequently to underreporting energy intake to a greater degree. Reduced reward value to expected tasty food has also been reported in adolescents after metabolic and bariatric surgery (132).

There is no golden standard method to assess dietary intake, but we cannot stop attempting to assess nutritional impact on different medical conditions and outcomes. Instead, we need to be aware of the limitations of the dietary assessment methods available, and by validating them in different populations we at least have a reliability estimate (136). We did not compare with other dietary assessment methods but our results from comparing reported energy intake derived from the diet history interviews (paper III) show that the instrument is not accurate enough for energy balance studies, at least not in this limited population. The surgical group appeared to have an energy imbalance of -616 kcal over the 16 day doubly labeled water period and the non-surgical group an imbalance of -229 kcal. But whether they lost an average of 1.4 kg or 0.5 kg, in the surgically and non-surgical group respectively, was not detected. A limitation in the design of the energy balance study is that weight was measured to the nearest 0.1 kg on calibrated electronic scales at the clinic at baseline but during the study period, weight was self-measured on home-scales and self-reported by the participants. Their instruments for body weight might not have detected their weights to the nearest 0.1 kg and differences in body weight might therefore have been undetected. However, if these undetected weight differences did occur, they are still close within the limitation of weight fluctuations in energy balance studies, due to hydration and content in the gastrointestinal tract, hence, not related to changes in energy stores (192).

Given suboptimal number of adolescents in paper III and the risks of inaccuracy of self-reported energy intake in the population of this thesis the results were expected and should be interpreted with caution. Nevertheless, the dietary assessment showed an association in the surgically treated young adults with obesity, and was used longitudinally in the same population, making the results between follow-ups more comparable than between groups.

6.2.2 DIETARY MICRONUTRIENT INTAKE AND ADHERENCE TO SUPPLEMENTATION

Energy intake is a proxy of total dietary intake. An underestimation of energy intake most likely results in an underestimation of micronutrients, depending on the micronutrient density of the misreported food items. However, the present thesis does not assess micronutrient intake from food alone, but from food and supplements together.

Subjective patient self-reported adherence, such as questionnaires or diaries, are practical in a clinical setting but vulnerable to overestimation of adherence compared with objective methods, such as electronic drug monitors or pharmacy claims (193). We did not compare with other methods, but there might indeed have been an overestimation of adherence in study II due to a number of reasons:

1. There is always a risk of socially desirable answering. However, monitoring adherence and providing support, was done by two different professions, maximizing the accuracy of responses, preferred where adherence is predicted to be poor (10, 138).
2. Loss to follow-up may cause an overestimation of adherence rates, where participants with the lowest adherence may have missed follow-up appointments.

However, a study assessing the association between support group attendance and adherence to supplementation after metabolic and bariatric surgery in adolescents indicated no association (194). In addition, the fact that there was no difference (in weight loss, BMI, BMI loss, and excess BMI lost) between those who attended all visits compared to those with incomplete data, which suggests that there was no systematic baseline bias in the present thesis.

3. Due to the generous criterion of "adherent" used in the present thesis, defined as participants' reported taking prescribed supplements three or more times weekly. If we had used a stricter criterion adherence rates would have been lower. However, this might have reduced the possibility to compare the already small groups.

All adolescents were assessed longitudinally, with the same questionnaire pre-surgery and through all follow-ups, overestimated or not differences in adherence between follow-ups should appear. Additionally, results show that reporting accuracy was mirrored in biochemistry, where adolescents reporting taking supplements also had more favorable serum levels of micronutrients (paper II). Hence, supporting the reliability of self-reported adherence data in the present thesis, with some agreement at group level.

6.2.3 BODY COMPOSITION ASSESSED WITH DUAL-ENERGY X-RAY ABSORPTIOMETRY

Dual-energy X-ray absorptiometry is often referred to as the gold standard method to assess body composition (153). While the DXA has high precision and accuracy it does have an upper body-weight limit, which limits the whole-body field-of-view of very large persons (153). Eight adolescents, 3 female and 5 male, were excluded pre-surgery from the DXA analyzes due to scanner safety and body weight restriction (>136.1 kg), possibly biasing the baseline body composition data. Due to upgrading of the DXA software it was possible to measure all participants at the follow-ups: with changed body weight restrictions, introduction of the possibility to measure by performing half-body scans, and to calculate body parts outside the measurement area e.g. a shoulder. Performing half-body scan has ben proven valid in studies using Lunar densitometers (153).

