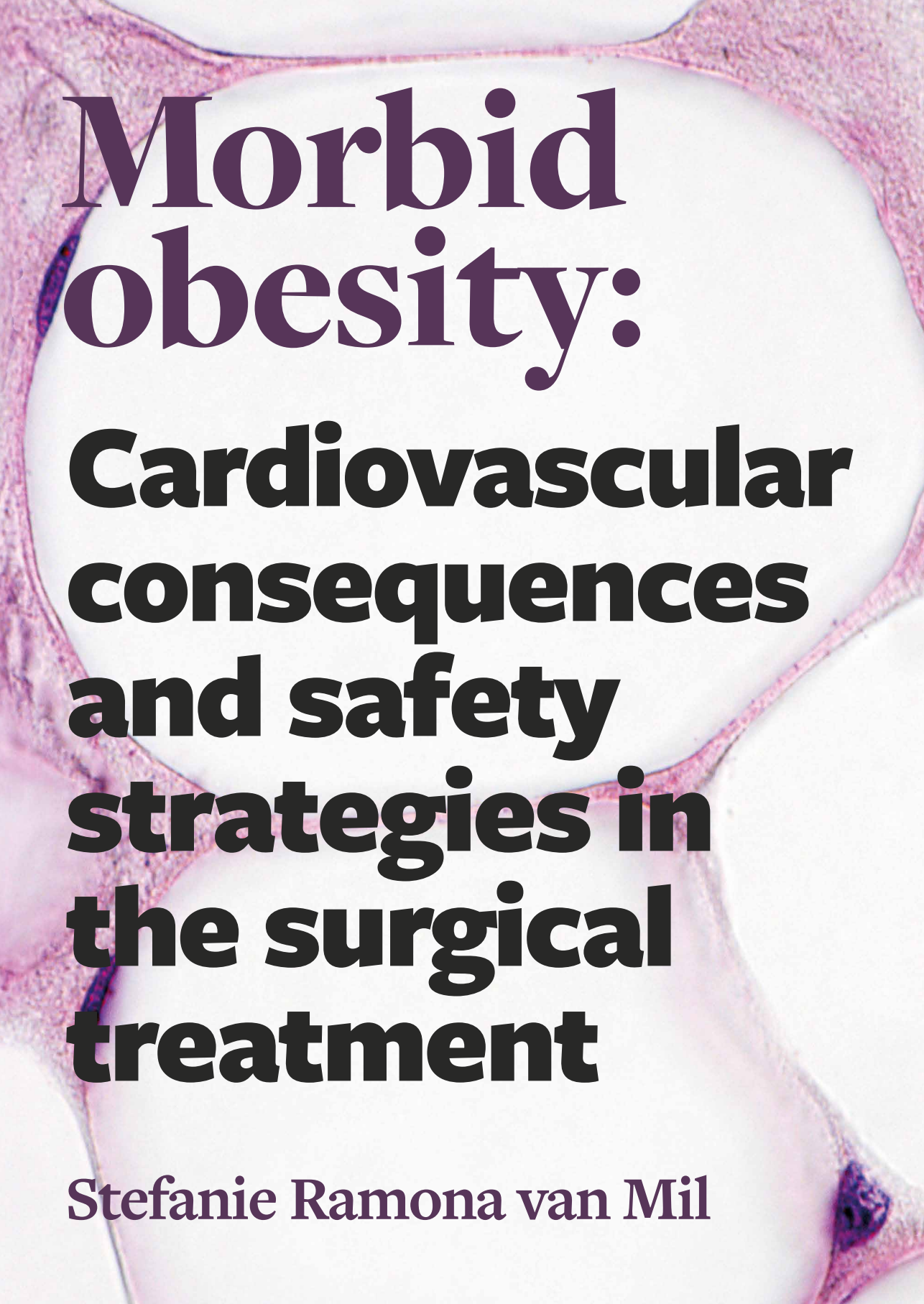

Morbid obesity:

Cardiovascular consequences and safety strategies in the surgical treatment

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Morbid Obesity:
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Morbide obesitas:
Cardiovasculaire consequenties en veiligheidsstrategieën in de chirurgische behandeling

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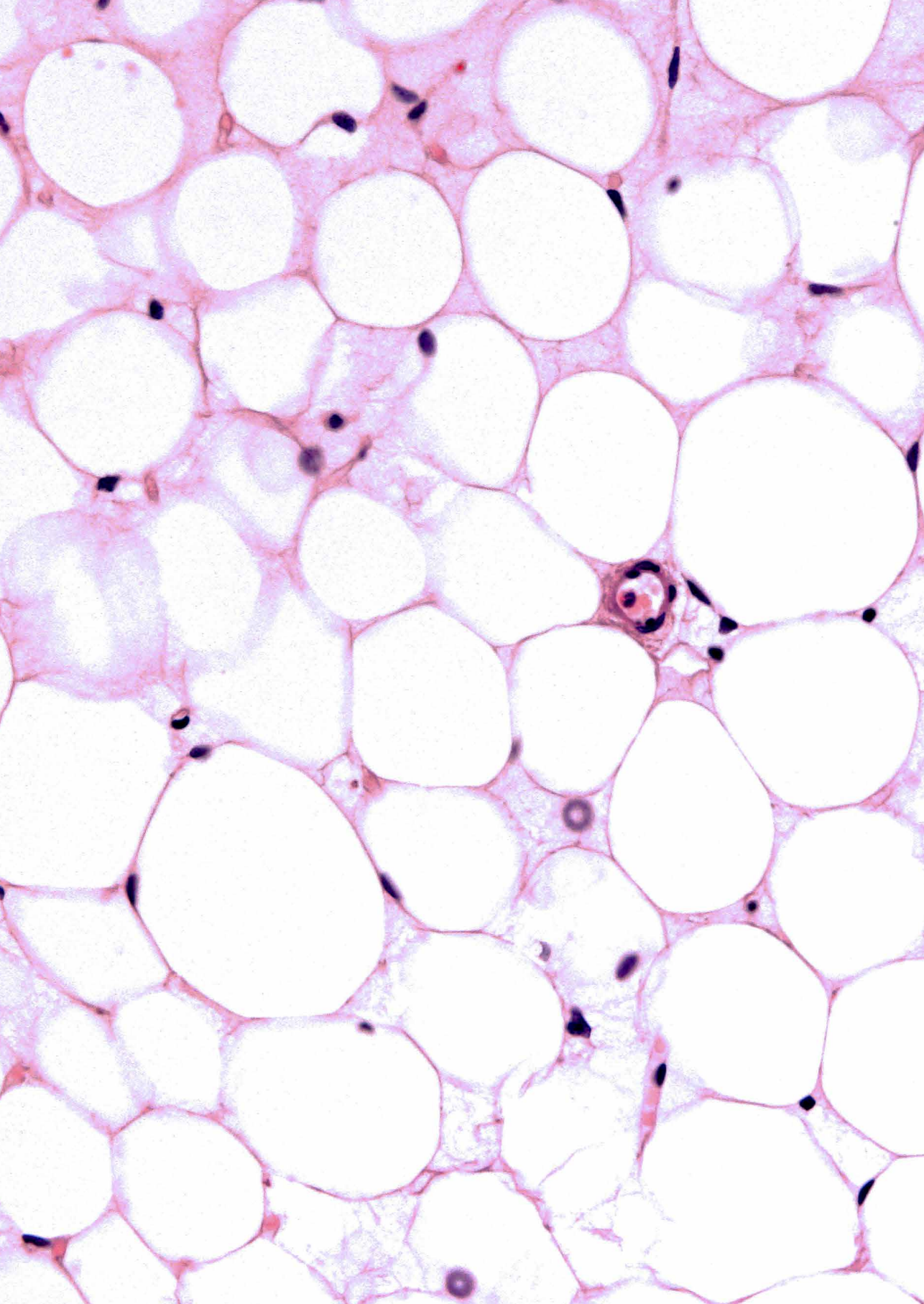
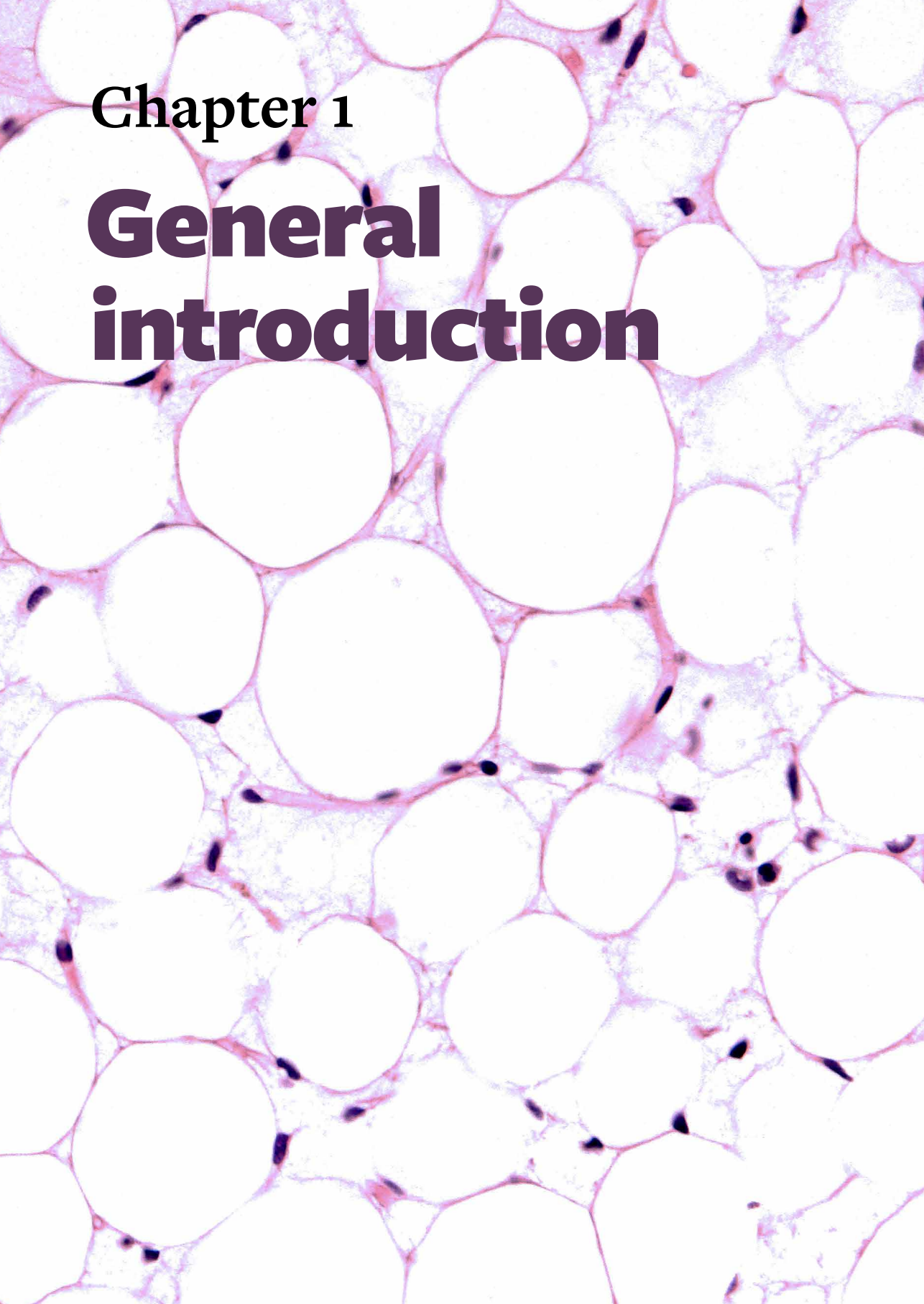
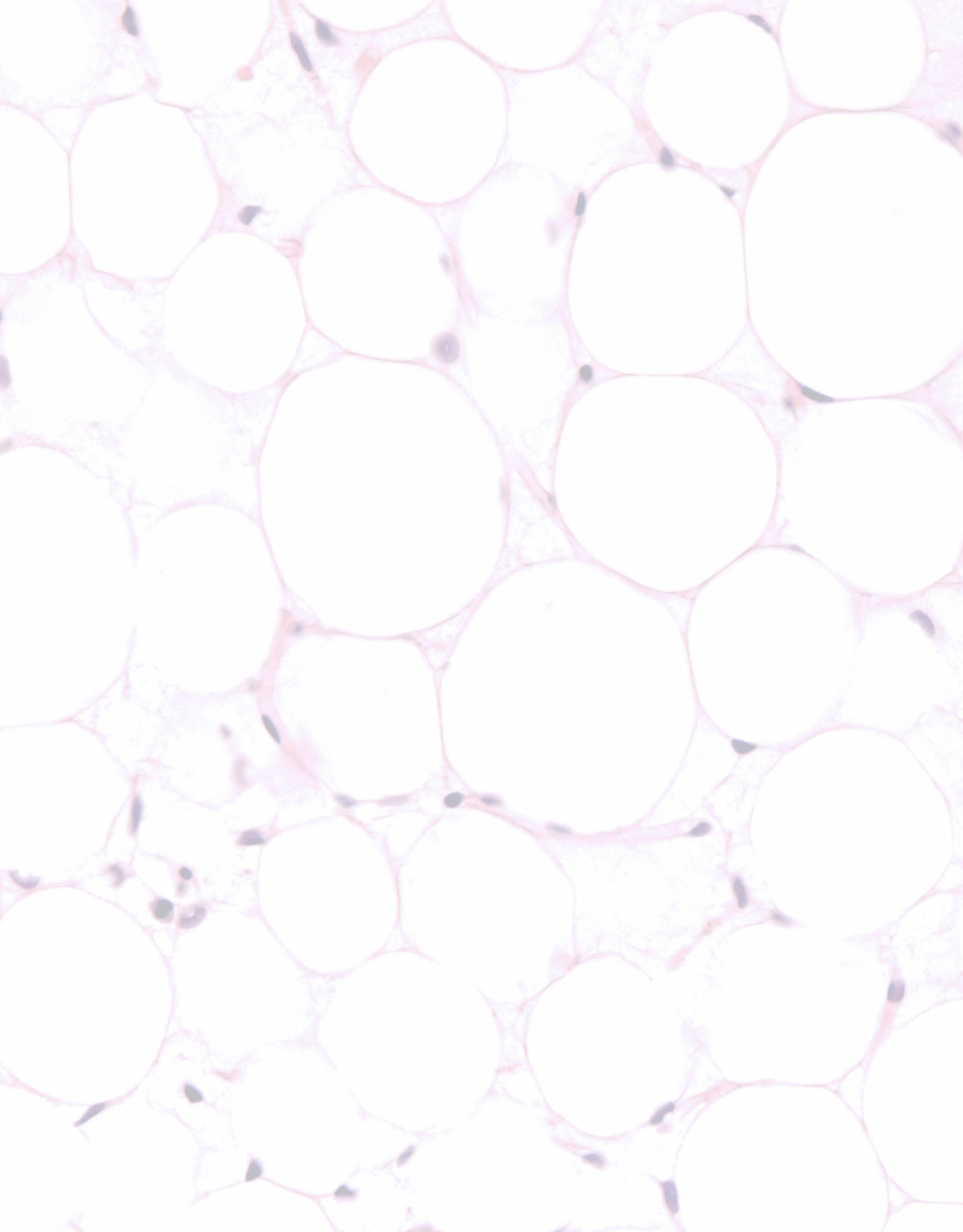




Chapter 1

General introduction



author: Stefanie R. van Mil

Obesity is both a significant and an increasing health care problem, the prevalence of which has nearly tripled since 1975. Level of obesity is graded using the body mass index (BMI), which is the ratio of body weight and squared body length. Normal weight is defined as a BMI between 18.5–25 kg/m^2. Once BMI exceeds 25 kg/m^2, a person is considered overweight. Obesity is defined as a BMI of 30 kg/m^2 or more, while morbid obesity is defined as a BMI exceeding 40 kg/m^2. In 2016, approximately 650 million people suffered from obesity worldwide, and this prevalence is still rising.[1]

Until very recently, obesity was not recognized as a disease, and within the general population, the deteriorating effects of obesity are still underestimated. Obesity's official recognition as a disease by the American Medical Association in 2013 raised awareness among physicians, increased access to treatment and spurred clinics worldwide to investigate the etiology, pathophysiology and treatment options for obesity.[2]

Interest in obesity as a disease is fueled by its association with myriad diseases, such as hypertension (HT), dyslipidemia, coronary artery disease, type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease, asthma, sleep apnea, musculoskeletal diseases, various forms of cancer and psychiatric diseases, all of which can result in reduced life expectancy.[2] The exact pathophysiology of obesity is poorly understood; many factors are proposed to exert an impact, such as the environment, genetics, the microbiome, hormones, peptides, central nervous system regulation, inflammation and adipose tissue (AT) biology.[3]

Due to the long list of obesity-associated diseases and their effects on life expectancy, scientists have been searching for the best treatment for obesity for decades. Unfortunately, lifestyle changes and medical treatment have not proven to be successful interventions in subjects suffering from morbid obesity. As early as the 1950s, interest in surgical procedures to accomplish weight loss existed; today, bariatric surgery is thought to be the only effective intervention to achieve both substantial and long-term weight loss and improvements in obesity-associated comorbidities.[3]

The first part of this thesis focuses on the effects of obesity on cardiovascular risk (CVR) factors, cardiovascular outcome measures and the role of AT and inflammation, while the second part focuses on bariatric surgery and the safety of such procedures.

Part I: Cardiovascular consequences of obesity

Cardiovascular disease and cardiovascular risk factors

Cardiovascular disease (CVD) is the leading cause of death in most countries,[4,5] although improved prevention strategies and treatment options have led to decreased CVD mortality over the past two decades. CVD comprises coronary heart disease, cerebrovascular disease, peripheral artery disease and both atherosclerotic and aneurysmatic aorta disease, in which coronary heart disease is the primary contributor to the number of cases with CVD.[6]

Smoking, dyslipidemia, HT, T2DM and obesity are the five leading modifiable risk factors responsible for more than half of CVD deaths.[7] Over 90% of CVD events occur in subjects with at least one major CVR factor.[8] The risk of a cardiovascular event increases with the presence of multiple risk factors. Additional modifiable risk factors, as described in the INTERHEART study in 2004, are psychosocial factors, consumption of fruits and vegetables, alcohol consumption and physical activity.[9]

Obesity and cardiovascular disease

Not only is obesity considered a major modifiable risk factor for CVD, it has also been associated with a higher prevalence of comorbidities, such as insulin resistance, T2DM, HT and dyslipidemia.[10,11] The prevalence of these so-called obesity-related diseases rises with increasing BMI,[10] and in addition, increases in BMI lead to higher all-cause mortality and cardiovascular mortality.[11,12] In fact, all-cause mortality rises by 30% when BMI increases by 5 kg/m^2.[11]

Ongoing debate exists regarding whether obesity is actually an independent risk factor for CVD. Different studies primarily attribute this effect of obesity to differences in classic CVR factors between non-obese and obese subjects rather than to obesity itself.[13,14] Even though these risk factors are known to be increased in obese subjects, the relationships of these risk factors with BMI in different levels of obesity are unclear; **Chapter 2** describes the relationships of these risk factors with BMI in both obese and non-obese subjects.

In non-obese subjects, women are relatively protected from CVD, particularly before menopause.[15] The prevalence of CVD in women approaches the prevalence in men in the seventh decade of life.[15,16] The mechanism behind this gender difference in CVD is still not fully understood;[17] **Chapter 3** investigates cardiovascular gender differences in morbidly obese subjects.

T2DM is known to cause micro- and macrovascular complications with significant morbidity and mortality rates.[18] It is also associated with atherosclerosis[19] and, as previously described, is a major modifiable risk factor for CVD; **Chapter 4** focuses on the effects of T2DM on CVD in morbidly obese subjects.

Atherosclerosis and inflammation in obesity

Atherosclerosis is the most common cause of CVD.[20] The process of atherosclerosis begins with the accumulation of foam cells in the intima, which leads to the formation of fatty streaks[21] and eventually atherosclerotic plaques.[22] Atherosclerosis is a multifactorial disease; endothelial dysfunction, inflammation, dyslipidemia and immunologic factors are contributors to its pathogenesis.

In recent decades, it has become evident that inflammation is critical in the development of atherosclerosis, which is therefore considered a low-grade chronic inflammatory disease.[23] Several inflammatory markers, such as C-reactive protein (CRP), leukocyte count and complement component 3 (C3), are associated with CVD.[24] Both the innate and adaptive immune systems are active in the various stages of atherogenesis,[20] from early binding of leukocytes to the vascular endothelium, increased transmigration of monocytes and foam cells into the intima

and degradation of collagen, making the plaque more vulnerable.[25,26] A crucial step in atherosclerosis is the activation of leukocytes in the circulatory system. After activation, different integrins are expressed on the leukocyte's cell surface. Expression of such integrins causes the enhanced adherence of leukocytes on the endothelium, after which they migrate into the arterial wall and form foam cells.[24]

Subjects with morbid obesity are also known to have increased levels of CRP[27,28] and C3,[29,30] and morbid obesity is therefore also considered a form of chronic low-grade systemic inflammation.[31] It is well established that AT secretes a great number of pro-inflammatory agents, which have been called adipokines.[32] In particular, AT secretes tumor necrosis factor a and interleukin 6, which are well known stimulators of CRP production in the liver.[33,34] The mechanism through which this cytokine production is initiated remains unclear;[35] however, cytokine-driven inflammation is thought to be critical in the pathophysiology of obesity-related diseases such as metabolic syndrome, CVD and T2DM.[32,35,36] The increased inflammation is thought to be the link between obesity and the increased risk of CVD in obese subjects; **Chapter 5** focuses on the differences in systemic inflammation in subjects with and without T2DM.

Part II: Treatment strategies for obesity

Weight loss strategies

Cardiovascular prevention strategies, as applied in the general population, are beneficial for subjects suffering from morbid obesity; however, weight loss itself is also known to prevent and improve many obesity-related diseases.[37] A loss of 5–10% of initial body weight can decrease blood pressure,[38,39] insulin resistance[40] and incidence of T2DM;[41,42] improve lipid profiles; reduce CRP levels;[43] and improve endothelial function.[44] Therefore, weight loss is considered one of the most important treatment modalities in subjects suffering from overweight and obesity.

Initial treatment of overweight and obesity comprises a comprehensive lifestyle intervention that includes dietary therapy, exercise and behavioral modification. However, the overall effects of these lifestyle interventions are small and often result in weight losses of only 5–7% of initial body weight and substantial weight regain over time.[45]

In subjects with BMI >30 kg/m² or BMI > 27 kg/m² and comorbidities who have not met weight loss goals with lifestyle interventions, drug therapy can be considered. Various agents are available, including orlistat, liraglutide and lorcaserin, that can induce weight reductions of 4–8%;[46] however, the role of drug therapy in obesity has been widely questioned due to concerns about efficacy, potential for abuse, side effects and cost. The effects of drug therapy on body weight slow and plateau over time, and most patients regain weight after discontinuation.

For many obese individuals, these behavioral and medical approaches to weight loss may be insufficient. Bariatric surgery is known to be the only effective intervention to achieve substantial and long-term weight loss with improvements of comorbidities.[47,48] According to international guidelines, subjects are eligible for bariatric surgery once their BMI surpasses 40 kg/m², or 35 kg/m² with one or more obesity-associated comorbidities.[49] More recently, international guideline committees suggested to offer bariatric surgery to subjects with BMI between 30.0–34.9 kg/m² and uncontrollable type 2 diabetes.[50]

Many procedures for accomplishing weight loss have been proposed, the most extensively investigated of which are the laparoscopic adjustable gastric banding, laparoscopic Roux-en-Y gastric bypass (LRYGB) and laparoscopic sleeve gastrectomy (LSG). However, the laparoscopic adjustable gastric banding has been gradually replaced by other bariatric procedures due to its modest amount of expected weight loss, high rate of revisional surgery and weight regain after removal of the band.[51] The LRYGB is considered the gold standard procedure in adults, although the LSG has gained widespread popularity due to its good results in terms of weight loss, the resolution of comorbidities, quality of life and low complication rates.[52–54] In recent years, the LSG has become the most commonly performed bariatric procedure.[55]

Obesity and bariatric surgery in children and adolescents

The prevalence and severity of obesity continues to rise. Unfortunately, this is true not only for adults but for children and adolescents as well.[52,56] In the United States, approximately 17% of all children suffer from obesity, and both the prevalence and severity increase with advancing age.[57] Childhood obesity is associated with health hazards during childhood as well as later in life, independent of adult BMI.[52,58,59] Early treatment is thought to be crucial; therefore, morbidly obese adolescents are increasingly being considered for bariatric surgery. Controversy exists regarding the ethics of bariatric surgery in adolescents; questions remain regarding the long-term safety and effectiveness of these procedures in adolescents. The LSG may be a safer alternative to the LRYGB in adolescents, because the procedure keeps the gastrointestinal tract intact, which results in the absence of dumping, less malnutrition and fewer vitamin disturbances.[60,61] This may be critical, since adolescents are known to have a low compliance to follow-up.[62] In the search for the best surgical options for morbidly obese adolescents, **Chapter 6** describes the results of both the LSG and LRYGB in young adults.

Efficacy and safety in bariatric surgery

With the increasing prevalence of obesity and obesity-related diseases, obesity-related healthcare costs have become a considerable economic burden.[63] Not only is bariatric surgery the best treatment in terms of weight loss, with substantial long-term results, it is also thought to be more cost-effective than the lifelong treatment of obesity-related diseases.[64] The number of bariatric procedures performed has therefore been rising in recent years, with over 600,000 bariatric procedures performed worldwide in 2014.[65] To improve the success rates and cost-effectiveness of these procedures, it is important to be aware of the adverse effects and complications associated with bariatric surgery and to continue to search for methods to improve its safety, efficiency and cost-effectiveness. For example, one requirement for both the bariatric surgeon and the bariatric clinic is to perform a minimum number of procedures annually (over 100 per clinic) to reduce morbidity and mortality.[66,67] Furthermore, medical industries are continuously searching for improvements in existing medical devices and developing new products to improve safety and efficiency.

In search of efficient and cost-effective healthcare, enhanced recovery after surgery (ERAS) protocols (or fast-track protocols) have been developed for different types of abdominal procedures.[68–70] Such protocols focus on the standardization of specific perioperative care based on the implementation of evidence-based interventions; **Chapter 7** describes an enhanced recovery after bariatric surgery (ERABS) protocol, including the results of the implementation of such a protocol on procedural times, length of stay in hospital, and number of complications and reoperations.

Furthermore, pre- and intraoperative checklists, to estimate perioperative risks, are regularly used as a safety tool in standardized surgical treatment programs. It is known that the proper use of these checklists results in lower rates of postoperative complications.[71] While the use of these checklists is thought to be best practice, the use of postoperative checklists to structurally monitor signs of possible complications and subsequent early interventions is not standard care, and literature on this subjects is scarce. An in-house-developed postoperative checklist for bariatric surgery and its effects on complication management in bariatric surgery is described in **Chapter 8**.

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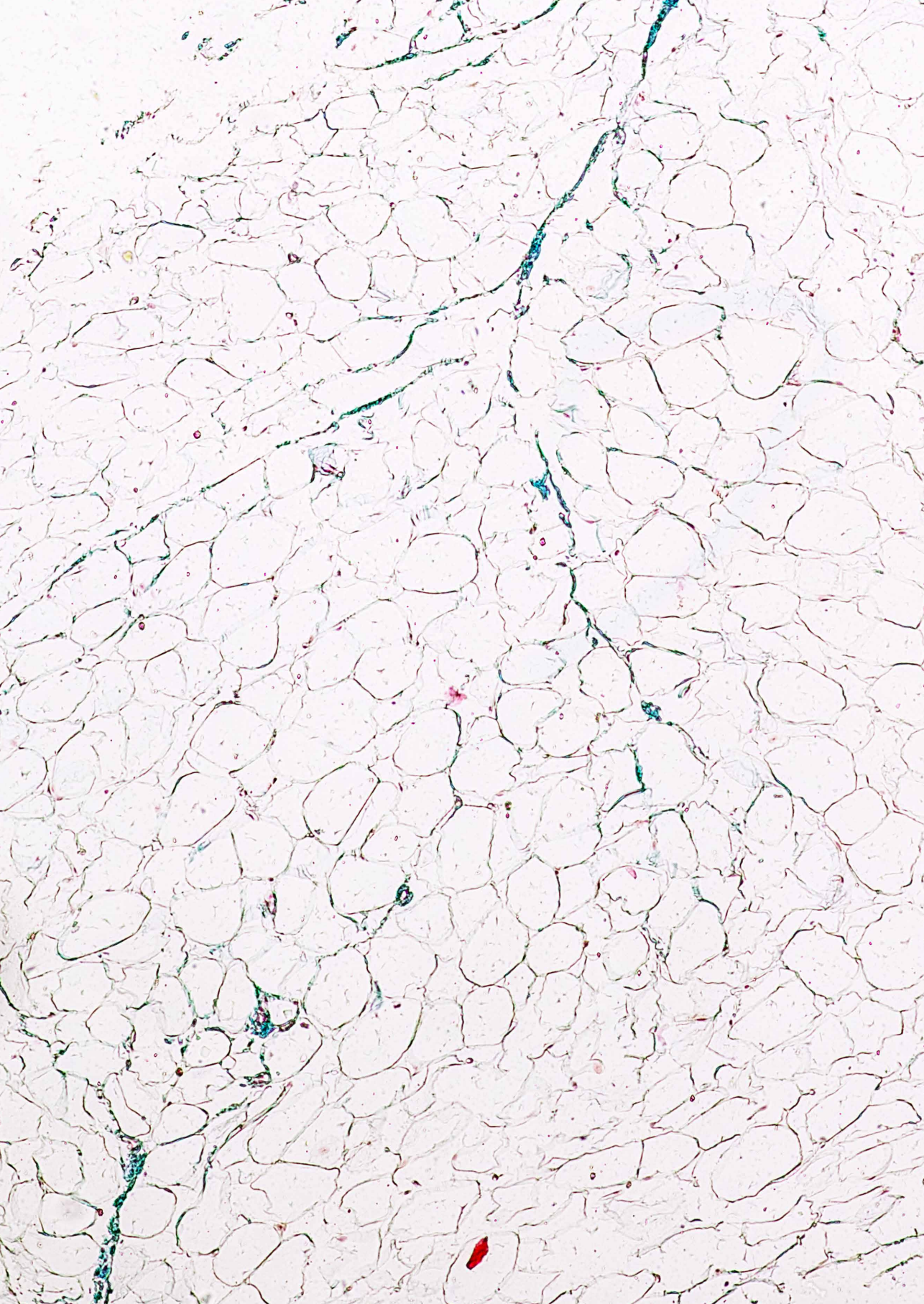
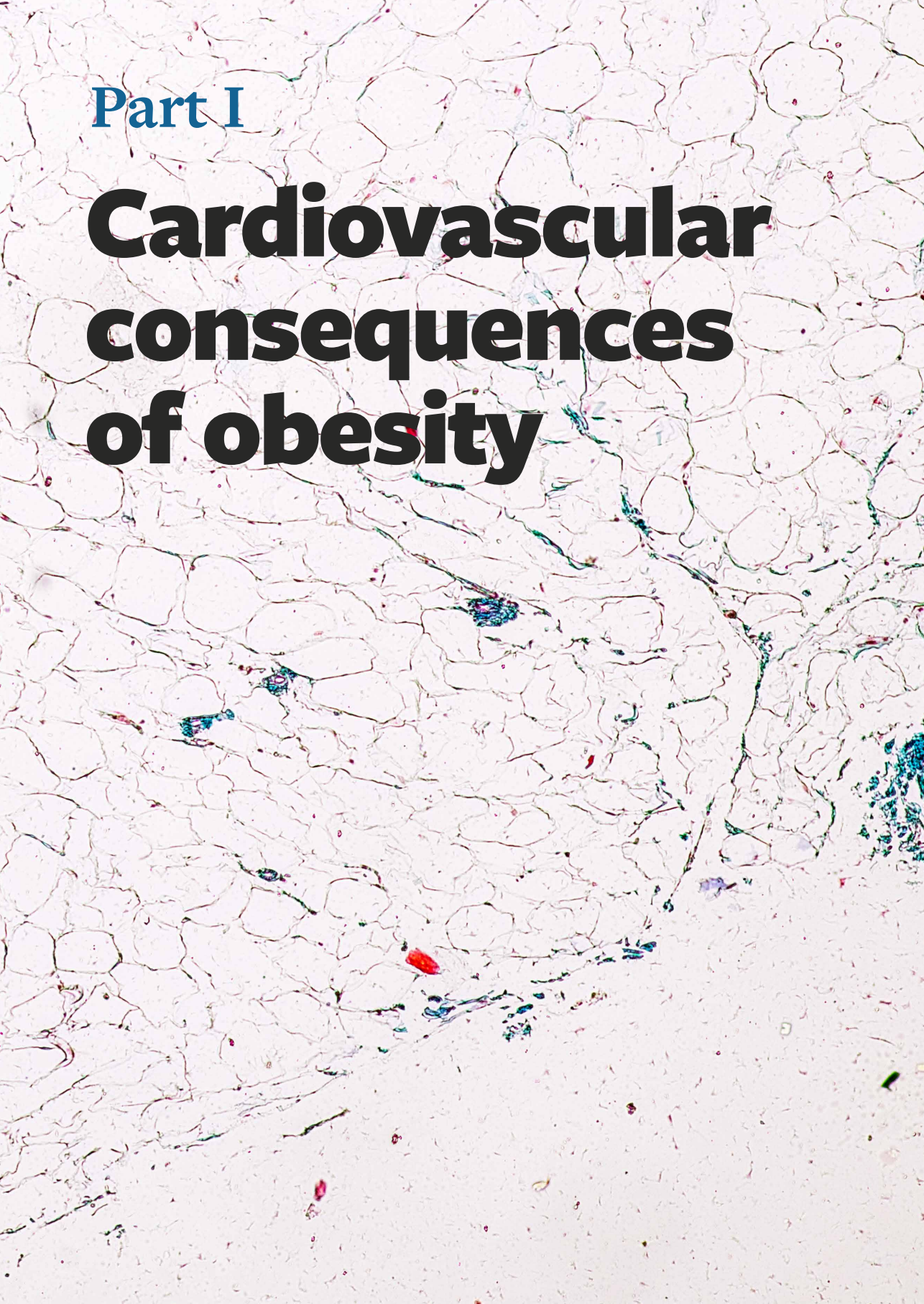
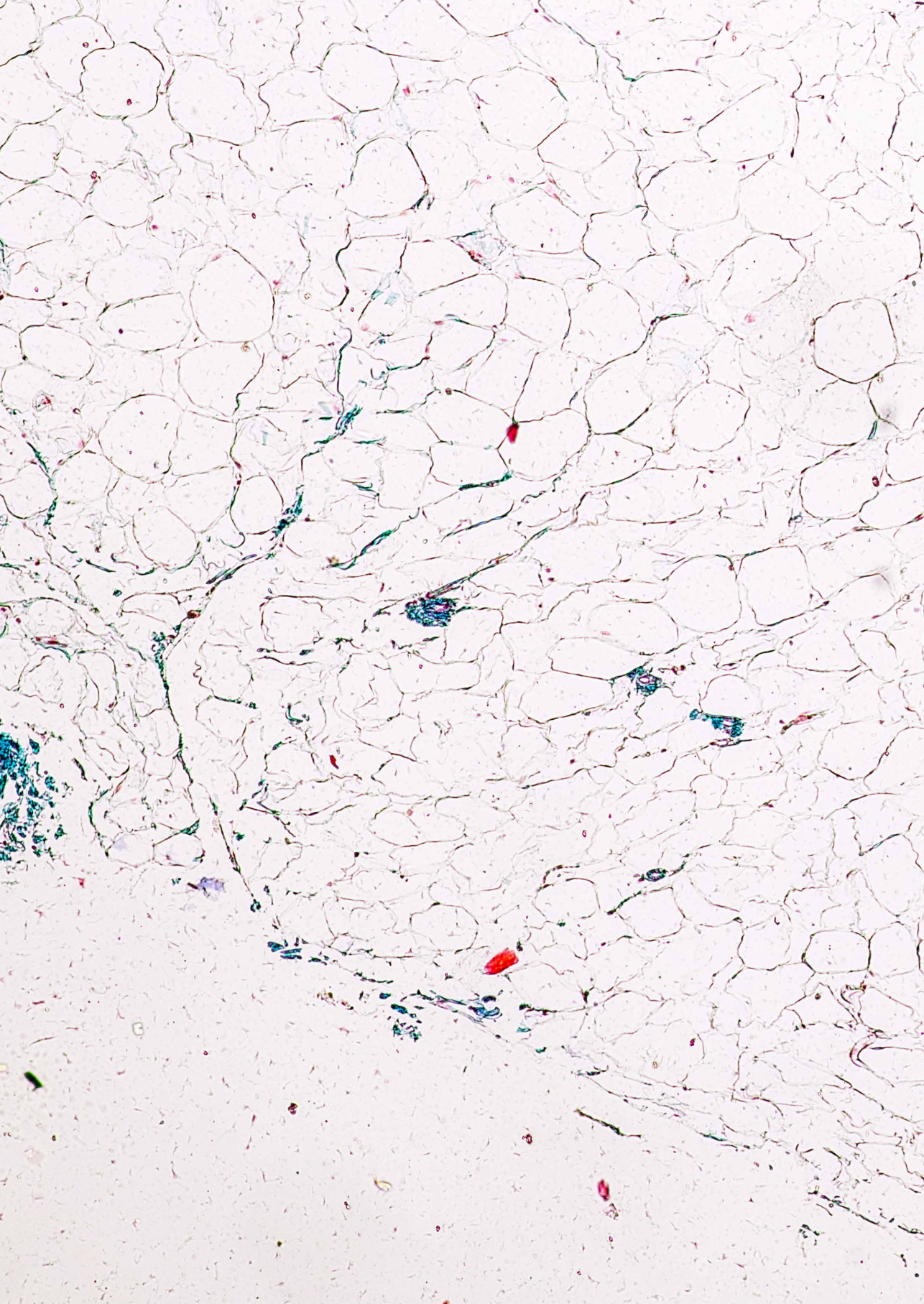


Part I

Cardiovascular consequences of obesity





Chapter 2

Discrepancies between BMI and classic cardiovascular risk factors

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Abstract

Background

Obesity is related to increased cardiovascular risk. It is unknown whether increasing levels of obesity also increase levels of cardiovascular risk factors and systemic inflammation. This study describes the relationship between classic cardiovascular risk factors and inflammatory markers with BMI in a group of obese and non-obese subjects.

Materials and methods

Obese subjects (BMI ≥ 30 kg/m²; n = 576; mean BMI = 43.8 [±7.58] kg/m²) scheduled for bariatric surgery were included. The reference population consisted of non-obese volunteers (BMI < 30 kg/m²; n = 377, mean BMI = 25.0 [±2.81] kg/m²). The relationship between BMI quintiles and the levels of cardiovascular risk factors was analyzed. Adipose tissue volumetry was performed in 42 obese subjects using abdominal CT-scans.

Results

The obese group included more women and subjects with type 2 diabetes mellitus, hypertension and current smokers. In obese subjects, HDL-C and triglycerides decreased with increasing BMI. Systolic and diastolic blood pressure, total cholesterol, LDL-C and apo-B were not related to BMI in the obese group, in contrast to the non-obese group. Inflammatory markers CRP, leukocyte count and serum complement C3 increased with increasing BMI in the obese group, while these relations were less clear in the non-obese group. The subcutaneous adipose tissue surface was positively correlated to BMI, while no correlation was observed between BMI and visceral adipose tissue.

Conclusions

Markers of inflammation are strongest related to BMI in obese subjects, most likely due to increased adipose tissue mass, while cardiovascular risk factors do not seem to deteriorate above a certain BMI level. Limited expansion capacity of visceral adipose tissue may explain these findings.

Introduction

Obesity has been associated to a higher prevalence of comorbidities, such as insulin resistance, type 2 diabetes mellitus (T2DM), hypertension (HT) and dyslipidemia.[1-2] The risk for these obesity-related comorbidities is elevated with increasing body mass index (BMI), at least up to a BMI of 40 kg/m².[1] Additionally, the excess body weight in obesity is known to increase all-cause mortality as well as cardiovascular mortality,[2-3] with the lowest mortality rates in subjects with a BMI between 20–25 kg/m².[2-4] An increase in BMI of 5 kg/m² can increase all-cause mortality with 30%, as well as mortality as a result of ischemic heart disease, stroke and T2DM.[2]

Although obesity may be an independent risk factor for cardiovascular disease (CVD), different studies attribute this effect of obesity mainly to differences in classic cardiovascular risk (CVR) factors between non-obese and obese subjects instead to obesity itself.[5-6] Classic CVR factors are widely used to estimate the risk of CVD or mortality and include systolic and diastolic blood pressure, glycated hemoglobin (HbA1c) and dyslipidemia[7] and the values of these classic CVR factors increase with increasing BMI. More recently, interest has increased in inflammation as a risk factor for CVD,[8] using C-reactive protein (CRP) and complement component 3 (C3) as markers of inflammation. Both CRP and C3 are associated with an increased risk of CVD[9-11] and increase with increasing BMI.[12-13]

In these studies, there has been an underrepresentation of morbidly obese subjects. Only a few studies investigated the relationships of BMI and markers of dyslipidemia in morbid obesity, and these studies suggest an “obesity paradox” in which LDL-C levels are actually lower in subjects with the highest BMI, when compared to moderately obese subjects,[14-15] but these studies only focused on markers of dyslipidemia and not on other CVR factors.