In paper I, skeletal muscle mass was calculated from DXA measurements of appendicular lean tissue mass, with equations validated in adults (187). Muscle mass in late stage of puberty adolescents (Tanner stage 5) is well predicted by the adult muscle mass equation, but has shown to overestimate muscle mass in pre-pubertal (Tanner stage <4) and early pubertal (Tanner stage 4) adolescents by 0.3 kg and 0.5 kg, respectively (154). However, the equation was chosen due to the longitudinal design of adolescent going through maturity (and Tanner staging), and due to the aim of assessing differences between surgically and non-surgically treated young adults at five years.

A study tracking longitudinal changes in adolescents with obesity showed that DXA tended to overestimate muscle mass compared to whole-body MRI (195). In the present thesis, paper I, muscle mass was 30.9±6.0 kg pre-surgery in the surgically treated adolescents and 27.1±6.3 kg at five years, while the non-surgically treated adolescents muscle mass was 29.7±6.6 kg at five years (Table 2, paper I). All body composition measurements were assessed with DXA and not compared to whole-body MRI, hence, overestimated or not, differences should appear. Additionally, both the means and the standard deviations of the measurements for the groups were similar, making them comparable.

Longitudinal changes in body composition can bias DXA measurements of both fat mass and fat free mass, especially if there is significant change over time (196). The surgically treated adolescents had significant changes in their body composition during the first year, however, this decreased thereafter (Table 2, paper I). Whether the non-surgically treated adolescents had a significant change over time was not under the scope of the study.

Despite the fact that the gap already was large between mean fat mass in the non-surgical and surgical adolescents, 63.3±15.3 vs. 39.2±16.2 kg, respectively (Table 2, paper I), the gap can be assumed to be even larger given the fact that DXA has shown to underestimate fat mass with greater underestimation with increased fat mass in adolescents with obesity (195).

6.3 DISCUSSION OF THE FINDINGS

6.3.1 DIETARY INTAKE

Dietary intake after gastric bypass has been estimated largely from adult cohorts. Outlined in the introductory chapter, both adults and adolescents report reduced energy intake (with reduced intake of high-fat- and high-sugar foods), and energy-dense food, especially during the semi-starvation phase during the first post-operative year, with a sustained reduced long-term energy intake (79, 128-131). Our finding of decreased long-term energy intake, but food weight returning to preoperative levels has not been reported before in adolescents after gastric bypass. This might reflect changes in food choices, with reduced intake of foods with high energy content, supported by the fact that dietary energy density and energy intake were lower compared with the non-surgically treated adolescents at five years, but food weight was not. However, due to the methodological issues discussed earlier, and our results from paper III, our conclusions regarding energy intake and dietary energy density in paper I, should be interpreted with caution, especially the comparison between groups.

There is no evidence to date to guide the estimation of protein requirements after gastric bypass in adolescents. Therefore the adult recommendation, of 60 grams, was an obvious choice as a cut-off (paper I) (9). However, the recommendation is graded D and is “primarily based on expert opinion”, protein requirement differ depending on age, sex, weight, muscle mass, physical activity. Nevertheless, our finding, that a higher protein intake might facilitate muscle preservation after gastric bypass in adolescents, mirrors findings from a systematic review in adults after gastric bypass (197). Result highlight the need of protein recommendations for young people undergoing gastric bypass, thus, more research is needed.