The purpose of this study was to investigate the relationship of BMI with classic CVR factors and markers of inflammation in obese and non-obese subjects covering a wide range of BMI.

Materials and methods

Design and study population

This was a cross-sectional study of obese and non-obese patients. This single center case-control study included all morbidly obese patients who underwent preoperative screening for bariatric surgery from September 2009 to April 2011 in our bariatric clinic. All patients visiting the clinic for preoperative screening were asked to participate without any restrictions. Approximately 90% of all evaluated patients underwent surgery, the other 10% did not continue in the program due to several reasons. Inclusion criteria for bariatric surgery were age between 18–60 years old, BMI ≥ 40 kg/m² or BMI ≥ 35 kg/m² with obesity-associated disease. The reference population consisted of non-obese subjects with a BMI < 30 kg/m² participating in observational studies in our outpatient clinic[16-17] from July 2009 to February 2013 and non-obese subjects referred to our clinic for CVR management. These observational studies aimed to evaluate novel CVR factors.

The cohort was divided in two groups according to BMI. The first group consisted of non-obese subjects (i.e. BMI < 30 kg/m²), hereafter referred to as "non-obese subjects." The second group consisted of obese and morbidly obese subjects (i.e. BMI ≥ 30 kg/m²), hereafter referred to as "obese subjects." Both subgroups were further divided into quintiles according to BMI.

Written informed consent was obtained from each individual and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. For this type of study, no approval of the institution's ethics committee was required.

Baseline characteristics

Baseline characteristics were collected according to a standard protocol in our clinic. Anthropometric measurements included weight, height, waist circumference and blood pressure. BMI (kg/m²) was calculated using both weight and height.

Laboratory tests

Standard non-fasting screening laboratory tests were performed. Total cholesterol, HDL-C and triglycerides (TG), as well as glucose and inflammatory marker CRP were analyzed using the LX20 or DxC analyzers (Beckman Coulter, Miami FL, USA). LDL-C values were calculated using the Friedewald formula. C3 and Apolipoprotein B (apo-B) were determined by rate nephelometry using IMAGE by commercially available kits (Beckman Coulter).

Adipose tissue depot analyses using abdominal CT-scans

Volumetry measurements, using abdominal CT-scans, were performed in order to analyze the relation between CVR factors and the volume of visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT). Within this cohort, 42 obese subjects underwent abdominal CT-scans within a period of two weeks after bariatric surgery for clinical reasons. An abdominal CT-scan is not part of the standard postoperative care in our department. The indication for these 42 abdominal CT-scans was a (suspected) complication.

Two investigators independently measured volumes of SAT and VAT in these scans. The CT-scans were exported as Digital Imaging and Communications in Medicine (DICOM) data and analyzed using an open source image analysis software package, OsiriX® (version 7.0, 32-bit). The methods of CT volumetric analyses using OsiriX® have been described previously.[18] Adipose tissue was identified by Hounsfield units (HU) with a range between –190 and –30 HU[19] and measured on a single slice at level L4–L5, since the amount of VAT at this level correlates best with total VAT volume.[19] The total amount of VAT was measured by selecting the abdominal cavity as "Region Of Interest." The total amount of SAT was calculated by subtracting the amount of VAT from the total amount of adipose tissue. The mean adipose tissue surface of both investigators was used in the analysis. Interobserver reliability was analyzed by computing the two-way mixed absolute agreement single-measures intraclass correlation coefficient (ICC). The interobserver reliability was 0.961 for VAT ($p < 0.001$) and 0.980 for SAT ($p < 0.001$).

Statistical analysis

All analyses were performed using SPSS (PASW) 18.0 software (SPSS Inc., Chicago, Illinois, USA). Continuous variables were presented as mean ± standard deviation (SD). Due to non-Gaussian distribution, both TG and CRP are described as median and minimum–maximum. Categorical data were described as an absolute number as well as a percentage of the total cohort. Differences between obese and non-obese subjects were analyzed using independent T-tests, chi-squared tests and Kruskall-Wallis tests. The relationship between BMI quintiles and metabolic and inflammatory parameters was analyzed using one-way ANOVA or the Kruskall-Wallis test in the case of non-Gaussian distribution.

Patients on statins were excluded from the analyses on the relation between BMI and total cholesterol, HDL-C, LDL-C, TG, C3, CRP and apo-B. Subjects on antihypertensive drugs were excluded from analyses on the relation between BMI and systolic and diastolic blood pressure. Subjects on glucose-lowering drugs were excluded from the analysis on the relation between BMI and glucose. Pearson's correlation coefficients were calculated in order to analyze the relationship of BMI with the different adipose tissue surfaces. Results were evaluated at a 95% confidence interval at a significance threshold of $p < 0.05$ (two-sided).

Results

The obese group consisted of 576 subjects (418 women and 158 men), with a mean age of 44.2 (±13.0) years and a mean BMI of 43.8 (±7.6) kg/m^2. The non-obese group consisted of 377 subjects (173 women and 204 men). The mean age was 58.7 (±13.0) years, and the mean BMI was 25.0 (±2.81) kg/m^2. Additional baseline characteristics of both groups are displayed in **Table 1**. The obese group included significantly more women than the non-obese group and was significantly younger. T2DM, HT and current smoking behavior were more prevalent in the obese group. The obese group had a significantly higher BMI and waist circumference, when compared to the non-obese subjects. Focusing on classic CVR factors, the mean systolic and diastolic blood pressure, LDL-C and glucose levels were significantly higher in the obese subjects then in non-obese subjects, while HDL-C was lower in the obese group.

Apo-B, C3 and CRP, which are thought to be related to CVR, were also elevated in the obese subjects. Only total cholesterol levels and triglyceride levels were not different between the groups (**Table 1**).

Table 1

Baseline characteristics of both obese and non-obese subjects in absolute numbers or mean value, with its percentage or SD, respectively, presented within brackets

	Non-obese (n=377)	Obese (n=576)	*p* -value
Sex (%)° female	173 (45.9%)	418 (72.6%)	*p* < 0.001
Age* (years)	58.7 (±13.0)	44.2 (±13.0)	*p* < 0.001
BMI* (kg/m2)	25.0 (±2.81)	43.8 (±7.58)	*p* < 0.001
Waist circumference* (cm)	93.5 (±10.6)	128.6 (±16.3)	*p* < 0.001
Medical history			
Type 2 diabetes°	41 (10.9%)	132 (22.9%)	*p* < 0.001
Hypertension°	107 (28.4%)	199 (34.5%)	*p* = 0.019
Dyslipidemia°	73 (19.4%)	96 (16.7%)	*p* = 0.436
Current smoking			*p* = 0.031
Yes°	70 (18.6%)	286 (24.3%)	
No°	306 (81.2%)	284 (74.7%)	
Systolic blood pressure* (mmHg)	125 (±14.3)	138 (±16.0)	*p* <0.001
Diastolic blood pressure* (mmHg)	76 (±9.6)	84 (±10.2)	*p* <0.001
Total cholesterol* (mmol/l)	5.26 (±1.28)	5.23 (±0.99)	*p* =0.745
HDL-cholesterol* (mmol/l)	1.49 (±0.45)	1.20 (±0.30)	*p* <0.001
LDL-cholesterol* (mmol/l)	3.18 (±1.11)	3.41 (±0.96)	*p* =0.008
Triglycerides† (mmol/l)	1.16 (0.3-9.7)	1.18 (0.3-9.5)	*p* =0.296
ApoB* (g/l)	0.97 (±0.305)	1.08 (±0.264)	*p* <0.001
CRP† (nmol/l)	19 (9.5-1542)	67 (9.5-486)	*p* <0.001
Complement C3* (mg/l)	1.07 (±0.226)	1.65 (±0.275)	*p* <0.001
Leukocytes* (10^9/l)	6.6 (±1.78)	8.5 (±2.32)	*p* <0.001
Glucose* (mmol/l)	5.7 (±1.59)	6.5 (±1.69)	*p* <0.001

° group differences were tested using χ^2

* group differences were tested using independent T-tests

† described as median (minimum-maximum) and analyzed using the Kruskal-Wallis test

In both the obese and non-obese group, no clear relation was observed between the level of BMI and the level of systolic blood pressure. In contrast, diastolic blood pressure increased with increasing BMI in the non-obese group, but no relation was observed between the level of diastolic blood pressure and BMI in the obese group.

A similar trend was observed in the level of LDL-C and apo-B in relation to BMI in both groups. HDL-C decreased with increasing BMI in both groups, although the decrease in the obese group stabilizes from the second quintile and up. The significant decrease can be solely explained by a relatively high HDL-C level in the first BMI quintile of the obese group. In contrast to all other classic CVR factor,

Table 2

Mean value (±SD) of cardiovascular risk factors and inflammatory markers in the different quintiles based on BMI of the obese group

	1st quintile BMI 33.8 (±2.39)	2nd quintile BMI 39.9 (±1.04)	3rd quintile BMI 43.0 (±0.93)	4th quintile BMI 47.1 (±1.49)	5th quintile BMI 54.9 (±5.26)	p-value*
Age (years)	56.4 (±9.8) n=115	43.5 (±11.3) n=115	40.6 (±10.3) n=116	38.8 (±11.5) n=115	41.6 (±11.6) n=115	$p < 0.001$
Sex (female)	59 (51.3%)	84 (73.0%)	92 (79.3%)	94 (81.7%)	89 (77.4%)	$p < 0.001$
Systolic blood pressure (mmHg)	132 (±14.3) n=33	137 (±14.9) n=62	139 (±16.3) n=73	139 (±15.4) n=76	142 (±18.2) n=54	$p = 0.096$
Diastolic blood pressure (mmHg)	82 (±9.5) n=33	84 (±9.6) n=62	84 (±9.3) n=73	85 (±11.3) n=76	85 (±10.8) n=54	$p = 0.581$
Total cholesterol (mmol/l)	5.4 (±1.1) n=58	5.4 (±1.1) n=81	5.1 (±1.0) n=98	5.2 (±0.9) n=92	5.1 (±1.0) n=94	$p = 0.063$
HDL-cholesterol (mmol/l)	1.33 (±0.37) n=58	1.22 (±0.27) n=81	1.17 (±0.27) n=98	1.15 (±0.29) n=92	1.19 (±0.30) n=94	$p = 0.005$
LDL-cholesterol (mmol/l)	3.4 (±1.0) n=56	3.6 (±1.0) n=79	3.3 (±0.9) n=95	3.5 (±1.0) n=91	3.3 (±0.9) n=92	$p = 0.422$
Triglycerides† (mmol/l)	1.52 (0.5-9.5) n=58	1.18 (0.3-5.3) n=81	1.14 (0.3-4.9) n=98	1.14 (0.3-8.1) n=92	1.10 (0.4-4.4) n=93	$p = 0.009$
ApoB (g/l)	1.06 (±0.276) n=57	1.11 (±0.287) n=81	1.07 (±0.267) n=98	1.09 (± 0.257) n=92	1.04 (±0.238) n=94	$p = 0.420$
CRP† (nmol/l)	33 (9.5-429) n=48	57 (9.5-238) n=64	76 (9.5-486) n=83	86 (9.5-286) n=64	100 (9.5-476) n=70	$p < 0.001$
Complement C3 (mg/l)	1.43 (±0.259) n=57	1.61 (±0.244) n=81	1.66 (±0.229) n=98	1.67 (±0.257) n=92	1.81 (±0.276) n=93	$p < 0.001$
Leukocytes (10^9/l)	7.5 (±2.45) n=111	8.5 (±2.14) n=111	8.7 (±2.27) n=115	8.7 (±2.04) n=112	9.3 (±2.34) n=114	$p < 0.001$
Glucose (mmol/l)	6.4 (±1.58) n=76	6.8 (±2.15) n=81	6.6 (±2.14) n=98	6.2 (±0.94) n=86	6.3 (±1.21) n=83	$p = 0.165$

* group differences were tested using one way ANOVA

† described as mean (minimum-maximum) and analyzed using the Kruskal-Wallis test

the triglyceride level showed a gradual increase with increasing BMI in the non-obese group, but a gradual decrease in the obese group (**Tables 2 and 3**).

Inflammatory markers, which are also related to CVR, followed a different pattern with BMI in both groups. Both CRP and leukocyte count were not related to BMI in the non-obese group. However, both parameters showed a clear relationship with BMI in the obese group. Complement C3 was the only parameter with a positive relationship with BMI in both the obese and non-obese group (**Tables 2 and 3**).

Table 3

Mean value (±SD) of cardiovascular risk factors and inflammatory markers in the different quintiles based on BMI of the non-obese group

	1st quintile BMI 20.8 (±1.45)	2nd quintile BMI 23.6 (±0.67)	3rd quintile BMI 25.3 (±0.34)	4th quintile BMI 26.6 (±0.54)	5th quintile BMI 28.8 (±0.69)	*p* -value*
Age (years)	53.8 (±15.1) n=75	60.4 (±12.7) n=77	59.6 (±12.1) n=74	58.0 (±13.7) n=76	61.5 (±9.8) n=75	*p* = 0.003
Sex (female)	47 (62.7%)	43 (55.8%)	26 (35.1%)	36 (47.4%)	21 (28.0%)	*p* < 0.001
Systolic blood pressure (mmHg)	124 (±13.9) n=52	125 (±14.4) n=40	126 (±15.4) n=24	122 (±13.6) n=33	132 (±13.8) n=23	*p* = 0.118
Diastolic blood pressure (mmHg)	73 (±8.5) n=52	74 (±10.1) n=40	81 (±9.9) n=24	76 (±9.0) n=33	80 (±8.8) n=23	*p* = 0.002
Total cholesterol (mmol/l)	4.9 (±1.4) n=58	5.2 (±1.4) n=46	5.6 (±1.1) n=34	5.5 (±1.0) n=46	5.4 (±1.3) n=24	*p* = 0.144
HDL-cholesterol (mmol/l)	1.62 (±0.46) n=58	1.53 (±0.45) n=46	1.50 (±0.38) n=34	1.36 (±0.44) n=46	1.32 (±0.46) n=24	*p* = 0.013
LDL-cholesterol (mmol/l)	2.8 (±1.2) n=58	3.1 (±1.2) n=46	3.5 (±1.0) n=34	3.4 (± 0.9) n=44	3.4 (±1.2) n=23	*p* = 0.034
Triglycerides† (mmol/l)	0.97 (0.3-3.4) n=58	1.05 (0.4-2.8) n=46	1.13 (0.6-3.2) n=34	1.37 (0.4-9.7) n=46	1.28 (0.6-4.8) n=24	*p* = 0.001
ApoB (g/l)	0.86 (±0.285) n=58	0.95 (±0.354) n=46	1.03 (±0.246) n=34	1.06 (±0.260) n=46	1.05 (±0.339) n=24	*p* = 0.005
CRP† (mg/l)	9.5 (9.5-295) n=56	14 (9.5-619) n=44	19 (9.5-105) n=32	19 (9.5-200) n=44	29 (9.5-1543) n=24	*p* = 0.069
Complement C3 (mg/l)	0.96 (±0.189) n=58	1.07 (±0.229) n=46	1.11 (±0.228) n=34	1.14 (±0.225) n=46	1.18 (±0.203) n=24	*p* < 0.001
Leukocytes (10^9/l)	6.5 (±1.89) n=75	6.6 (±1.99) n=77	6.4 (±1.81) n=74	6.5 (±1.37) n=76	7.1 (±1.72) n=75	*p* = 0.142
Glucose (mmol/l)	5.5 (±1.53) n=75	5.7 (±1.67) n=72	5.8 (±1.83) n=68	5.5 (±1.14) n=71	6.2 (±1.64) n=64	*p* = 0.082

* group differences were tested using one way ANOVA

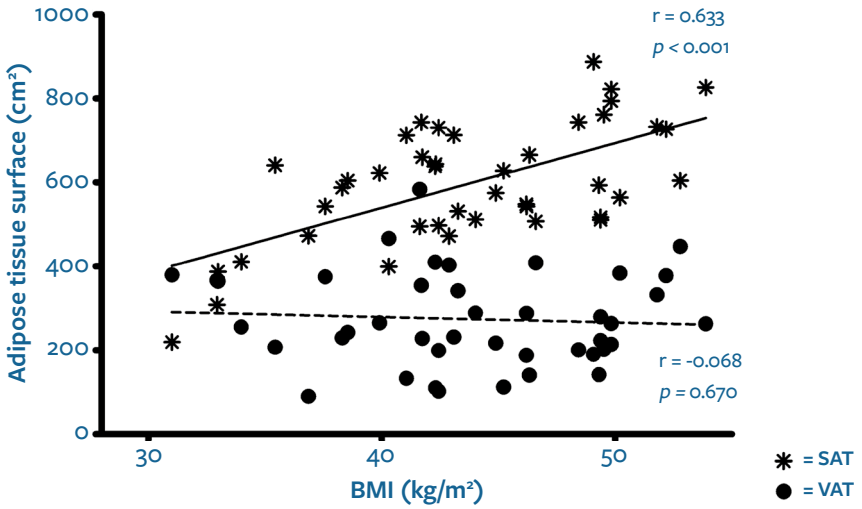
† described as mean (minimum-maximum) and analyzed using the Kruskal-Wallis test

Adipose tissue in subcutaneous and visceral depots by CT-scans

Forty-two abdominal CT-scans of obese patients were performed in the perioperative period for bariatric surgery. No significant differences in baseline characteristics were seen between obese subjects who did or did not undergo an abdominal CT-scan. A positive correlation of BMI with SAT surface was found ($r = 0.633$, $p < 0.001$), while no significant correlation of BMI with VAT surface was observed ($r = -0.068$, $p = 0.670$; **Figure 1**). There were no significant correlations between the surface areas of VAT and SAT on the one hand, and the classic CVR factors or inflammatory markers on the other.

Figure 1

Correlation of BMI and adipose tissue surfaces in obese subjects (n=42)



Discussion

Although diastolic and systolic blood pressure and the levels of LDL-C, glucose and apo-B were significantly increased in our obese subjects, the level of BMI in this group did not seem to influence the level of CVR factors. Therefore, derangement of CVR factors overall appears to reach a plateau at a certain level of obesity. A clear explanation for these observations is lacking.

One explanation for this finding may be the different metabolic effects of VAT and SAT. Central adiposity is strongly associated with metabolic disturbances, such as insulin resistance, dyslipidemia and systemic inflammation, which play essential roles in the pathogenesis of CVD.[20,21] Furthermore, it is also associated with both cardiovascular mortality, cancer mortality and overall mortality.[20] More specifically, fat distribution may play an important role in the risk of metabolic disease and CVD,[22] in which VAT is most strongly related to measures of metabolic disease.[21] The present study suggests that VAT appears to have limited potential for expansion. Therefore, it can be hypothesized that after saturation of the VAT depot, further increases in obesity (i.e. BMI) result in fat storage in other depots, such as SAT. As a result, the detrimental effects of VAT will not increase with increasing BMI in morbid and superobese subjects, as suggested by the present data.

Expansion of SAT at the expense of VAT may protect obese subjects from further deterioration of their CVR factors. The adipose tissue expandability model states that adipose tissue in general has a maximum potential for expansion in a given individual.[23] Once this degree of maximal expansion is reached the adipose tissue is no longer able to safely store excess energy and the lipid flux to non-adipose organs will increase, resulting in ectopic fat accumulation. Storage of lipids in ectopic sites, such as hepatocytes or beta cells, can eventually result in metabolic disturbances as seen in obese patients.[24,25] However, none of these studies evaluated the expansion capacity of VAT and SAT in the course of increasing obesity in humans. It should be noted that a limitation of the present study is the small number of abdominal CT-scans in the obese group. Furthermore, due to the lack of abdominal CT-scans in the non-obese group, our data concerning the different

adipose tissue depots only apply to obese subjects. Future studies investigating this issue should include measurements of adipose tissue depots.

In contrast to the previously mentioned CVR factors, inflammatory markers showed a clear relationship with the level of obesity in the obese group, while CRP and leukocyte count did not show an association with BMI in the non-obese group. Adipose tissue is known to secrete several adipokines that in part may cause increases in CRP as suggested by the relationship found in obese subjects between BMI and CRP. We did not use a highly sensitive CRP assay, which may in part explain the lack of association in the non-obese subjects. However, the inflammatory marker C3 did increase with increasing BMI in both the non-obese and obese group, and C3 levels have been shown to be associated with CRP levels.[26] Although systemic inflammation is positively related to BMI, classical CVR factors seem to reach a maximal level at BMI 35–40 kg/m^2. Increased CVR in subjects with BMI > 40 kg/m^2 may depend more on systemic inflammation and less so on classic CVR factors.

One unexpected finding of this study was the paradoxical decrease in TG with increasing BMI in our obese subjects, causing a peak level of TG within the group of subjects with a BMI between 26–35 kg/m^2. A limitation in our measurement of TG is that fasting venipuncture was not a requirement within our cohort; we were unable to distinguish between fasting and non-fasting subjects. However, the latest guidelines on lipid measurements questions the need for fasting measurements since normal food intake does not largely affect lipids levels and the intra-individual variability in TG remains comparable throughout the day.[27,28] Additionally, it is unlikely that non-fasting TG levels were mainly measured in subjects with a BMI between 26–35 kg/m^2. Therefore, we assume that the combination of fasting and non-fasting TG levels cannot explain the paradoxical trend in TG levels in the obese group. Porter et al.[29] previously noticed an increase of TG levels with increasing visceral fat volume. However, in the group with the highest visceral fat volumes, TG levels decreased with increasing subcutaneous fat volumes,[29] which is in line with our findings. They suggested that SAT may have beneficial effects on triglyceride metabolism in those subjects with large VAT volumes. Unfortunately, the molecular mechanism behind these findings has not been determined yet.

Even though excess body weight is known to increase all-cause mortality and cardiovascular mortality, previous studies only included subjects with a BMI up to 35 kg/m^2.[5,20,22] However, 1.5–6% of all adults in developed countries are known to be morbidly obese,[30] with a BMI > 40 kg/m^2 and this prevalence is still rising. Much interest exists on the treatment of these morbidly obese subjects, in order to achieve significant weight loss and resolution of obesity-related comorbidity and thereby, prevention of preterm mortality. The Prospective Studies Collaboration has demonstrated that overall mortality, as well as cardiovascular mortality, increases with increasing BMI, at least up to a BMI of 50 kg/m^2.[2] Furthermore, overweight and obesity are associated with an early onset of CVD, not only resulting in higher mortality, but also in a greater portion of life lived with CVD morbidity.[31] These findings should urge clinicians to intensify CVR management in obese subjects. The current CVR management should not be simply assumed to be suitable for morbidly obese patients. Previous studies reveal that HT in obese patients is of a different phenotype than HT in the lean population. In addition, not all antihypertensive drugs appear to be equally effective in obesity-related HT as in HT in lean patients.[32,33] Furthermore, current guidelines for the treatment of dyslipidemia may not be suitable in obesity. Obese subjects are thought to require more intensive treatment for dyslipidemia with higher doses of lipid-lowering drugs.[34] Nevertheless, our data suggest that classic CVR factors do not further deteriorate with increasing BMI, from a BMI of approximately 35 kg/m^2 and higher. This suggests that the increased cardiovascular mortality in obesity is not caused by deterioration of classic CVR factors, but that obesity is an independent CVR factor itself. The increased cardiovascular mortality in obese patients[2,35] may be influenced by other factors, such as systemic inflammation or non-atherosclerotic heart disease. Future studies should distinguish between different cardiovascular mortality causes in morbidly obese subjects, such as atherosclerotic heart disease, hypertensive heart disease, cardiomyopathies or heart failure.[36]

The distinct difference in baseline characteristics between the non-obese and obese groups in this study is a major limitation, even though the results were adjusted for comorbidity. When interpreting our results, we should keep in mind that patients on antihypertensive or lipid-lowering drugs were excluded from the

analysis when the drug would interfere with the CVR factor under investigation. Therefore, the relationships may not be applicable in subjects who already receive treatment for CVR reduction. These excluded subjects could elevate the level of the specific risk factor if they were added to the analysis after cessation of their therapy. However, we do not have these data and felt that the use of antihypertensive and lipid-lowering drugs would disturb the natural relationship between BMI and the risk factors. Therefore, these confounding factors were excluded with the realization that the data may be biased. Regardless of this limitation, the results of this study provide new insights in CVR in a population of high interest, since obesity and morbid obesity is reaching epidemic proportions[37] with substantial economic burden, not only in terms of medical costs, but also in terms of non-medical costs (e.g. absenteeism and personal costs).[38] Our future perspective is to analyze CVR factors in relation to BMI in a larger population in which we are able to match on age and gender and correct for confounding factors. The level of obesity should become a part of the currently available CVR calculators.

In conclusion, obesity is related to an increased risk on metabolic disease and CVD and mortality, but this increased risk may not be solely explained by deterioration of classic CVR factors. The lack of correlation of CVR factors and BMI in obese subjects may be explained by the expansion of SAT with increasing BMI after saturation of the VAT compartment. In order to reduce the risk of CVD and mortality in obese subjects, treatment may need to focus on reduction of systemic inflammation and on non-atherosclerotic heart diseases.

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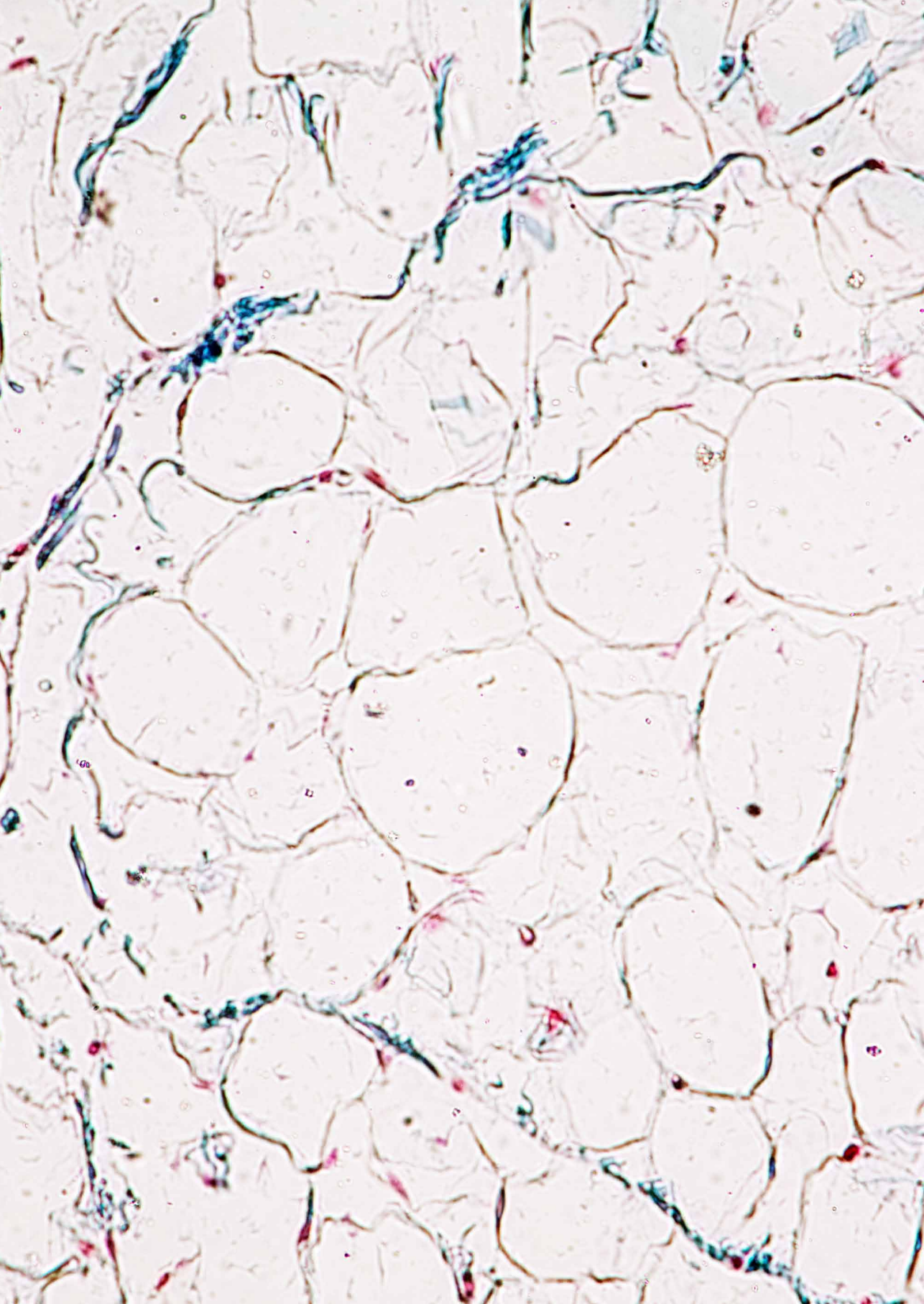

Chapter 3

The effect of sex and menopause on carotid intima media thickness and pulse wave velocity in morbid obesity

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Abstract

Background

Women are relatively protected from cardiovascular disease compared to men. Whether this is also the case in high-risk patients like the morbidly obese is not known. The current study investigated whether the association between sex and cardiovascular risk factors and outcomes can be demonstrated in subjects suffering from morbid obesity.

Materials and methods

Two hundred subjects enrolled in a study evaluating cardiovascular risk factors in morbid obesity underwent extensive laboratory screening. Structural vascular changes were determined by carotid intima media thickness (cIMT) and pulse wave velocity (PWV) measurements reflected functional changes. Gender differences were analyzed using univariate and multivariable linear regression models. Results of these models were reported as B coefficients with 95% confidence intervals.

Results

The group consisted of 52 men and 148 women, with a mean age of 41 (±11.8) years and a mean body mass index (BMI) of 42.7 (±5.2) kg/m^2. Both cIMT and PWV were significantly higher in men than in women. The most important determinants for cIMT differences were waist circumference, age, high-density lipoprotein cholesterol and mean arterial pressure. The gender differences for PWV remained after adjustments for these covariables.

Conclusions

Morbid obesity is associated to sex-specific differences in vascular function. However, differences in structural vascular changes seem to depend on classic cardiovascular risk factors rather than being sex dependent.

Introduction

Even though cardiovascular disease (CVD) is one of the major causes of death in both men and women at all ages, the prevalence in women is relatively low before menopause.[1] This prevalence approaches similar rates for men and women in their seventh decade of life. Women are relatively protected against CVD and require a heavier risk factor load before developing CVD.[2] The exact mechanism behind this remarkable sex differences in CVD is still not fully understood.[3]

Focusing on classic cardiovascular risk (CVR) factors, hypertension and smoking are more prevalent in men than in women.[1] Women have lower total cholesterol levels[4] and higher high-density lipoprotein cholesterol (HDL-C) values[1] than men. These sex differences in cardiovascular risk factors diminish after menopause.[1,2,4]

When studying outcome measures for subclinical atherosclerosis, such as common carotid intima media thickness (cIMT) measurements or pulse wave velocity (PWV), previous studies showed that both cIMT[5–8] and PWV[9,10] are higher in men than in women. These sex differences also decrease after menopause.[3,5]

Obese subjects have increased levels of classic CVR factors[11–13] and higher cIMT and PWV values[14–16] and both overall and cardiovascular mortality is higher in obese subjects.[17,18] Sex differences in cardiovascular mortality persist in different levels of overweight and obesity, although the differences may attenuate in obese individuals.[19] It is unclear whether these sex differences persist in morbidly obese subjects. The purpose of this study was to investigate sex differences in CVR factors in morbid obese subjects and to investigate differences in structural and functional outcome measures in terms of cIMT and PWV.

Materials and methods

Study population

This is a report from the ASSISI study. This prospective cohort study aims to investigate the effects of bariatric surgery on CVR factors in morbid obesity and comprises 200 patients, included in the study between April 2015 and April 2016. All subjects met the international criteria for bariatric surgery[20] (i.e. BMI ≥ 40 kg/m² or BMI ≥ 35 kg/m² and obesity-related comorbidity, aged 18–65 years). This obesity-related comorbidity includes hypertension, type 2 diabetes, dyslipidemia, respiratory disease, severe joint disease and severe obesity-related psychological problems. Subjects with a previous cholecystectomy, a previous bariatric procedure, an acute inflammatory disease within 6 weeks prior to inclusion or immune-modulating medication were excluded. All data presented here are baseline data, which were collected at study entry.

The study was approved by the independent Regional Medical Ethical Committee Rotterdam (Maasstad Hospital, Rotterdam, the Netherlands, ABR no. NL47891.101.14) and all subjects gave written informed consent. The ASSISI study is registered in the Dutch Trial Register (NTR5172). Reporting of the study conforms to STROBE statement.[21]

Definition of menopause, type 2 diabetes, hypertension and hypercholesterolemia

Female subjects were considered postmenopausal based on a history of secondary amenorrhea of ≥ 1 year.[22] Women who had previously undergone hysterectomy were excluded from the analysis in pre- and postmenopausal women.

Type 2 diabetes mellitus (T2DM) was defined as a glycated hemoglobin (HbA1c) level ≥ 48 mmol/mol (6.5%)[23] and/or the use of glucose-lowering medication. Hypertension was defined by a systolic blood pressure > 140 mmHg, a diastolic blood pressure > 90 mmHg and/or the use of antihypertensive medication.[24] Hypercholesterolemia was defined as low-density lipoprotein cholesterol (LDL-C) levels > 2.5 mmol/l and/or the use of lipid-lowering drugs.[24]

Baseline characteristics

Baseline characteristics were obtained during standard preoperative screening by the endocrinologist prior to bariatric surgery and included medical history and current medication profile. Smoking within 6 months prior to inclusion was considered "active smoking." Smoking before these 6 months was considered "previous smoking." Anthropometric characteristics included height, weight, waist circumference and blood pressure. The body mass index (in kg/m^2) and mean arterial pressure (MAP) were calculated.

Laboratory measurements

Extensive preoperative laboratory testing was carried out in all participants. Freshly drawn blood was used for all clinical and hematological chemistry measurements. C-reactive protein (CRP), glucose, total cholesterol, HDL-C and triglycerides (TG) were determined using the DxC analyzer (Beckman Coulter). LDL-C values were calculated using the Friedewald formula. Apolipoprotein B (Apo-B) was determined by rate nephelometry using IMAGE analyzer (Beckman Coulter). HbA1c was measured using an HPLC G8 analyzer (Tosoh Bioscience).

Carotid intima media thickness

cIMT measurements were performed by one observer, according to the consensus guidelines for carotid ultrasound for CVD risk assessment as described previously.[25] The measurements were carried out using the ART-LAB (Esaote, Italy) by a trained and experienced sonographer, who was unaware of the patient's medical history. Ultrasound scans were performed with the patients lying in a supine position with the head resting comfortably and the neck slightly hyperextended and rotated in the opposite direction of the probe. The ultrasound images were obtained from the distal 1 cm of the far wall of each common carotid artery (CCA) using B-mode ultrasound producing two echogenic lines. These lines represent the combined thickness of the intimal and medial layers of the arterial wall. Each CCA has been imaged in three different projections: CCA right side 90–120–150, and CCA left side 210–240–270 degrees. The segments were measured semi-automated in triplicate.

Pulse wave velocity

PWV measurements were carried out using the Mobil-O-Graph (I.E.M., Germany) as previously described.[26] The Mobil-O-Graph uses an inflatable cuff to measure the PWV. The cuff was placed on the patient's bare left upper arm. Cuff size was selected based on the patient's upper arm circumference. Triplicate manual measurements were performed. PWV has been calculated by the provided software and was expressed in m/s.

Statistical analysis

All analyses were performed using SPSS (PASW) 18.0 software (SPSS Inc., Chicago, Illinois, USA). Data are given as mean ± standard deviations. Skewed variables are given in median and interquartile range (IQR). Categorical data were described in an absolute number as well as a percentage of the total group. Differences between males and females were analyzed using independent T-tests for continuous data with normal distribution, chi-squared tests for categorical data and independent samples Mann–Whitney U tests for continuous data with non-normal distribution. For statistical analysis cIMT was defined as the mean of the six individual measurements, as described above, and PWV was defined as the mean of three individual measurements. Systolic and diastolic blood pressure were integrated in the mean arterial pressure (MAP), which is the sum of 1/3 systolic blood pressure and 2/3 diastolic blood pressure.[27-29]

The associations between cIMT and PWV with sex were evaluated with univariate linear regression analysis. Since cIMT is a skewed variable logarithmic transformation was performed on this variable. Within the models this transformed variables is named "log cIMT". The log cIMT showed a normal distribution with skewedness of 0.414 and a kurtosis of –0.329 and is thereby an appropriate dependent variable for the models. Covariables in further analyses included age, BMI, waist circumference, smoking habit, TG, HDL-C, LDL-C, CRP, HbA1c and MAP. Correlations between covariables (multicollinearity) were checked for confounding and interaction effects were checked using stratified analysis. Within the regression model for log cIMT, a significant interaction effect was observed between HDL-C and TG, while waist circumference was a significant confounder. In

the PWV model, sex and waist circumference interacted. Other confounding factors were ignored in the analyses for having a low correlation or small effect on the outcome measures. After stratification for the confounder "waist circumference", the association between log cIMT and sex was evaluated with multivariable linear regression analysis (model: backward stepwise). The following variables were entered into the model: sex, age, BMI, waist circumference, smoking habit, TG, HDL-C, LDL-C, CRP, HbA1c, MAP and the interaction effect "HDL-C x TG". The association between PWV and sex was assessed in a multivariable linear regression analysis (model: backward stepwise), including sex, age, BMI, waist circumference, smoking habit, TG, HDL-C, LDL-C, CRP, HbA1c, MAP and the interaction effect "sex x waist circumference".

In addition, the effect of menopausal status in women on cIMT as well as PWV was assessed using ANOVA tests and univariate and multivariable linear regression analysis (model: backward stepwise). The relationships of cIMT and PWV with age in both premenopausal and postmenopausal women as well as men were observed using scatterplots with LOESS smooth lines ($\alpha = 0.50$). Due to high correlation with menopausal state, we eventually removed age from the models (spearman's rho = 0.770, $p < 0.001$). No significant confounding factors or interaction effects were observed. The following variables were entered in both the log cIMT and PWV model: menopausal status, smoking habit, waist circumference, TG, HDL-C, LDL-C, CRP, HbA1c and MAP. Results of these models were reported as B coefficients with 95% confidence intervals.

Results

The total cohort included 200 subjects, 52 men and 148 women, with a mean age of 41 (±11.8) years and a mean BMI of 42.7 (±5.2) kg/m². Men had a significantly higher waist circumference and were more likely to suffer from T2DM and myocardial infarction. Systolic and diastolic blood pressure, HbA1c and triglyceride levels were increased in men, while HDL-C, LDL-C and CRP were significantly higher in female subjects. Details are displayed in **Table 1**.