Alcohol intake increased from baseline and seemed to be higher at five years compared with the non-surgically treated controls. This could speculatively relate to age-related trends and, potentially, a lower threshold to go out and socialize following surgery. Although, there was no difference in alcohol consumption behavior (hazardous consumption and heavy episodic drinking) between the groups, it should still raise a red flag. Gastric bypass patients run an elevated risk of alcohol dependence (198, 199), coupled with the young age and high prevalence of mental health problems before surgery, in the AMOS adolescents (84, 177, 178). This has been shown to be a risk factor for alcohol abuse after metabolic and bariatric surgery (198). Our findings therefore support guidelines “all adolescent patients undergoing surgery should be routinely screened and counseled on the risk of alcohol misuse and abuse” (8), and in addition, they should be offered counseling after surgery to mitigate the risk of falling into alcohol dependence.

Energy intake is a proxy of total dietary intake, therefore an underreporting likely results in an underestimation of all macronutrients, as found in a study of adolescents with overweight underreporting reflected to all macronutrients and not a specific one (200). However, validating the dietary assessment method for macronutrients was not in the scope of this thesis.

6.3.2 SUPPLEMENTATION ADHERENCE AND BIOCHEMISTRY

The present research confirms earlier findings that calcium intake from food declines following gastric bypass (110, 133, 134). Adolescence is a crucial time for bone formation, were intake of calcium is of great importance. Adolescents had high prevalence of pre-surgery vitamin D insufficiencies and this continued over time, regardless of reported adherence to supplementation. More importantly, adherence to supplementation did not prevent secondary hyperparathyroidism. Hence, higher preventative vitamin D supplementation should be implemented.

Adolescence is also a crucial time for growth and muscular development, with increased blood volume and an elevated need for iron (201). Both male and female participants had iron deficiency at five years, suggesting that iron supplementation should be given to both sexes after gastric bypass in adolescence. Iron deficiency in male following gastric bypass has also been reported in adults (202). The high prevalence of long-term iron deficiency and anemia in the present thesis has ben reported earlier in adolescents following metabolic and bariatric surgery (85). Our findings emphasizes the need for regular monitoring after gastric bypass surgery in adolescence. Monitoring for anemia especially in female adolescents is essential as maternal anemia could be detrimental for offspring.

The high prevalence of iron deficiency in the present thesis might also have affected adherence, as iron deficiency in adolescence may adversely affect cognitive ability and behavior (201).

Because of its effectiveness to provide elemental iron, ferrous sulfate (Fe^{2+}) is the gold standard oral iron therapy. However, its gastrointestinal adverse-effects may have contributed to lower adherence in the present thesis, as seen in adult gastric bypass patients (203). Participants showed less adherent to iron supplementation compared with all other supplemental regimens, indicating greater challenges with iron supplementation. However, this was not further investigated in the present thesis.

Adherence to medical regimens in adolescents with chronic disease has been estimated around 50% (143), and corresponds well with our findings. Long-term self-reported adherence was lower than earlier reported after gastric bypass surgery (144, 204, 205), and might even be lower due to differences in the criterions used for adherence. However, our study adds to the research in adolescent behavior after gastric bypass, with longitudinal adherence data showing that adherence was stable, in contrast to findings in adults (205).

6.3.3 BODY COMPOSITION

Long-term body composition changes have not been previously reported in adolescents after gastric bypass surgery. Given the between-sex results in the surgically treated group and the within-sex results between the surgically and the non-surgically treated adolescents it seems like male preserve their muscle mass better than female after gastric bypass in adolescence (paper I), mirroring changes seen in adults following gastric bypass surgery (129). As discussed in paper I, this might be due to hormonal differences between the sexes (206). Even though there was large differences in body weight (25kg) between surgically and non-surgically treated males at five years, the surgically treated males had similar fat-free- and muscle mass as compared to the non-surgically treated males. Females, on the other hand, followed a theoretically more plausible trajectory, with lower fat mass, fat-free mass, and muscle mass as compared to the non-surgically treated females, likely reflecting the fact that it takes more muscle mass to carry a higher weight (38 kg difference between the groups).