Table 1

Differences in baseline characteristics in male and female subjects and pre- and postmenopausal subjects

	Male	Female	*p* -value	Premenopausal	Postmenopausal	*p*- value
Number	52	148		98	45	
Age (years)	43.7 (±11.0)	40.6 (±12.0)	*p* =0.098#	34.1 (±9.4)	53.4 (±4.2)	*p* <0.001#
Medical history (n,%)						
Diabetes mellitus type 2	18 (34.6%)	22 (14.9%)	*p* =0.002*	10 (10.2%)	11 (24.4%)	*p* =0.025*
Hypertension	22 (42.3%)	47 (31.8%)	*p* =0.169*	21 (21.4%)	25 (55.6%)	*p* <0.001*
Hypercholesterolemia	15 (28.8%)	43 (29.1%)	*p* =0.977*	18 (18.4%)	25 (55.6%)	*p* <0.001*
Active smoker	14 (26.9%)	37 (25.0%)	*p* =0.273*	25 (25.5%)	10 (22.2%)	*p* =0.872*
BMI (kg/m2)	43.9 (±6.5)	42.3 (±4.6)	*p* =0.100#	42.3 (±4.1)	42.4 (±5.5)	*p* =0.904#
Waist circumference (cm)	139 (±12.4)	126 (±11.5)	*p* <0.001#	127 (±10)	125 (±14)	*p* =0.342#
Systolic blood pressure (mmHg)	145 (±17)	137 (±19)	*p* =0.009#	132 (±14)	149 (±20)	*p* <0.001#
Diastolic blood pressure (mmHg)	86 (±10)	80 (±9)	*p* <0.001#	78 (±9)	83 (±10)	*p* =0.002#
HbA1c (mmol/mol)	47 (±18)	42 (±10)	*p* =0.035#	40 (±7.2)	45 (±12.5)	*p* =0.005#
Triglycerides (mmol/l)	2.69 (1.60 - 3.72)	1.63 (1.10 - 2.17)	*p* <0.001§	1.54 (1.02 - 2.08)	1.71 (1.27 - 2.27)	*p* =0.112§
LDL-cholesterol (mmol/l)	2.8 (±0.9)	3.2 (±1.0)	*p* =0.027#	3.08 (±0.90)	3.41 (±1.09)	*p* =0.072#
HDL-cholesterol (mmol/l)	1.0 (±0.2)	1.3 (±0.3)	*p* <0.001#	1.27 (±0.29)	1.40 (±0.27)	*p* =0.010#
Apo B (g/l)	1.12 (±0.31)	1.13 (±0.30)	*p* =0.875#	1.10 (±0.28)	1.20 (±0.34)	*p* =0.090#
Lipoprotein (a) (mg/l)	143 (45 - 314)	211 (85 - 575)	*p* =0.036§	220 (78 - 568)	187 (99 - 584)	*p* =0.773§
CRP (mg/l)	4 (2 - 8)	7 (4 - 11)	*p* <0.001§	8 (4 - 13)	6 (3 - 10)	*p* =0.164§
Leukocytes (10^9/l)	8.4 (±2.3)	8.8 (±2.5)	*p* =0.450#	9.1 (±2.4)	8.2 (±2.7)	*p* =0.033#

* chi squared

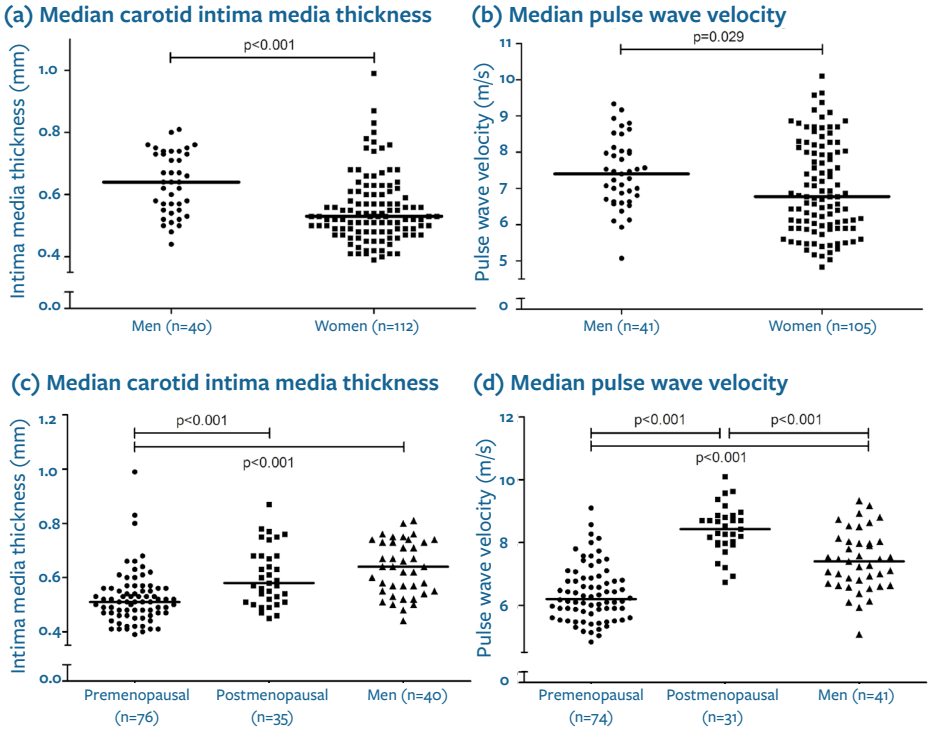
independent T-test

§ Independent samples Mann-Whitney U test

The median cIMT was measured in 152 study subjects and was significantly higher in men than in women (0.638 mm [IQR 0.549–0.735] and 0.529 mm [IQR 0.478–0.600], respectively, $p < 0.001$). Furthermore, median PWV was measured in 146 subjects and was also significantly higher in men in comparison with women (7.3 m/s [IQR 6.6–8.0] and 6.8 m/s [IQR 5.9–8.0], respectively, $p = 0.029$; **Figure 1**).

Figure 1

Differences in median cIMT and PWV in women versus men (a + b) and in pre- and postmenopausal women versus men (c + d)



Using univariate linear regression, female sex was associated with a decrease in log cIMT (beta: –0.362, adjusted R^2: 0.125, $p < 0.001$). In the multiple regression analysis, after stratification for the confounder waist circumference, age, HDL-C and MAP were significant contributors to log cIMT. After adjustment for age, HDL-C and MAP, female sex was no longer significantly associated with a lower log cIMT in subjects with a relatively low waist circumference. Within the subgroup of subjects with a waist circumference of 129 cm or higher, it appears that female sex gives a decrease of 4.7% in cIMT after adjustment for covariables. Additional data are displayed in **Table 2**.

In a univariate analysis, female sex was negatively associated with PWV (beta: –0.165, adjusted R^2: 0.020, $p = 0.047$). In the multivariable analysis, age, BMI, MAP, CRP and HbA1c were significant contributors to PWV. Female sex was associated with a lower PWV, when adjusted for these variables. Based on the

appearance of the interaction effect "sex x waist circumference," the effect size of female sex on PWV depended on the waist circumference. To be more precise, the advantage of women over men, in terms of PWV, diminishes with increasing waist circumference. Additional data are displayed in **Table 3**.

Table 2

Impact of sex on subclinical atherosclerosis (log cIMT). The impact of sex on log cIMT was evaluated with multiple linear regression analysis (backward stepwise analysis).

Parameter	log cIMT in subjects with waist < 129 cm		log cIMT in subjects with waist ≥ 129 cm	
	B coefficient (95% CI)	*p*-value	B coefficient (95% CI)	*p*-value
Constant	-0.340 (-0.427; -0.252)	$p < 0.001$	-0.517 (-0.660; -0.374)	$p < 0.001$
Female gender[a]	—	---	-0.047 (-0.080; -0.014)	$p = 0.006$
Age	0.004 (0.002; 0.005)	$p < 0.001$	0.003 (0.002; 0.004)	$p < 0.001$
HDL cholesterol	-0.057 (-0.112; -0.001)	$p = 0.044$	---	---
Mean Arterial Pressure	---	---	0.002 (0.000; 0.003)	$p = 0.016$

a Male subjects were scored by 0, female subjects were scored by 1

Table 3

Impact of sex on arterial stiffness (PWV). The impact of sex on PWV was evaluated with multiple linear regression analysis (backward stepwise analysis).

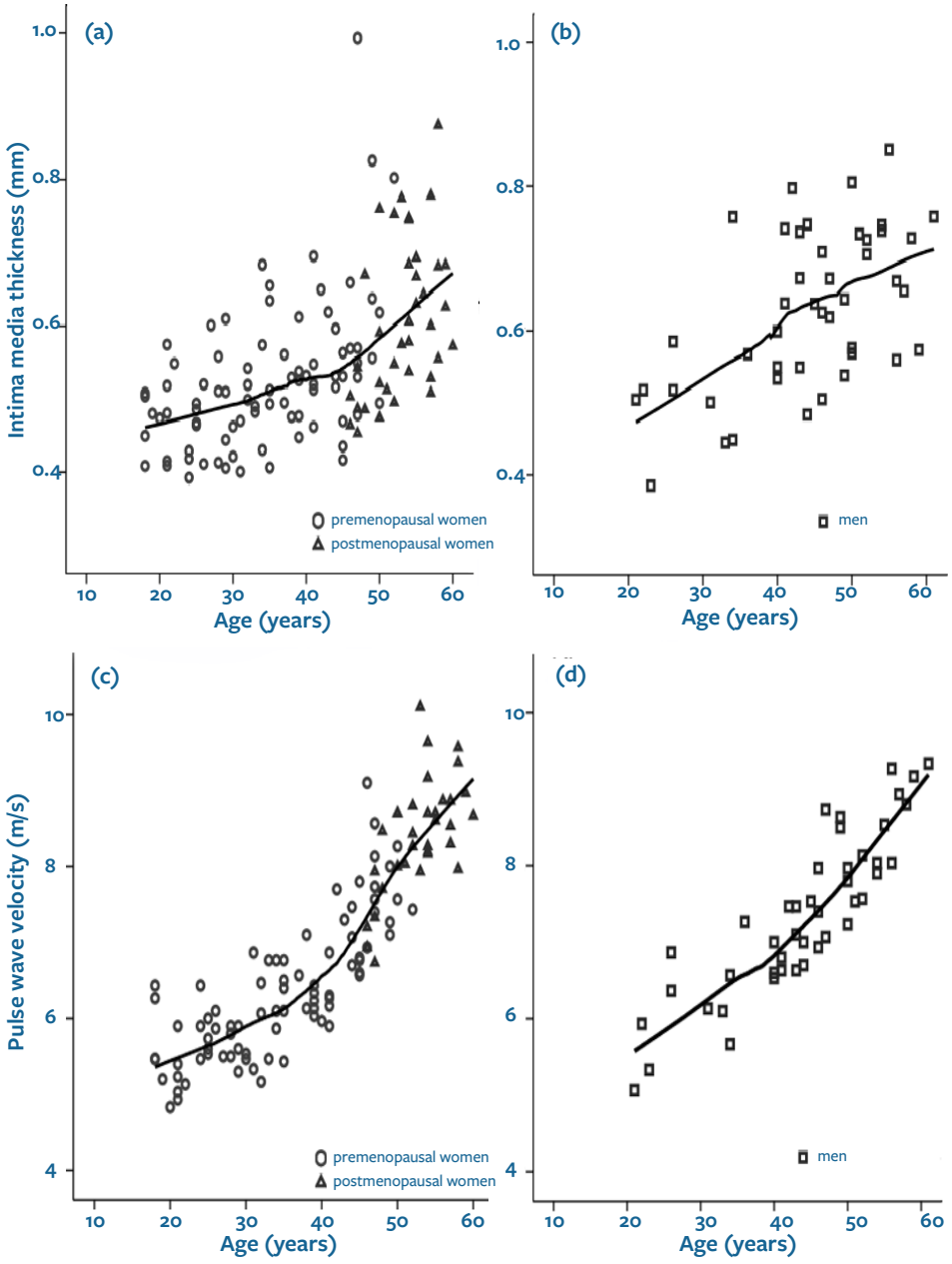
Parameter	PWV	
	B coefficient (95% CI)	*p*-value
Constant	-0.005 (-1.094; 1.084)	$p = 0.993$
Female sex[a]	-1.242 (-2.495; 0.011)	$p = 0.052$
Age	0.083 (0.074; 0.091)	$p < 0.001$
BMI	0.015 (-0.003; 0,034)	$p = 0.100$
Mean Arterial Pressure	0.026 (0.017; 0.034)	$p < 0.001$
CRP	-0.013 (-0.027; 0.000)	$p = 0.051$
HbA1c	0.009 (0.001; 0.016)	$p = 0.021$
Waist x sex	0.012 (0.002; 0.021)	$p = 0.021$

a Male subjects were scored by 0, female subjects were scored by 1

Among women, there was a non-linear relation between age and both cIMT and PWV, with an increased inclination of the LOESS smooth line from an age of approximately 45 years, while this relation in men appeared to be more or less linear (**Figure 2**). The female group consisted of 98 premenopausal and 45 postmenopausal women. Five women were excluded from further analyses, due to a history of hysterectomy. Postmenopausal women were significantly more likely to suffer from comorbidities such as T2DM, hypertension and hypercholesterolemia. Systolic and diastolic blood pressure, HbA1c and HDL-C were significantly higher in postmenopausal women, than in premenopausal women (**Table 1**).

Figure 2

Relationship of age and cIMT and PWV in pre- and postmenopausal women (a + c) and in men (b + d)



Median cIMT was significantly higher in postmenopausal women, when compared with premenopausal women (0.591 mm [IQR 0.517–0.684] and 0.512 mm [IQR 0.465–0.563], respectively, $p < 0.001$). Additionally, PWV was also significantly higher in postmenopausal women than in premenopausal women (8.5 m/s [IQR 8.0–8.8] and 6.2 m/s [IQR 5.6–6.9], respectively, $p < 0.001$). Even though no significant differences were observed in cIMT between men and postmenopausal women, PWV was significantly higher in the postmenopausal women than in men (**Figure 1**).

Postmenopausal state was associated with a higher log cIMT in univariate analysis (beta: 0.363, adjusted R^2: 0.124, $p < 0.001$) as well as after adjustment for covariables (**Table 4**). Menopausal status was also positively associated with PWV in both univariate linear regression model (beta: 2.067, adjusted R^2: 0.542, $p < 0.001$) and a multivariable regression analysis (**Table 4**).

Table 4

Impact of menopausal state on subclinical atherosclerosis (log cIMT and PWV). The impact of menopausal state on log cIMT and PWV was evaluated with multiple linear regression analysis (backward stepwise analysis).

Parameter	log cIMT		Parameter	PWV	
	B coefficient (95% CI)	*p* -value		B coefficient (95% CI)	*p* -value
Constant	-0.550 (-0.683; -0.418)	$p < 0.001$	Constant	0.983 (-0.364; 2.330)	$p = 0.151$
Menopause[a]	0.037 (0.006; 0.067)	$p = 0.020$	Menopause[a]	1.452 (1.132; 1.771)	$p < 0.001$
HbA1c	0.002 (0.000; 0.003)	$p = 0.035$	HbA1c	0.035 (0.018; 0.052)	$p < 0.001$
MAP	0.002 (0.001; 0.003)	$p = 0.002$	CRP	-0.019 (-0.038; -0.001)	$p = 0.041$
HDL	---	---	MAP	0.044 (0.030; 0.057)	$p < 0.001$

a Premenopausal women were scored by 0, postmenopausal women were scored by 1

Discussion

Sex differences in CVR factors and outcome measures for subclinical atherosclerosis do not only exist in lean and overweight subjects but persist in subjects with obesity and morbid obesity. Even though obesity is associated with an increased risk of cardiovascular disease and mortality, morbidly obese women are still relatively protected in comparison to men. However, as previously seen in lean and obese women, this advantage appears to diminish in postmenopausal morbidly obese women.

The sex differences in classic CVR factors within this study are comparable to previously described differences;[1,2,4] men had higher systolic and diastolic blood pressure and increased triglyceride levels, while women had higher HDL-C levels and higher CRP levels. In contrast to previous reports,[4] women within this cohort had higher LDL-C levels in comparison with men. However, men were more likely to suffer from T2DM and the prescription of lipid-lowering drugs is part of the protocolled treatment of diabetic patients. This could explain the lower LDL-C levels in men.

Within this study, cIMT and PWV were used as outcome measures for atherosclerosis. Both measures were significantly lower in morbidly obese women in comparison with morbidly obese men, suggesting an advantage for women in terms of CVD and cardiovascular mortality. However, after adjustment for covariables, it appeared that cIMT was not so much influenced by sex, but by differences in waist circumference, age, HDL-C and MAP. Age is the main contributor to an increase in cIMT. Overall, cIMT is known to be lower in lean and overweight women, compared with men,[5-8] but this difference appears to diminish with increasing weight.[3o] Unfortunately, our study only included morbidly obese subjects and no non-obese controls. No firm statements can be made on the differential effect of increasing weight on cIMT in men and women. However, obesity has been shown to affect cIMT[5,6] negatively and within lean subjects cIMT is correlated with BMI.[6] It was thought that this effect of weight on cIMT may be more profound in women than in men,[7] but our data do not support this hypothesis.

In contrast to cIMT, PWV was still associated with sex after adjustments for covariables in morbidly obese patients. As previously described,[31,32] age and blood pressure were the main contributors to PWV. In addition, female sex was associated with lower PWV, although this effect also depended on waist circumference. It has been suggested that sex is a major contributor to PWV in lean and overweight subjects[33] and our data now show that this relationship persists in subjects with obesity and morbid obesity.

Women are relatively protected against CVD, but this advantage diminishes in postmenopausal women.[2,34] Hormonal imbalances may play an important role in the development of CVD, although some hormone replacement studies do not support this hypothesis.[34] In general, premenopausal women have lower cholesterol, LDL-C, TG and apo-B levels than men and higher HDL-C levels.[19] After menopause both LDL-C and total cholesterol increase,[19] where HDL-C shows a small decline.[1] In our morbidly obese population, the differences in CVR profile between pre- and postmenopausal women were small. Postmenopausal women had a significantly increased blood pressure, in agreement with the current literature,[2] but no disadvantages were seen in the lipid-associated markers. In contrast, HDL-C was actually higher in postmenopausal women in comparison with premenopausal women. Our data suggest that the difference in CVR factors between pre- and postmenopausal women attenuates in morbidly obese subjects.

Within the current study, both cIMT and PWV were significantly increased in postmenopausal women compared with premenopausal women. These relationships persisted after adjustment for covariables. In addition to menopausal status, cIMT was mainly determined by HbA1c and MAP, whereas PWV was mainly determined by HbA1c, MAP and CRP. Age and blood pressure are two of the major determinants of these cardiovascular outcome measures.[31,32] We decided to remove age from the multivariable analyses, due to the high correlation of age and menopausal status. It can be suggested that the differences in cIMT between pre- and postmenopausal women are solely explained by age differences. However, **Figure 1** reveals that the effect of age on cIMT or PWV increases after an age of approximately 45 years, suggesting an effect of menopausal status on top of the effect of age. Since

menopausal status was the factor of interest and since the high correlation suggests that the majority of information on age was included in the menopausal state, it seemed justified to remove age from this analysis. However, within this study, we cannot differentiate the absolute effect of age and the absolute effect of menopause, which is a limitation of this study. The effect of menopausal state on PWV may be clinically relevant. However, when not considering age as a significant contributor to cIMT, being postmenopausal only increases the cIMT value with 3.7%, making the effect on cIMT rather irrelevant. Furthermore, it is important to realize that the hormonal effects of menopause may also appear in subjects suffering from hormonal disbalance due to obesity itself, such as polycystic ovary syndrome. None of the postmenopausal women were formerly diagnosed with polycystic ovary syndrome, and all of these women were aged 45 years or older. However, we are not informed on the effects of hormonal disbalance on cardiovascular risk factors, cIMT and PWV in the premenopausal women.

As previously mentioned, the lack of non-obese control patients is one of the limitations of this study. It was previously suggested that differences in cIMT and PWV diminish with increasing weight. With the addition of a non-obese cohort, the relation of weight with cIMT and PWV in different weight groups could have been investigated. Another limitation of this study is the difference in baseline characteristics between men and women. Multivariable linear regression analysis was used to adjust for differences in the baseline, in order to be able to make statements on the effect of sex on cIMT and PWV. We decided to use MAP as a marker for hypertension. Since we were not informed on the duration of hypertension and the effect of treatment within the group of subjects suffering from hypertension, the current MAP was the most objective parameter on blood pressure effects on cIMT and PWV. Due to a small number of subjects within this cohort and no available follow-up data, conclusions were drawn on surrogate outcome measures for CVD and not on real clinical outcomes such as cardiovascular events. Unfortunately, not all subjects within this study underwent cIMT or PWV measurements due to technical problems. Baseline characteristics were presented on the entire study group and not on the subgroups that underwent cIMT and PWV measurement since the entire study group was representative for the groups that underwent cIMT and PWV measurements.

In conclusion, commonly described sex differences in cardiovascular outcome measures, such as cIMT and PWV, persist in morbidly obese subjects. Differences in cIMT cannot be explained by sex alone and are mainly related to waist circumference, age, HDL-C and MAP. The advantage of women over men appears to diminish in morbidly obese women after menopause. The advantage in CVR translates into both lower cIMT and PWV values for premenopausal women. Morbidly obese women are, nevertheless, at higher risk of developing CVD then their leaner counterparts.

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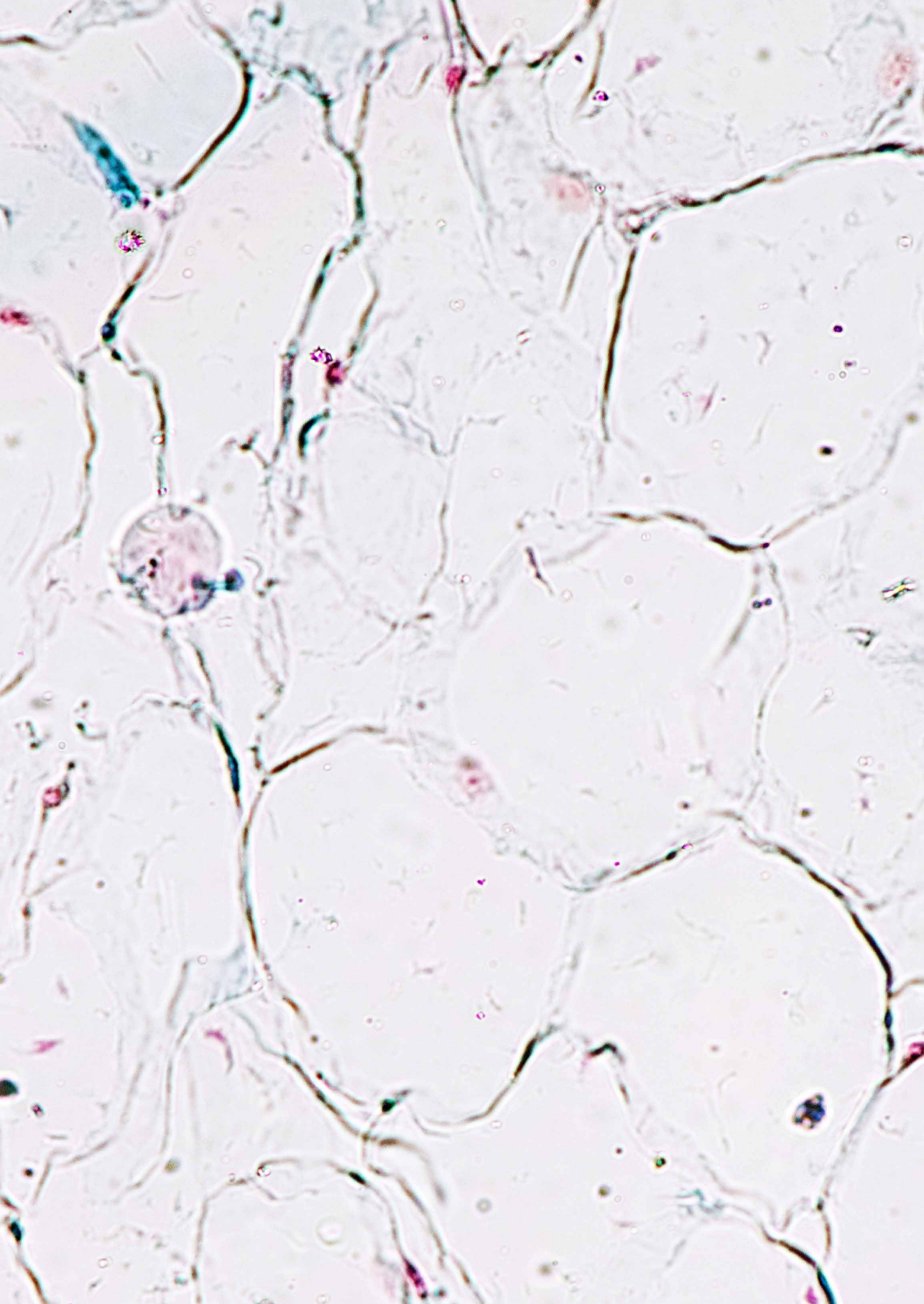

Chapter 4

Contribution of type 2 diabetes mellitus to subclinical atherosclerosis in subjects with morbid obesity

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Abstract

Background

Type 2 diabetes mellitus (T2DM) and obesity are both related to increased risk of cardiovascular disease and mortality. Early atherosclerotic vascular changes can be detected by non-invasive tests like carotid intima media thickness (cIMT) and pulse wave velocity (PWV). Both cIMT and PWV are significantly impaired in T2DM and in obese patients, but the additional effect of T2DM on these vascular measurements in obese subjects has not been evaluated.

Materials and methods

200 morbidly obese patients with or without T2DM were enrolled in a prospective cohort study and underwent extensive laboratory testing, including cIMT and PWV measurements. The cohort was divided into a group with and a group without T2DM.

Results

Within this cohort, 43 patients (21.5%) were diagnosed with T2DM. These patients were older and had more often (a history of) hypertension as compared to patients without T2DM. HbA1c levels were significantly increased, while LDL-cholesterol was significantly lower and the use of statins higher than in non-diabetic participants. cIMT and PWV were significantly increased in subjects suffering from T2DM. The variability in cIMT and PWV was related to differences in age and systolic blood pressure, but not to the presence of T2DM.

Conclusions

While T2DM negatively affects the vasculature in morbid obesity, hypertension and age seem to be the major risk factors, independent from the presence of T2DM.

Introduction

Type 2 diabetes mellitus (T2DM) is a growing chronic health problem worldwide, and its micro- and macrovascular complications cause significant morbidity and mortality.[1] T2DM is associated with atherosclerosis[2] and is a major risk factor for cardiovascular disease (CVD).[3-4] Atherogenic dyslipidemia is a key factor linking T2DM to CVD and includes reduced levels of high-density lipoprotein cholesterol (HDL-C) and increased levels of triglycerides (TG) and small dense low-density lipoprotein cholesterol (LDL-C).[3] LDL-C lowering therapy can modify the cardiovascular risk in adults suffering from T2DM, although the risk of CVD remains higher than in non-diabetic adults.[3] Both the onset and the progression of atherosclerosis are more rapid in T2DM patients.[1] In addition, the disease may cause premature aging of the cardiovascular system.[5]

Vascular health can be easily monitored by measuring carotid intima media thickness (cIMT) using carotid ultrasound. cIMT is an easy and non-invasive method for the detection of structural signs of carotid atherosclerosis, which is a significant indicator of subclinical atherosclerosis and of future CVD.[1,3,6-8] Close associations have been seen between cIMT and conventional cardiovascular risk factors, such as smoking status, hypertension and dyslipidemia.[8-9] Patients suffering from T2DM are also known to have an increased cIMT in comparison to non-diabetic controls,[8] and the presence of T2DM increases the likelihood of early carotid atherosclerosis.[9] Both hyperglycemia and hyperinsulinemia are associated with an increased risk of atherosclerotic CVD, and changes in cIMT are correlated with changes in fasting plasma glucose, HbA1c and insulin levels.[1,9]

Another measure for vascular health is arterial stiffness, which is an independent risk factor for CVD and mortality.[3,4,10,11] The "gold standard" measurement for arterial stiffness is the measurement of the pulse wave velocity (PWV).[4,5] Subjects suffering from T2DM are known to have a higher PWV than non-diabetic subjects.[4]

Both cIMT and PWV are also known to be increased in patients suffering from obesity[4,9,12] and obesity is also strongly associated with cardiovascular risk and the occurrence of coronary heart disease.[4] Furthermore, obese subjects are more likely to develop T2DM. It is unknown whether suffering from T2DM worsens vascular conditions in morbidly obese subjects. As cIMT and PWV may be used as prospective markers for vascular disease, we selected these markers to establish the effect of T2DM on the vascular status in morbidly obese subjects.

Materials and methods

Study population

The data for this study are derived from the ASSISI study, a prospective cohort study established between April 2015 and April 2016 and including 200 patients scheduled for bariatric surgery within out bariatric clinic. All met the international IFSO criteria for bariatric surgery[13] (i.e. patients with a BMI ≥ 40 kg/m^2 or patients with a BMI ≥ 35 kg/m^2 and obesity-related comorbidity, aged 18–65 years). Patients with a previous cholecystectomy, a previous bariatric procedure, an acute inflammatory disease within 6 weeks prior to inclusion or using immune-modulating medication were excluded from this study. All data presented here were collected at study entry, before bariatric surgery.

The study was approved by the independent Regional Medical Research Ethics Committee Rotterdam (Maasstad Hospital, Rotterdam, the Netherlands, ABR no. NL47891.101.14) and all patients gave written informed consent. The ASSISI study is registered in the Dutch Trial Register (NTR5172).

Definitions

T2DM was defined as a glycated hemoglobin (HbA1c) level ≥ 48 mmol/mol (6.5%)[14] and/or previously diagnosed T2DM using glucose-lowering medication. Hypertension was defined by a systolic blood pressure > 140 mmHg and/or the use of antihypertensive medication.[15] Hypercholesterolemia was defined as LDL-C > 2.5 mmol/l and/or the use of lipid-lowering drugs.[15]

Baseline characteristics

Baseline characteristics were obtained during standard preoperative screening by the internist prior to bariatric surgery and included the medical history and current medication.[16] Anthropometric characteristics included height, weight, waist circumference and blood pressure.

Laboratory measurements

Preoperative laboratory testing was carried out in all participants using non-fasting samples. C-reactive protein (CRP), glucose, total cholesterol, HDL-C and TG were determined using the DxC analyzer (Beckman Coulter, Crea, CA, USA). LDL-C values were calculated using the Friedewald formula. HbA1c was measured using an HPLC G8 analyzer (Tosoh Bioscience, King of Prussia, PA, USA). Apo-B was determined by rate nephelometry using IMAGE analyzer (Beckman Coulter).

Carotid intima media thickness

cIMT measurements were performed according to the consensus guidelines for carotid ultrasound for CVD risk assessment, as described previously.[17] The measurement was carried out using the ART-LAB (Esaote, Italy) by a trained and experienced sonographer, who was unaware of the patient's medical history. Ultrasound scans were performed with the patients lying in a supine position with the head resting comfortably and the neck slightly hyperextended and rotated in the opposite direction of the probe. The ultrasound images were obtained from the distal 1 cm of the far wall of each common carotid artery (CCA) using B-mode ultrasound producing two echogenic lines. These lines represent the combined thickness of the intimal and medial layers of the arterial wall. Each CCA was imaged in three different projections: CCA right side, 90–120–150, and CCA left side, 210–240–270 degrees. The segments were measured semi-automated in triplicate.

Pulse wave velocity

PWV measurements were carried out using the Mobil-O-Graph (I.E.M., Germany), as previously described.[18] The Mobil-O-Graph uses an inflatable cuff to measure the PWV. The cuff was placed on the patient's bare left upper arm. Triplicate manual measurements were performed. PWV was calculated by the provided software and was expressed in m/s.

Statistical analysis

All analyses were performed using SPSS (PASW) 18.0 software (SPSS Inc., Chicago, Illinois, USA). Data are given as mean ± standard deviations. Skewed variables are given in median and interquartile range (IQR). Categorical data were described in an absolute numbers and percentages. Differences between subjects with and without T2DM were analyzed using independent T-tests, chi-squared tests, Fisher's exact tests and independent samples Mann–Whitney U tests. For statistical analysis, cIMT was defined as the mean of the six individual measurements, as described above, and PWV was defined as the mean of three individual measurements. Systolic and diastolic blood pressure were integrated in the mean arterial pressure (MAP), which is the sum of 1/3 systolic blood pressure and 2/3 diastolic blood pressure.

The association between cIMT and PWV, both intermediate measures of subclinical atherosclerosis, with T2DM was evaluated with univariate linear regression analysis. To evaluate the effects of both the occurrence of T2DM as well as the severity of dysregulation of glucose homeostasis, linear regression analyses were performed using both the previously described definition of T2DM and the HbA1c level. In further analyses, covariables included gender, age, smoking status, BMI, waist circumference, TG, HDL-C, LDL-C, CRP and MAP. Correlations between covariables (multicollinearity) were checked for confounding and interaction effects using stratified analysis. Within the regression models of T2DM and HbA1c on both cIMT and PWV, a significant interaction effect was observed between HDL-C and TG, while gender was a significant confounder. Other confounding factors were ignored in the analyses for having a low correlation (< 0.30) or small impact on the outcome measures. After stratification for gender, the associations of both T2DM and HbA1c level on cIMT and PWV were evaluated with multivariable linear regression analysis (model: backward stepwise). The following variables were entered into the models: gender, age, smoking status, waist circumference, TG, HDL-C, LDL-C, CRP, HDL-C x TG and MAP. Results of these models were reported as B coefficients with 95% confidence intervals. Goodness of fit was evaluated with the adjusted R^2. A p-value < 0.05 (two-sided) was considered a statistically significant difference.

Results

The total cohort included 200 patients, 52 men and 148 women, with a mean age of 41 (±11.8) years and a mean BMI of 42.7 (±5.2) kg/m². Within this cohort, 43 patients (21.5%) were diagnosed with T2DM. T2DM patients were older and suffered more frequently from hypertension. In addition, these patients had more frequently a history of myocardial infarction. While mean HbA1c values were significantly increased in diabetes patients, their LDL-C levels were significantly lower than in non-diabetics. Diabetic patients were more frequently treated with lipid-lowering drugs and antihypertensive drugs. Of all diabetic patients, 35 patients (81.4%) were treated with glucose-lowering drugs; 13 patients received monotherapy with metformin, eight received a combination of insulin and metformin, 10 received a combination of metformin with another oral glucose-lowering drug, and four received another treatment. Additional characteristics are displayed in **Table 1**.

The median cIMT was significantly increased in patients suffering from T2DM, when compared to non-diabetics (0.576 mm [IQR 0.531–0.726] and 0.540 mm [IQR 0.481–0.634], respectively, $p = 0.016$). The median PWV was also significantly higher in diabetic patients compared to non-diabetics(7.6 m/s [IQR 6.9–8.4] and 6.8 m/s [IQR 5.9–8.0], respectively, $p = 0.005$; **Figure 1**).

Figure 1

Median carotid intima media thickness (a) and pulse wave velocity (b) in morbidly obese patients with and without type 2 diabetes mellitus

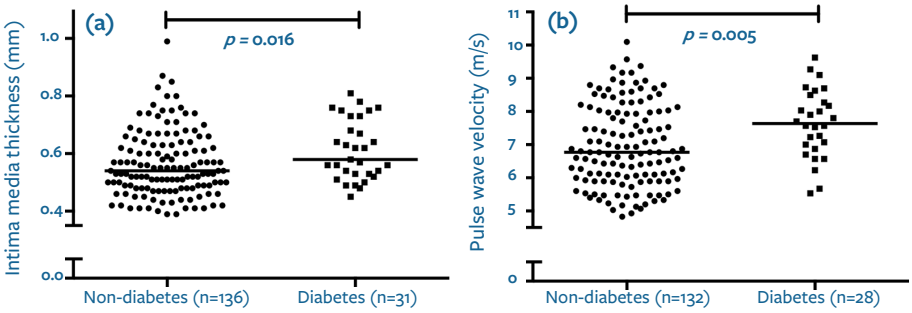

Table 1

Baseline characteristics

	Non-diabetes	Diabetes	*p* -value
Number	157	43	
Age (years)	39.8 (±12.1)	47.4 (±8.3)	*p* <0.001a
Female gender	123 (78.3%)	25 (58.1%)	*p* =0.007b
Medical history (n,%)			
Hypertension	77 (49.0%)	31 (72.1%)	*p* =0.007b
Hypercholesterolemia	124 (79.0%)	34 (79.1%)	*p* =0.990b
Stroke	3 (1.9%)	2 (4.7%)	*p* =0.293c
Myocardial infarction	2 (1.3%)	4 (9.3%)	*p* =0.020c
Medication use (n,%)			
Lipid lowering agents	10 (6.4%)	21 (48.8%)	*p* <0.001b
Antihypertensive agents	38 (24.2%)	27 (62.8%)	*p* <0.001b
Smoking habbit (n,%)			*p* =0.861b
No	68 (43.3%)	19 (44.2%)	
Former smoker	50 (31.8%)	12 (27.9%)	
Yes	39 (24.8%)	12 (27.9%)	
BMI (kg/m2)	42.7 (±5.2)	42.7 (±5.2)	*p* =0.990a
Waist circumference (cm)	129 (±12.9)	132 (±13.5)	*p* =0.102a
Systolic bloodpressure (mmHg)	138 (±19)	143 (±19)	*p* =0.143a
Diastolic bloodpressure (mmHg)	81 (±10)	82 (±11)	*p* =0.671a
cIMT (mm)	0.540 (0.481 - 0.634)	0.576 (0.531 - 0.726)	*p* =0.016d
PWV (m/s)	6.8 (5.9 - 8.0)	7.6 (6.9 - 8.4)	*p* =0.005d
HbA1c (mmol/mol)	38 (±4)	61 (±17)	*p* <0.001a
Triglycerides (mmol/l)	1.70 (1.13 - 2.44)	1.96 (1.26 - 2.93)	*p* =0.073d
LDL-cholesterol (mmol/l)	3.3 (±0.9)	2.5 (±0.9)	*p* <0.001a
HDL-cholesterol (mmol/l)	1.2 (±0.3)	1.2 (±0.3)	*p* =0.699a
Apo B (g/l)	1.16 (±0.30)	1.00 (±0.25)	*p* =0.002a
Lipoprotein a (mg/l)	196 (80 - 568)	126 (43 - 361)	*p* =0.201d
CRP (mg/l)	5 (3 - 10)	6 (3 - 12)	*p* =0.577d
Leukocytes (10^9/l)	8.5 (±2.3)	9.3 (±3.0)	*p* =0.082a
Complement C3 (mg/l)	1.48 (±0.23)	1.49 (±0.22)	*p* =0.928a

a independent T-test
b chi squared
c fisher's exact
d Independent samples Mann-Whitney U test

Univariate linear regression showed that the presence of T2DM was associated with an increased cIMT (crude beta: 0.048, adjusted R^2: 0.021, $p = 0.033$). Additionally, higher HbA1c levels were associated with an increased cIMT (crude beta: 0.001, adjusted R^2: 0.019, $p = 0.041$). In a multiple regression analysis, both T2DM and HbA1c did not contribute to the cIMT after stratification for gender and adjusted for age, LDL-C, HDL-C and MAP. The other parameters included in the analysis did not have any significant effect on the cIMT.

Using univariate analysis, T2DM was associated with increased PWV (crude beta: 0.685, adjusted R^2: 0.039, $p = 0.007$). Furthermore, HbA1c levels were also associated with an increased PWV (crude beta: 0.023, adjusted R^2: 0.043, $p = 0.005$). In the multivariable analysis, stratified for gender and after adjustment for age, waist circumference and MAP, T2DM was not associated with increased PWV. HbA1c tended to show a small contribution to PWV in men only (**Table 2**).

Table 2

Impact of HbA1c levels on pulse wave velocity (PWV). The impact of HbA1c level on PWV was evaluated with multiple linear regression analysis (backward stepwise analysis).

Parameter	PWV in male		PWV in female	
	adj. B coefficient (95% CI)	*p* -value	adj. B coefficient (95% CI)	*p* -value
Constant	0.714 (-0.567; 1.996)	$p = 0.265$	-1.086 (-2.628; 0.457)	$p = 0.166$
HbA1c	0.007 (0.000; 0.014)	$p = 0.060$	---	---
Age	0.082 (0.070; 0.095)	$p < 0.001$	0.085 (0.075; 0.096)	$p < 0.001$
Waist circumference	---	---	0.016 (0.007; 0.025)	$p = 0.001$
Mean Arterial Pressure	0.026 (0.014; 0.038)	$p < 0.001$	0.027 (0.016; 0.037)	$p < 0.001$

Discussion

Vascular disease as measured by cIMT and PWV is significantly worse in morbidly obese subjects suffering from T2DM, in comparison to their non-diabetic counterparts. This is in line with previously described differences in non-obese subjects.[4,8] Our data suggest that the presence of T2DM is not a significant contributor to the levels of cIMT and PWV within the morbidly obese subjects after adjustment for age, blood pressure and lipid profile. PWV was mainly determined by differences in gender, age, waist circumference and blood pressure.

cIMT and PWV values are increased in both T2DM[8] and obesity.[4,9,12] However, the impact of having T2DM in a morbidly obese population on subclinical atherosclerosis has not been described before. Our study suggests that, patients with T2DM and morbid obesity have a significantly impaired vascular function, compared to their non-diabetic obese counterparts. However, it should be noted that other cardiovascular risk factors, linked to T2DM, may have a greater impact on vascular function, than T2DM itself. The consequence of our study is that in subjects with morbid obesity and T2DM one should consider more strict targets of conventional cardiovascular risk factors.

In general, it is well known that cIMT is mainly influenced by age and gender in which men and elderly people have an increased cIMT when compared to women and young subjects.[19-23] In terms of classic cardiovascular risk factors, blood pressure is the main contributor to increased cIMT. Blood pressure influences cIMT in for example young healthy subjects,[20,23,24] in lean subjects suffering from T2DM[25] and in elderly patients with cardiovascular risk factors.[21] Additionally, a decrease in blood pressure, for example by administering antihypertensive drugs, can provide a decrease in measured cIMT.[26] The second important cardiovascular risk factor to influence cIMT is dyslipidemia[20-22] and intensive lipid-lowering therapy can also positively influence cIMT,[26-28] although this effect was not observed in diabetic subjects.[29] The results in these non-obese study populations are in agreement with the results in our study. Smoking habit is also thought to influence cIMT in

different populations,[20-23] but this association was not observed in our morbidly obese subjects.

The determinants of arterial stiffness, measured as the PWV, have been less well studied compared to cIMT. In healthy middle-aged and elderly subjects, not suffering from T2DM or CVD, PWV is mainly determined by age, blood pressure and waist circumference,[30] which is in accordance with the results in our morbidly obese population. Fasting glucose levels are thought to have a modest impact on PWV and only when diabetic and cardiovascular patients are included in the study group.[30] Additionally, both HbA1c[25] and TG[24] levels are thought to play a role in the development of arterial stiffness, although that effect is only seen in selected subjects and cannot be confirmed in all studies or patient groups. Both parameters were no major determinant of PWV within our morbidly obese study population.

Obesity is both a major and modifiable risk factor for the development of metabolic and CVD.[12] Weight loss can be an important pillar in the prevention strategy for cardiovascular events. For example, bariatric surgery can significantly reduce cardiovascular morbidity and mortality. One study showed that cIMT values were significantly decreased 1 year after bariatric surgery.[31] An interesting finding in the current study is the fact that the degree of obesity, in terms of both BMI and waist circumference, did not influence the value of cIMT or PWV. It can be suggested, that being morbidly obese indeed increases the values of PWV and cIMT, but that the level of obesity does not really matter once a certain BMI threshold is surpassed (ceiling effect). A certain ceiling effect was previously described for markers of dyslipidemia[32,33] and may be true for other cardiovascular risk factors or vascular outcome measures, such as cIMT and PWV. Consequently, once morbid obesity is a fact, further increment of body weight may not cause further deterioration of subclinical atherosclerosis.