6.3.4 ENERGY EXPENDITURE

At a first glance, adolescent after gastric bypass had lower resting energy expenditure than the non-surgically treated adolescents at five years (paper III). However, when adjusted for body composition there was no difference in resting energy expenditure, hence reflecting differences in body composition as fat-free mass to a great degree determines resting energy expenditure (147). This implies a difference in non-resting energy expenditure between the groups, but does not tell where the difference lays. As we did not detect any differences in physical activity, we can only speculate on whether the difference lays in dietary induced thermogenesis, as has been speculated in adults (150) or in non-exercise thermogenesis, seen in adults (166-169), or in both. The answer therefore remains to be explored.

6.3.5 EVALUATION OF ENERGY REPORTING

All dietary assessment methods, both prospective and retrospective, in all age categories report significant underestimation of energy intake when compared to total energy expenditure measured by doubly labeled water (190, 207). Individuals with overweight or obesity tend to underreport in a greater extent than individuals with normal weight through all ages (190, 207). As discussed in paper III, there could possibly be a higher reporting bias in adolescents with obesity compared with previously reported in adolescents with normal weight (182). In the present thesis, there might also be a higher reporting bias with higher weight, reported by others (200, 207, 208). Even though our results show an association in the surgically treated young adults at five years, we cannot draw any conclusions whether their reported energy intake was associated, or not, with total energy expenditure during the previous years of follow up, as our study was limited to a “snapshot” of a 16-day period during the five-year follow up. Hence, results concerning energy intake should be interpreted with caution.

7 CONCLUSION: CLINICAL AND RESEARCH IMPLICATIONS, AND ETHICAL CONSIDERATIONS

Gastric bypass in adolescents with severe obesity resulted in a long-term weight loss of 28% while adolescents on conventional medical nutrition therapy gained 13% over five years. Energy intake and dietary energy density might be important factors in weight loss following gastric bypass surgery in adolescents. Male lost more fat mass than female following surgery while muscle mass was more preserved in male. Adequate protein intake might facilitate preservation of muscle mass following surgery.

Long-term adherence rates to vitamin and mineral supplements were stable around 50% and were mirrored in a more favorable biochemistry and lower prevalence of deficiencies. Hence, supporting the reliability of the self-reported data on group level. However, assessment of adherence and support thereof, tailored and individualized for each patient is important. This would reduce the risk of exacerbating pre-existing micronutrient abnormalities, which if left untreated could lead to endocrine complications associated with gastric bypass surgery. Our results support current recommendations to: (i) screen for micronutrient deficiencies prior to surgery; (ii) optimize monitoring of supplements while continuing screening for micronutrient deficiencies; and (iii) monitoring serum levels of vitamins and minerals in individuals because large differences in uptake and adherence are prevalent. Furthermore, both male and female should be prescribed iron supplementation and higher preventative doses of vitamin D supplementation.

Despite large difference in weight and similar fat-free mass, five years after gastric bypass surgery or conventional medical nutrition therapy total energy expenditure was similar between the groups.

A major problem with evaluation studies, which occurs when the study is completed, is whether the method is accurate enough to be used. Our results underpin the importance of refining the procedures applied in dietary assessment methods and to validate them for energy intake in this population.

7.1 CLINICAL IMPLICATIONS

There are a number of important clinical implications of the research reported in this thesis.

Firstly, it is vital to ensure the best standard of care in this vulnerable period of life. Adolescents must be treated within multidisciplinary teams preferentially in accredited adolescent obesity centers, or institutions with the necessary knowledge and clinical experience. This is especially important because current clinical practices in adolescent metabolic and bariatric surgery are grounded in what we know about adults. Accredited adolescent obesity centers are more likely to have a critical eye in research interpretation and relevant clinical experience from the adolescent population.

Secondly, in order for bariatric dietitians to accurately assess the suitability, prevention, and treatment in adolescent metabolic and bariatric surgery patients, adolescent-specific guidelines for macro- and micronutrient requirements need to be established.

Thirdly, to avoid vitamin and mineral deficiencies in future adolescent metabolic and bariatric surgery candidates, there is a need for adolescent-specific i) standardized cut-off points for deficiencies, ii) appropriate interventions for deficiencies, iii) recommendations on the appropriate type, dose, formulation and routes of administration for dietary supplements supporting adherence.