When analyzing the impact of diabetes on cIMT or vascular function, differences in cardiovascular risk management between diabetics and non-diabetics can affect the results. For example, one important pillar of the treatment for type 2 diabetes is the reduction of diabetic dyslipidemia with prescription of statins.

Within our morbidly obese population, diabetic patients were more likely to use statins and therefore their mean LDL-C level was significantly lower than in the non-diabetic group. The differences in cIMT and PWV between diabetics and non-diabetics may be limited due to the extensive use of statins in diabetics. However, a previous study showed that statin use does not influence cIMT in diabetic patients without previous CVD[29] and only aggressive treatment goals, such as LDL-C ≤ 70 mg/dl, can influence the progression of cIMT.[34] Another important target in the treatment of diabetic patients is the prevention of micro- and macrovascular complications by administration of antihypertensive drugs. Within our cohort, the diabetic patients were more likely to be diagnosed with hypertension and to be treated with antihypertensive drugs. Diabetic patients with hypertension are known to have increased cIMT values and increased cIMT progression over time.[35,36] Even though the actual value of systolic and diastolic blood pressure was not significantly different between the diabetic and non-diabetic subject in our cohort, it was previously shown that treatment with antihypertensive drugs had a positive influence on cIMT and progression of cIMT, independent of the level of blood pressure.[35] Therefore, the effect of type 2 diabetes on cIMT in this study may be limited due to the excessive use of antihypertensive agents within this group.

In conclusion, although T2DM negatively affects the vasculature in morbid obesity, age and hypertension seem to be the main risk factors independent from the presence of T2DM.

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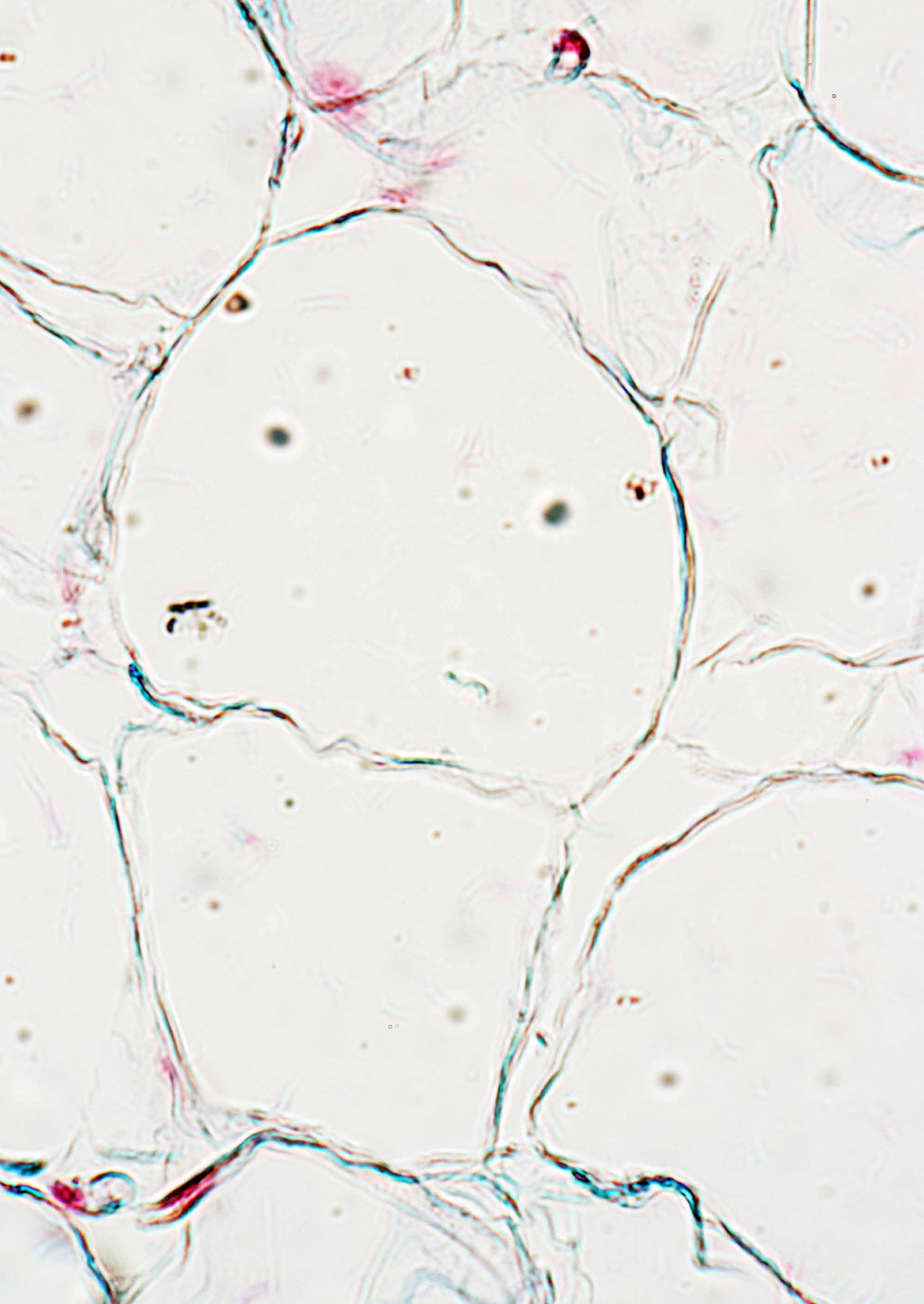

Chapter 5

The association of type 2 diabetes mellitus with increased systemic inflammation and leukocyte activation in morbidly obese patients

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Abstract

Background

Obesity is associated with type 2 diabetes mellitus (T2DM), and both are considered forms of low-grade systemic inflammation. In lean subjects, T2DM is associated with increased systemic inflammation and leukocyte activation, which results in micro- and macrovascular complications. This study investigates systemic inflammation and leukocyte activation in morbidly obese subjects with and without T2DM.

Materials and methods

Systemic inflammation, leukocyte activation markers, intima media thickness and pulse wave velocity were assessed in morbidly obese subjects scheduled for bariatric surgery. Differences between diabetic and non-diabetic subjects were assessed using independent T-tests and nonparametric tests. Multiple regression analyses were used to adjust for group differences.

Results

The total cohort consisted of 200 subjects (148 women, mean age 41.4 [±11.8] years, mean BMI 42.7 [±5.2] kg/m^2). 43 subjects (21.5%) suffered from T2DM. Leukocyte count was significantly increased in T2DM (p = 0.041); no other markers of inflammation differed between diabetics and non-diabetics. After correction for group differences, CRP was also associated with T2DM (p = 0.011). cIMT and PWV were significantly higher in T2DM (p = 0.033 and p = 0.007, respectively).

Conclusions

Systemic inflammation and leukocyte activation in morbid obesity are not increased in subjects suffering from T2DM. The micro- and macrovascular changes seen in these patients are likely influenced by other factors, such as traditional cardiovascular risk factors. Treatment of this specific patient group should likely focus not on the reduction of inflammation but on weight loss and the improvement of cardiovascular risk factors.

Introduction

Obesity is a major risk factor for the development of type 2 diabetes mellitus (T2DM). The continuing rise of the obesity prevalence results in a continuously increasing prevalence of T2DM, with its micro- and macrovascular complications causing a major disease burden worldwide.[1]

Obesity is considered a form of low-grade systemic inflammation,[2] and such inflammation is thought to be a significant factor in the development of the micro- and macrovascular complications seen in T2DM.[3] Markers of systemic inflammation, such as C-reactive protein (CRP), are associated with insulin sensitivity and β-cell dysfunction.[1,4] Insulin signaling can be further impaired by expansion of adipose tissue, since this is associated with an increased production and release of pro-inflammatory cytokines, such as tumor necrosis factor α.[4]

Different mechanisms are responsible for inflammation through hyperglycemia, one of which is the activation of leukocytes.[5] Activated leukocytes express an increased number of cell surface integrins, such as CD11b and CD66b, and can thereby adhere to the intact endothelium and migrate into the subendothelial space, which is the first step in the generation of atherosclerosis[6] and microvascular changes, as seen in T2DM.[7,8] Previous studies showed increased leukocyte activation in non-obese subjects suffering from T2DM.[9,10] The current study investigates differences in systemic inflammation and leukocyte activation between subjects with and without T2DM in a morbidly obese population.

Materials and methods

Study population

This prospective cohort study included 200 patients scheduled for bariatric surgery in the Franciscus Gasthuis, Rotterdam, the Netherlands. All subjects met the international IFSO criteria for bariatric surgery[11] (i.e. patients with BMI ≥ 40 kg/m², or BMI ≥ 35 kg/m² and obesity-related comorbidity). Subjects with previous cholecystectomy, previous bariatric procedure, acute inflammatory disease within

6 weeks prior to inclusion or immune-modulating medication were excluded from this study. The study was approved by the independent Regional Medical Ethical Committee Rotterdam (Maasstad Hospital, Rotterdam, the Netherlands, ABR no. NL47891.101.14) and all subjects gave written informed consent. This study is registered in the Dutch Trial Register (NTR5172).

Definitions

T2DM was defined as glycated hemoglobin (HbA1c) level ≥ 48 mmol/mol (6.5%)[12] and/or previously diagnosed T2DM using glucose-lowering medication. Hypertension was defined by systolic blood pressure > 140 mmHg and/or the use of antihypertensive medication.[13] Hypercholesterolemia was defined as LDL-cholesterol > 2.5 mmol/l and/or the use of lipid-lowering drugs.[13]

Baseline characteristics

Baseline characteristics were obtained during standard preoperative screening by the endocrinologist prior to bariatric surgery and included medical history and current medication profile. Anthropometric characteristics included height, weight, waist circumference and blood pressure. Body mass index (BMI; in kg/m^2) was calculated using weight and height.

Laboratory measurements

Systemic inflammation was investigated using the laboratory measures CRP, leukocyte count and markers of leukocyte activation. The leukocyte activation markers of interest were CD11b (ITGAM, leukocyte adhesion and migration marker), CD66b (CEACAM8, neutrophil degranulation marker) and CD35 (CR1, complement receptor type 1).

Freshly drawn blood was used for all clinical and hematological chemistry measurements, which were analyzed in the Department of Clinical Chemistry, Franciscus Gasthuis. CRP was determined using the DxC analyzer (Beckman Coulter), and white blood cell counts were determined automatically using a DxH800 analyzer (Beckman Coulter). The degree of leukocyte activation was measured by flow cytometry on fresh blood samples collected in EDTA tubes;

this method has been previously described in detail.[14] In summary, the cell surface expression of two pairs of leukocyte activation markers was detected using fluorescent labeled monoclonal antibodies (MoAbs, Beckman Coulter). Antibodies for CD45 were used to differentiate leukocytes from erythrocytes and platelets. Two separate tubes were prepared in triplicate: 1) a combination of 2.5 µL each of CD11b, CD66b and CD45 and 2) a combination of 2.5 µL each of CD35 and CD45. 20 µL of blood from an EDTA-anti-coagulated blood sample was added to all tubes. Cells were incubated for 15 minutes in the dark at room temperature. After incubation, erythrocytes were lysed by adding 500 µL of lysing solution (1.5 M ammonium chloride, 100 mM potassium hydrogen carbonate, 0.82 mM EDTA, pH 7.4) for 15 minutes.

Samples were measured until at least 1,000 monocytes were acquired or for a maximum of 5 minutes per sample using a flow cytometer (FC500, Beckman Coulter) with a 488 nm Argon ion laser and CXP software. The fluorescence intensity of each cell type was expressed as the mean fluorescence intensity, given in arbitrary units (au). Before each use, the optics and settings of the flow cytometer were checked with Flow-Check and Flow-Set beads (Beckman Coulter).

Carotid intima media thickness

cIMT measurements were performed according to the consensus guidelines for carotid ultrasound for CVD risk assessment as described previously.[15] The measurement was conducted using the ART-LAB (Esaote, Italy) by trained and experienced sonographers, who were unaware of patients' medical histories. Ultrasound scans were performed with the patients lying in a supine position, with the head resting comfortably and the neck slightly hyperextended and rotated in the opposite direction of the probe. The ultrasound images were obtained from the distal 1 cm of the far wall of each common carotid artery (CCA) using B-mode ultrasound producing two echogenic lines. These lines represent the combined thickness of the intimal and medial layers of the arterial wall. Each CCA has been imaged in three different projections: CCA right side 90–120–150 and CCA left side 210–240–270 degrees. The segments were measured semi-automated in triplicate.

Pulse wave velocity

PWV measurements were conducted using the Mobil-O-Graph (I.E.M., Germany) as previously described.[16] The Mobil-O-Graph uses an inflatable cuff to measure the PWV. The cuff was placed on the patient's bare left upper arm. Triplicate manual measurements were performed. PWV was calculated by the provided software and was expressed in m/s.

Statistical analysis

All analyses were performed using SPSS (PASW) 25.0 software (SPSS Inc., Chicago, Illinois, USA). Data are given as mean ± standard deviations. Skewed variables are given in median and interquartile range (IQR). Categorical data were described in an absolute number as well as a percentage of the total group. Outliers in leukocyte activation markers were identified in the dataset and removed when appropriate.

Differences between subjects with and without T2DM were analyzed using independent T-tests, chi-squared tests, Fisher's exact tests and independent samples Mann–Whitney U tests. For statistical analysis, cIMT was defined as the mean of the six individual measurements, as described above, and PWV was defined as the mean of three individual measurements.

Differences in systemic inflammation and leukocyte activation between subjects with and without T2DM were analyzed using a multiple regression analysis, with adjustment for baseline group differences, and were reported as β-coefficients and their *p*-values with a significance threshold of $p = 0.05$ (two-sided).

Results

The total cohort consisted of 200 morbidly obese subjects, of whom 43 (21.5%) suffered from T2DM. The group consisted of 148 women and 52 men, with a mean age of 41.4 (±11.8) years and a mean BMI of 42.7 (±5.2) kg/m^2. Subjects with T2DM were older, suffered more frequently from hypertension and were more likely to use lipid-lowering medication. Furthermore, the proportion of men was higher in the group suffering from T2DM. Both markers for subclinical atherosclerosis

were increased in subjects with T2DM when compared to non-diabetics; the median cIMT was 0.576 [IQR 0.531–0.726] mm and 0.540 [IQR 0.481–0.633] mm, respectively ($p = 0.033$), and the median PWV was 7.6 [IQR 6.9–8.4] m/s and 6.8 [IQR 5.9–8.0] m/s, respectively ($p = 0.007$; **Table 1**).

Regarding inflammation in particular, only the leukocyte count was significantly increased in T2DM. No significant differences were observed in CRP or the different markers for leukocyte activation.

Table 1

Baseline characteristics

	Non-diabetic subjects	Diabetic subjects	*p*-value
Number	157	43	
Gender (female)	123 (78.3%)	25 (58.1%)	$p = 0.007$
Age (years)	39.8 (±12.1)	47.4 (±8.3)	$p < 0.001$
Medical history			
Hypertension	77 (49.0%)	31 (72.1%)	$p = 0.007$
Hypercholesterolemia	124 (79.0%)	34 (79.1%)	$p = 0.990$
Stroke	3 (1.9%)	2 (4.7%)	$p = 0.293$
Myocardial infarction	2 (1.3%)	4 (9.3%)	$p = 0.020$
Medication use			
Lipid lowering drugs	10 (6.4%)	21 (48.8%)	$p < 0.001$
Beta blokking agents	9 (5.7%)	12 (27.9%)	$p = 0.117$
Smoking habbit			$p = 0.861$
No	68 (43.3%)	19 (44.2%)	
Quited smoker	50 (31.8%)	12 (27.9%)	
Yes	39 (24.8%)	12 (27.9%)	
BMI (kg/m^2)	42.7 (±5.2)	42.7 (±5.2)	$p = 0.990$
Waist circumference (cm)	129 (±12.9)	132 (±13.5)	$p = 0.102$
Systolic bloodpressure (mmHg)	138 (±18.5)	143 (±18.6)	$p = 0.143$
Diastolic bloodpressure (mmHg)	81 (±9.7)	82 (±11.3)	$p = 0.671$
cIMT (mm)	0.540 (0.481 - 0.633)	0.576 (0.531 - 0.726)	$p = 0.033$
PWV (m/s)	6.8 (5.9 - 8.0)	7.6 (6.9 - 8.4)	$p = 0.007$
Laboratory values			
HbA1c	38 (±3.8)	61 (±17.3)	$p < 0.001$
CRP (mg/L)	5 (3 - 10)	6 (3 - 12)	$p = 0.430$
Leukocyte count (x10^9/L)	8.5 (±2.3)	9.3 (±3.0)	$p = 0.041$
CD35 on monocytes (au)	7.22 (±3.02)	6.74 (±2.43)	$p = 0.340$
CD35 on granulocytes (au)	10.65 (±5.57)	10.46 (±4.68)	$p = 0.831$
CD11b on monocytes (au)	33.82 (±7.99)	32.67 (±8.61)	$p = 0.413$
CD11b on granulocytes (au)	46.90 (±15.27)	46.85 (±15.40)	$p = 0.985$
CD66b on granulocytes (au)	5.98 (±1.91)	6.06 (±1.66)	$p = 0.793$

In a multiple regression analysis, both leukocyte count (beta: 1.643, $p = 0.001$) and CRP (beta: 3.496, $p = 0.011$) appeared to be increased in T2DM, when adjusted for age, gender, hypertension and statin use. No significant differences were seen in the other markers for leukocyte activation (**Table 2**). When the model focused on HbA1c levels instead of the presence of T2DM, similar results were found (**Table 3**).

Table 2

The effect of type 2 diabetes mellitus on inflammatory markers after adjustment for group differences*

Dependent variable	β-coefficients	p-value
CRP (mg/L)	3.496	$p = 0.011$
Leukocyte count (x10^9/L)	1.643	$p = 0.001$
CD35 on monocytes (au)	-0.306	$p = 0.596$
CD35 on granulocytes (au)	0.274	$p = 0.797$
CD11b on monocytes (au)	-1.257	$p = 0.441$
CD11b on granulocytes (au)	-0.913	$p = 0.759$
CD66b on granulocytes (au)	-0.268	$p = 0.462$

*adjusted for age, gender, history of hypertension and statin-use

Table 3

The effect of glycated hemoglobine on inflammatory markers after adjustment for group differences*

Dependent variable	β-coefficients	p-value
CRP (mg/L)	0.139	$p = 0.001$
Leukocyte count (x10^9/L)	0.036	$p = 0.013$
CD35 on monocytes (au)	0.010	$p = 0.570$
CD35 on granulocytes (au)	0.019	$p = 0.555$
CD11b on monocytes (au)	-0.048	$p = 0.320$
CD11b on granulocytes (au)	-0.131	$p = 0.139$
CD66b on granulocytes (au)	-0.012	$p = 0.262$

*adjusted for age, gender, history of hypertension and statin-use

Discussion

Although previous studies suggest increased leukocyte activation and systemic inflammation in non-obese diabetic patients when compared to non-diabetics, within our cohort of morbidly obese subjects, no differences were observed in leukocyte activation between diabetics and non-diabetics. Diabetics in our cohort did demonstrate higher CRP and leukocyte levels, which suggests a higher degree of systemic inflammation.

The leukocyte activation markers CD11b and CD66b reflect the early adhesion of leukocytes to the endothelium,[9] which is essential for the development of atherosclerosis and microvascular diabetic complications.[3] Since both obesity and T2DM are considered low-grade inflammatory diseases that affect micro- and macrovascular health, it was expected that the combination of obesity and T2DM would have an exaggerated effect on vascular health. Previous studies showed increased mortality rates in subjects with T2DM when BMI was increased, and within the different BMI groups, subjects with T2DM had higher mortality rates than non-diabetic subjects.[17-18] In the present study, cIMT and PWV were used as surrogate markers for atherosclerosis. In non-obese subjects, both cIMT and PWV are known to be increased in T2DM,[19-21] which is confirmed here in obese subjects. Inflammation is thought to significantly contribute to these changes. In our study, both CRP and leukocyte counts were associated with the presence of diabetes but not with vascular changes. Therefore, the differences in cIMT and PWV between morbidly obese diabetics and non-diabetics cannot be explained by differences in systemic inflammation and leukocyte activation.

It should be noted that the current study only investigates a small portion of all known inflammatory markers, with special interest in leukocyte activation. However, multiple mechanisms have been suggested to influence this low-grade systemic inflammation, such as the increased production of pro-inflammatory cytokines by adipose tissue[2] and the increased formation of reactive oxygen species and oxidative stress.[3] Dalmas et al.[2] investigated multiple and different markers of inflammation, such as hsCRP, interleukin 6, ICAM-1 and VCAM-1, in a group of

morbidly obese subjects. They did not differentiate between diabetic and non-diabetic subjects, but they did report a lack of correlation between inflammatory markers and cIMT in these obese subjects. cIMT was determined by changes in classic cardiovascular risk factors, such as hypertension and dyslipidemia. Values of cIMT and PWV are known to be determined primarily by age, gender, blood pressure and lipid profile.[22-25] The differences in cIMT and PWV found here could be explained by differences in these variables. Another limitation of our study is the lack of a lean control group to verify whether or not the markers of inflammation, as measured in the current study, are indeed increased in subjects suffering from morbid obesity.