Fourthly, our findings lend support to the necessity of close follow-up and monitoring of biochemistry before and after metabolic and bariatric surgery. This should include increased dietitian involvement for personalized patient-centered nutritional management to address specific challenges, and to provide ongoing support for self-management to encourage supplementation adherence.

Finally, the diet history interview is not a clinically useful tool in young adults with obesity or severe obesity.

7.2 RESEARCH IMPLICATIONS

To date, most of the nutritional recommendations for the adolescent gastric bypass surgery patient have been hypothesized from research in adults. Because adolescence is a period of rapid growth and development, they are different in their maturation cognitively and physically. To this end, a number of significant research implications follow.

First, for ethical and practical reasons our studies were based on a non-randomized setting with adolescents undergoing gastric bypass surgery and a non-surgically treated control group. Larger randomized studies of adolescents undergoing gastric bypass surgery or standardized best practice medical nutrition therapy are needed to corroborate our results. Only when we are aware of the specific challenges in the adolescent population, we can put the appropriate interventions into action.

Second, in order to develop adolescent-specific nutritional guidelines for gastric bypass patients there is an urge for future nutritional research in the adolescent population. More research is needed in: (i) protein needs and muscle mass preservation; (ii) vitamin and mineral needs; (iii) cut-offs for micronutrient deficiencies; (iv) methods for adherence assessment; (v) criterion adherence; (vi) and appropriate interventions to improve adherence. In adults, clinically practical patient-support interventions such as combination pills (reduced pill burden), increased frequency in clinic visits, and technical medication-taking reminders, have shown to improve medication taking adherence with 10, 15, and 33%, respectively (193). This warrants further research in adolescents.

Third, to determine whether surgery is indicated in adolescence it is important to describe the patients overall situation. Dietary intake is much more than macro and micronutrients. It also includes dietary behaviors such as the choices of foods, meal pattern, portion size, and eating related behavior. These aspects of dietary intake were not addressed in the present thesis and warrants further exploration. For example, consumption of dairy food products has been reported to decrease after gastric bypass in adults (209), and hypocalcaemia has been speculated to be due to intolerance to calcium-rich foods after gastric bypass (79). In the present thesis we found reduced intake from calcium despite supplementation adherence. Hence, it would be interesting to find out whether dairy food products decrease after gastric bypass also in adolescents. This is especially important in light of the decreased bone mineral density and bone mineral content seen in adolescents after gastric bypass (127). Eating related behavior (binge eating, emotional eating, and uncontrolled eating) has been associated with less weight loss after gastric bypass surgery in the AMOS adolescents (179). Therefore, food choices, meal pattern, and portion sizes are of particular interest in order to target the specific needs regarding dietary guidance in the adolescent gastric bypass population.

Moreover, binge eating (loss of control with very large portions) before surgery has been associated with higher alcohol intake after surgery in adults (210). Binge eating among AMOS adolescents before surgery was 37% (179), but the association to alcohol intake has not been investigated. Therefore, this warrants further investigation.

Fourth, energy expenditure following gastric bypass surgery in adolescents remains to be further explored. It is intriguing to speculate that non-exercise activity thermogenesis and/or dietary energy thermogenesis may be greater after gastric bypass surgery, as reported in adults (99, 129, 166-169). To fully understand the mechanisms behind weight gain and weight regain, new methods are needed for the study of energy balance to be conducted over lengthy periods in free-living conditions.

Finally, it is unclear which dietary assessment method is best to use in the adolescent, or young adult, population with obesity or severe obesity. Further research is therefore needed to find ways to improve existing dietary assessments, develop new assessment methods and technologies, and to validate them to provide accurate agreement in this population. The accuracy of assessing dietary intake is essential for interpreting relationships between diet and disease, to describe or follow trends in dietary pattern, food choices and nutrient intake in different populations, and to compare intake to recommendation guidelines (190, 207).

This research is important in order to give the bariatric dietitian evidence-based tools for optimizing the nutritional care of future adolescent metabolic and bariatric surgery patients, to move from experience-based best practice to evidence-based practice in assessing, educating, and monitoring the adolescent gastric bypass patient.

7.3 ETHICAL CONSIDERATIONS

Growing medical knowledge and refined medical technologies warrant new and important ethical and moral considerations. Should metabolic and bariatric surgery be performed in adolescents with severe obesity?

Medical nutrition therapy is, and should probably always be, the cornerstone of obesity treatment, at any stage or age. Unfortunately, results are not convincing for combating the lifetime threat of adolescent severe obesity, with only 10% achieving clinical relevant effect after 3 years of therapy (48, 211). Although it is alleged that harms are few with medical nutrition therapy (60), is it harmless to fail repeated weight loss attempts in this vulnerable time of life? Disordered eating behaviors, including frequent dieting, in adolescence are associated with increased BMI, as reviewed by Yoon et al. (212).

The adolescent with severe obesity, receiving no treatment or an ineffective treatment, will risk a lifetime with comorbidities and a poor health-related quality of life (8). Without effective intervention, many of these comorbidities will shorten the lifespan of the individual (24, 28-31, 33-36).

Although metabolic and bariatric surgery is safe and effective in adolescent severe obesity, there are controversies for the surgery procedures to be performed in this population (8). As outlined earlier, metabolic and bariatric surgery will reduce obesity related mortality. In fact, research show great benefit from metabolic and bariatric surgery when performed during adolescence and early adulthood, especially when in risk of end-organ damage (213).

There are also potential risks, including the risk associated with gastric bypass surgery (earlier mentioned in Table 3, page 13), but maybe most importantly the ethical considerations regarding autonomy. With a lack of maturity in adolescents, the responsibility to assess what is in their best interest lays on their caregivers, to give consent based on the adolescents' assent and autonomy. It is of paramount importance to clearly communicate the expected results and changes, benefits and potential risks, and the necessity of adherence to lifelong follow-up with supplements (214).

7.3.1 GREATEST NEED, UTILITY, AND RESPONSIBILITY

It has been suggested that regardless of the most common moral principles; greatest need, utility, and responsibility; metabolic and bariatric surgery should be given a high priority when budgeting resources in health care in adults (215). I will try to put this in the perspective of adolescent metabolic and bariatric surgery (and whether it is ethical or not).

- **Greatest need:** The medical definition of health "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" (216), has remained over 70 years. Adolescents suffering from severe obesity will most likely still be suffering severe obesity in adulthood, with risk of even greater severity of comorbidities (Table 2, page 7) and an increased risk of early death.

- **Utility:** In health care, utility converts to production of better health per used unit of resources (44, 47). Adolescent metabolic and bariatric surgery show improvements in weight loss, long-term weight loss, quality of life, and recovery from comorbidities (Table 3, page 13).
- **Responsibility:** In society there is a stigmatization towards people with obesity, who are often perceived as being weak-willed, sloppy, lazy, and with a lack of motivation (217). In addition, they are often perceived as being responsible for their ill health (218). This weight stigma is detrimental and only adds barriers to the sufferers. It is also contra-productive; as it counteracts motivation, contributes to binge eating, social isolation, reluctance of going to follow-ups at healthcare services, and decrease physical activity (219). No one should be held responsible for a chronic disease, regardless of age. If adolescents are not mature enough to make their own decision about their own healthcare, how can they be accounted for taking personal responsibility for their chronic disease?

The benefits and the risks, in any treatment option, should be weighed against each other. If repeated attempts with conventional medical nutrition therapy for obesity is not effective to the individual posed, metabolic and bariatric surgery should not be withdrawn as an alternative therapy to adolescents with severe obesity (8). Making early decision to treat adolescent severe obesity with surgery might, in some cases, be the path to go in order to maximize outcome and minimize devastating risks with non-effective treatment options. Although metabolic and bariatric surgery may seem extreme, it decreases the risk of heart disease, diabetes, cancer, and stroke and reduces weight and BMI. Hence, metabolic and bariatric surgery is a potential lifesaver in adolescent with severe obesity. In addition, the more and better research we do on the adverse effects, the better care we can provide to avoid or mitigate them.

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