Recent studies focus on the development of new therapeutics for T2DM and cardiovascular disease with special interest in lowering systemic inflammation.[26-27] In light of the results of the current study, these new therapeutics may not be the most appropriate therapy for T2DM in morbid obesity.

In conclusion, systemic inflammation and leukocyte activation in morbid obesity are not increased in subjects suffering from T2DM. The micro- and macrovascular changes seen in these patients are probably influenced by other factors, such as classic cardiovascular risk factors. Treatment of this specific patient group should likely focus not on the reduction of inflammation but on weight loss and the improvement of classic cardiovascular risk factors.

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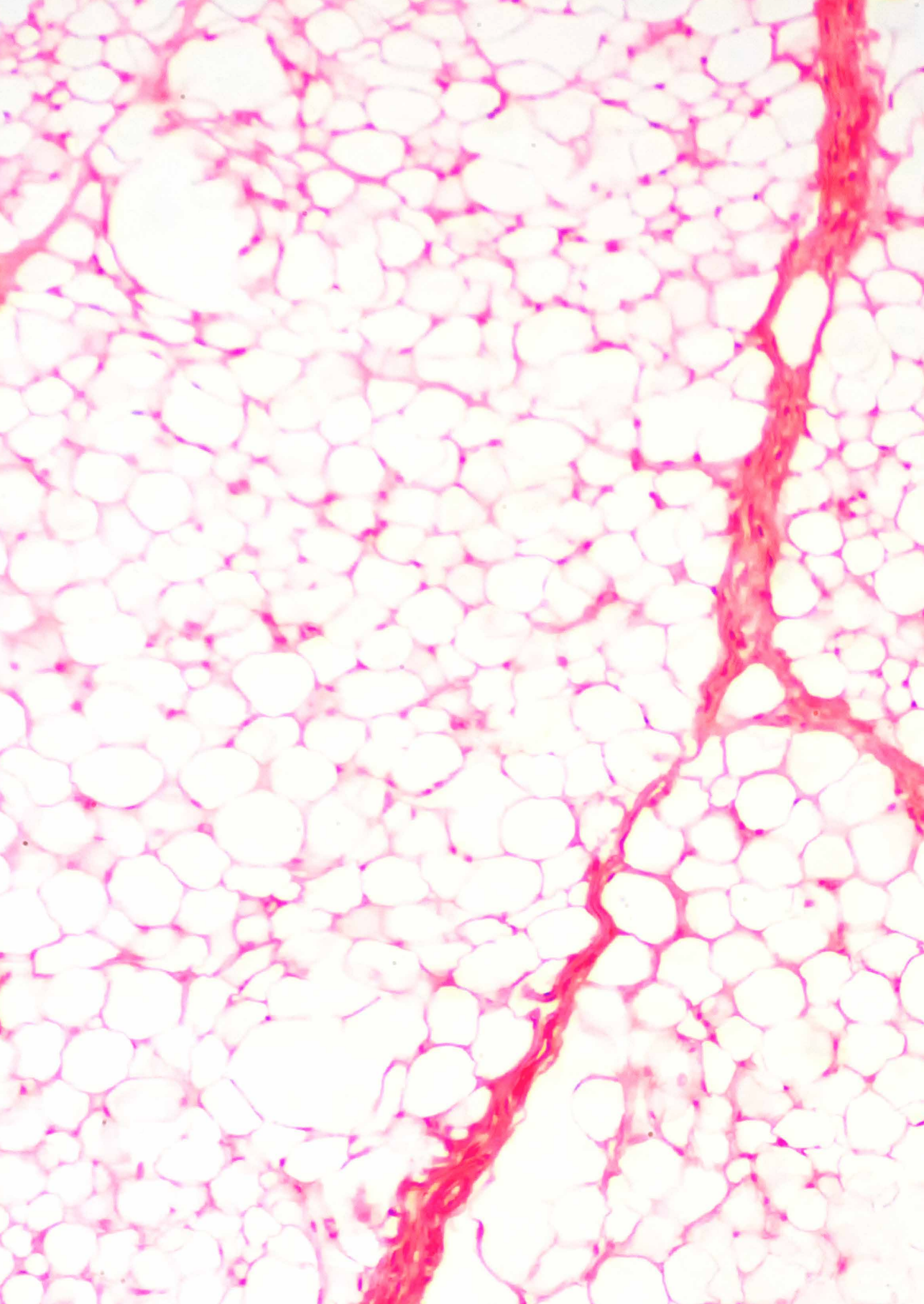
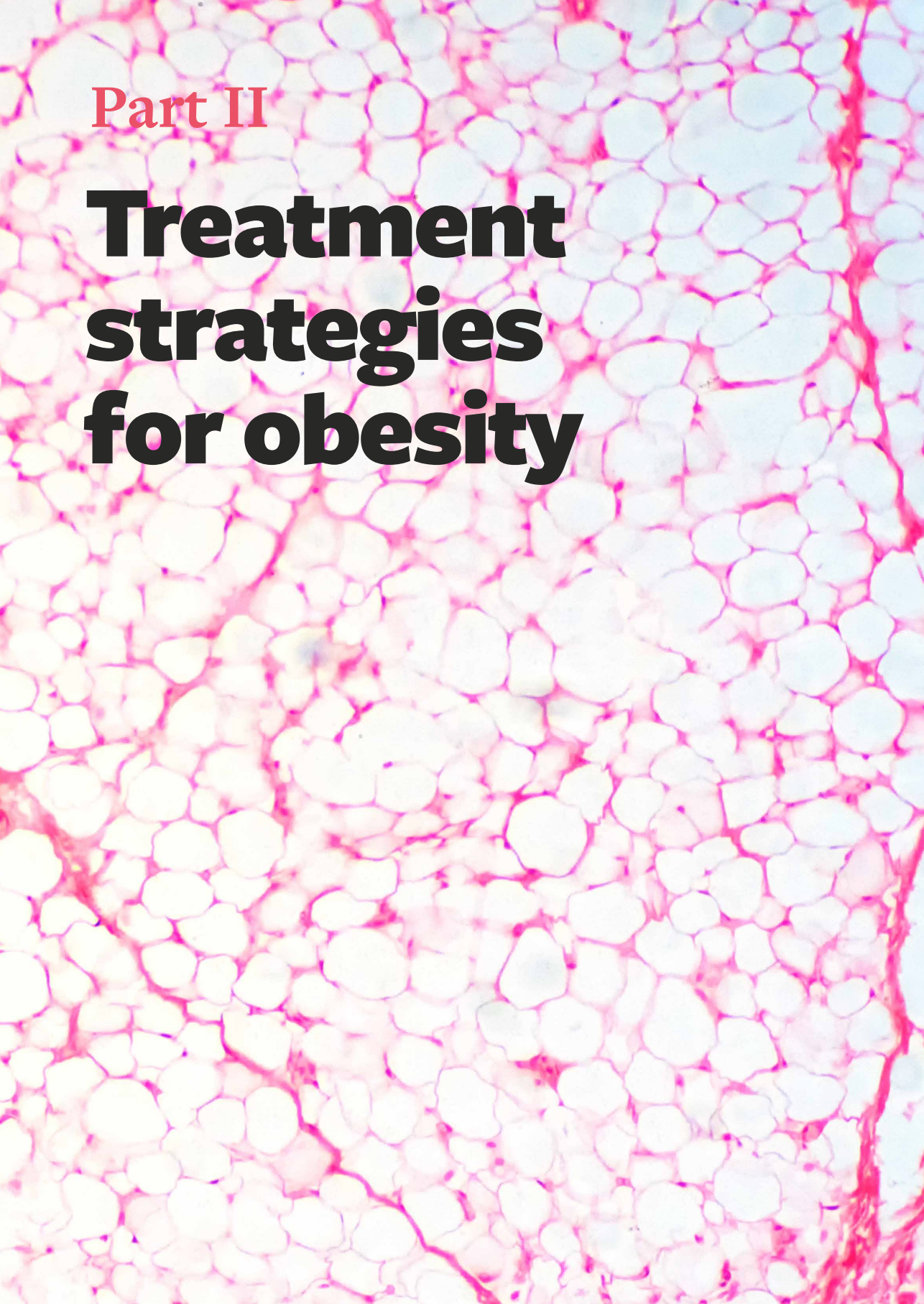
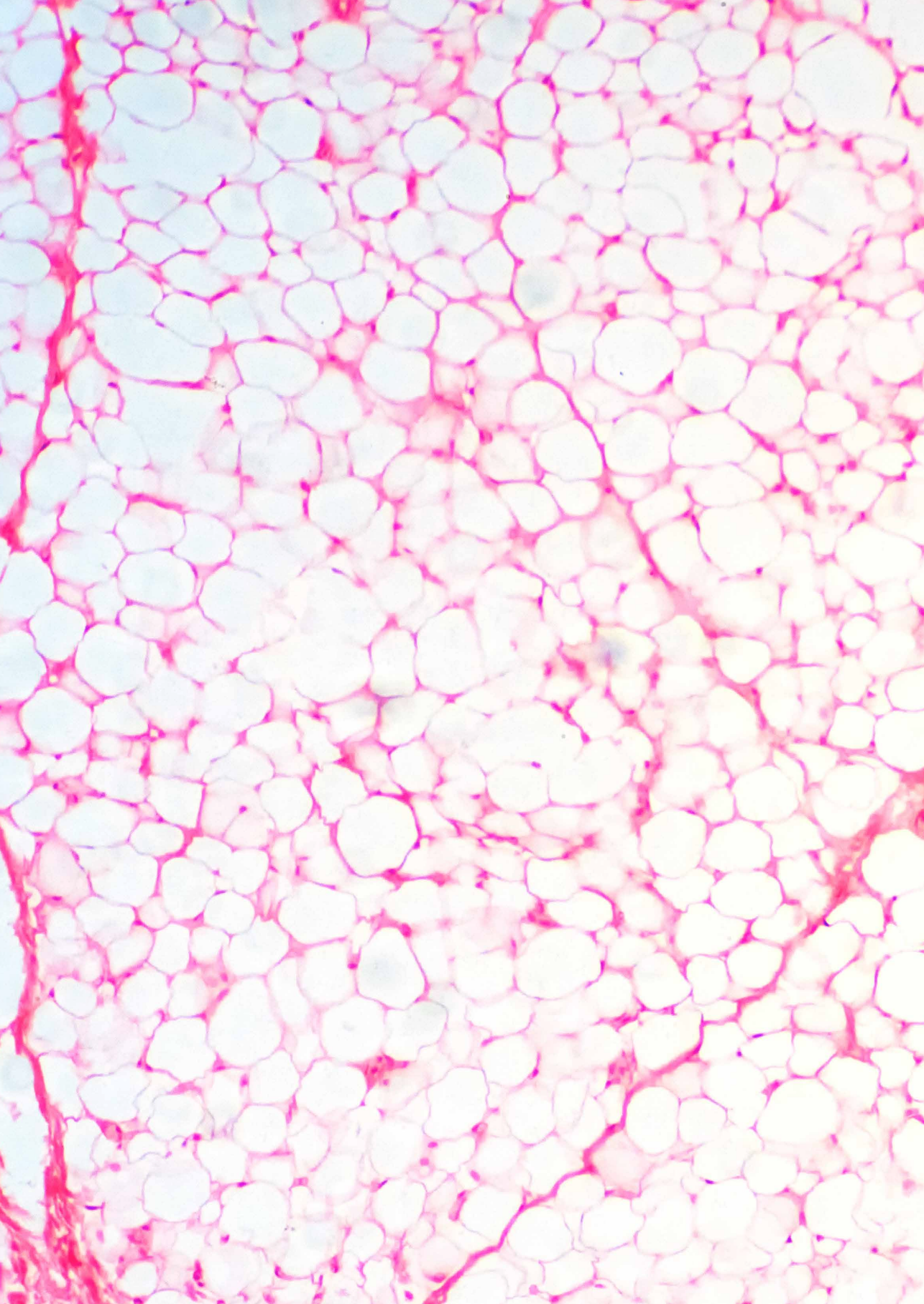


Part II

Treatment strategies for obesity





Chapter 6

Laparoscopic sleeve gastrectomy versus gastric bypass in late adolescents; what is the optimal surgical strategy?

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Abstract

Background

Interest in bariatric surgery in adolescents is increasing, since adolescent obesity equals increased health risks in adult life. To define the preferred procedure for a randomized controlled trial in adolescents, this study compares outcomes of LSG and LRYGB in late adolescence in our center.

Materials and methods

Data on baseline characteristics, operative details and follow-up were collected retrospectively in all patients (age 18–20 years) who underwent LSG or LRYGB in our clinic. Outcomes were analyzed using nonparametric tests.

Results

65 adolescents (54 female; median age 19 years) were included; 45 subjects underwent LSG; 20 patients underwent LRYGB.

Significant differences in percentage of excess weight loss (%EWL) were observed at 2-year follow-up; 69.4% in LRYGB (n = 6) versus 96.8% in LSG (n = 23), $p = 0.01$. No differences were observed in postoperative mortality, complication rate or resolution of comorbidities between both procedures.

Conclusions

LSG showed significantly better results than LRYGB in terms of %EWL after 2 years in this selected group of older adolescents. Considering these results in LSG patients and the theoretical advantages of LSG (normal diet options, preservation of an intact GI-tract, less vitamin disturbances and better quality of life), LSG may be an appropriate bariatric technique to perform in morbidly obese adolescents.

Introduction

Bariatric surgery is the only effective intervention to achieve substantial long-term weight loss and improvement of comorbidities[1,2] in adults. With the increasing prevalence of childhood and adolescent obesity[3–5] and their related health risks both at current age[6–8] as well as later in life,[4,9] early treatment is of major importance and morbidly obese adolescents are increasingly being considered for bariatric surgery. However, there is controversy regarding the ethics of bariatric surgery in adolescents, with questions on long-term safety and effectiveness of bariatric surgery in adolescents remaining unanswered.

The laparoscopic Roux-en-Y gastric bypass (LRYGB) is considered the gold standard procedure in adults, although the laparoscopic sleeve gastrectomy (LSG) has gained widespread popularity due to its good results in terms of weight loss, resolution of comorbidities,[4,10] quality of life[1] and a low complication rate.[4,11] LSG may be a safe alternative for LRYGB in adolescents, since the procedure keeps the gastrointestinal tract intact, resulting in no dumping, less malnutrition[5] and fewer vitamin disturbances.[12] Additionally, LSG allows secondary bariatric options in case of failure more easily than LRYGB. Early treatment of morbid obesity is thought to prevent many health risks, but what is the best surgical option for adolescents with morbid obesity?

In the Netherlands, legislation only allows surgeons to perform bariatric surgery in adolescents under the age of 18 years in study models. Our institute considers bariatric surgery for morbidly obese adolescents aged 15–18 years, comparing the effects of lifestyle intervention with bariatric surgery. The aim of the current study was to analyze the results of both LSG and LRYGB in older adolescents (18–20 years), and to extrapolate these results to the group 15–18 years old in order to determine the preferred bariatric technique in this specific patient group.

Materials and methods

Study population

This retrospective cohort study included all consecutive patients (aged 18–20 years) who underwent LSG or LRYGB in the bariatric clinic of the Sint Franciscus Gasthuis in Rotterdam, the Netherlands, between October 2006 and June 2014. In general, inclusion criteria for bariatric surgery are body mass index (BMI) ≥ 40 kg/m^2, or BMI ≥ 35 kg/m^2 with obesity-associated comorbidities, according to the multidisciplinary protocol.[13]

Surgical technique

Both LSG and LRYGB are performed with a five-trocar approach. LSG is, as previously described,[11] calibrated over a 34-Fr bougie, starting 2–4 cm proximal to the pylorus. LRYGB is created with a small pouch (15 cc), which is anastomized over 3 cm with a linear stapler to a 150 cm alimentary limb followed by an entero-enterostomy created with a 60 cm biliopancreatic limb, and clip or suture closure[14] of both mesenterial defects.

Allocation to a certain type of bariatric procedure occurred according to both patient's and doctor's preferences; extreme sweet eaters and patients suffering from gastro-esophageal reflux disease (GERD) were allocated to the LRYGB, since better results in terms of weight loss and postoperative complaints were expected in these patients.

Baseline characteristics

Baseline characteristics were collected at set time intervals according to our standard protocol: at the outpatient's preoperative screening, postoperative period (clinical phase), and follow-up at 3–6 months postoperatively and then annually. Weight (in kg) and BMI (in kg/m^2) were the main measurements for anthropometry. Additionally, weight loss was described as the percentage of excess weight loss (%EWL), using the following formula:
%EWL = (preoperative BMI – current BMI) / (preoperative BMI – 25) x 100%.

Data on present comorbidity and medication use were collected during all visits to the outpatient clinic during follow-up.

Statistical analysis

All analyses were performed using SPSS (PASW) 18.0 software (SPSS Inc., Chicago, Illinois, USA). The results of LSG were compared to the results of LRYGB. Baseline characteristics sex, smoking habit, alcohol use and ASA classification, as well as medical history, were described as a percentage of the total cohort. Other baseline characteristics were presented as median value. Differences between both procedures, LSG and LRYGB, were analyzed using nonparametric tests. Results were evaluated at a significance threshold of $p < 0.05$.

Results

The patient cohort consisted of 65 adolescents, of whom 45 underwent LSG and 20 LRYGB. In 10.3% of these patients, allocation to a certain procedure was based on patient characteristics, such as super obesity, GERD and extreme sweet eating behavior; in the rest of the patients, the type of procedure performed was based on the patient's preference. There were 11 men and 54 women, with a median age of 19 years [interquartile range (IQR) 19–20] and median BMI 44.8 kg/m^2 [IQR 41.8–49.4]). There was no difference in preoperative BMI in both groups (Table 1). Significant differences were observed in sex, with 100% female in LRYGB and 75.6% female in LSG ($p = 0.014$), and in surgical operation time: median surgical operation time was 71 minutes [IQR 51–86] in LRYGB and 47 minutes [IQR 37–57] in LSG ($p < 0.001$). Additional baseline characteristics are displayed in Table 1.

Reintervention, due to complications, was necessary in two patients: one in each group. The patient with LSG developed anastomotic leakage and was treated with laparoscopic drainage, stenting and eventually a reoperation in which a revision to LRYGB was performed. The patient with LRYGB developed a subphrenic hematoma, which required coiling of the splenic artery and laparoscopic drainage of an infected hematoma. None of the patients in this cohort died during the early postoperative phase or follow-up.

Table 1

Baseline characteristics in absolute numbers or median value, with its percentage or interquartile range, respectively, presented within brackets

	Total (n=65)	LSG (n=45)	LRYGB (n=20)	*p* -value*
Sex (%) female	54 (83.1%)	34 (75.6%)	20 (100%)	*p* = 0.014
Age (years)	19 (19-20)	19 (19-20)	19 (18.3-20)	*p* = 0.187
BMI (kg/m2)	44.8 (41.8-49.4)	44.8 (40.8-48.8)	45.0 (42.8-49.7)	*p* = 0.363
Waist circumference (cm)	136 (123-144)	134 (117-144)	137 (127-144)	*p* = 0.339
Medical history				
Type 2 diabetes	3 (4.6%)	2 (4.4%)	1 (5.0%)	*p* = 1.000
Hypertension	2 (3.1%)	2 (4.4%)	0 (0%)	*p* = 1.000
Dyslipidemia	3 (4.6%)	2 (4.4%)	1 (5.0%)	*p* = 1.000
GERD	6 (9.2%)	3 (6.7%)	3 (15.0%)	*p* = 0.361
Smoking				*p* = 0.135
Yes	25 (38.5%)	17 (37.8%)	8 (40.0%)	
No	36 (55.4%)	26 (57.8%)	10 (50.0%)	
Alcohol				*p* = 0.255
Occasionally	24 (36.9%)	15 (33.3%)	11 (55.0%)	
No	36 (55.4%)	25 (55.6%)	9 (45.0%)	
ASA classification				*p* = 0.420
ASA1	1 (1.5%)	1 (2.2%)	0 (0%)	
ASA2	30 (46.2%)	23 (51.1%)	7 (35.0%)	
ASA3	33 (50.8%)	20 (44.4%)	13 (65.0%)	
ASA4	1 (1.5%)	1 (2.2%)	0 (0%)	

* group differences were tested using nonparametric tests

In the overall adolescent study group, five patients (including three LRYGB patients) did not attend any follow-up visit. Median follow-up was 22 months [IQR 8–47] in the remaining 43 LSG patients and 18 months [IQR 11.5–28.5] in LRYGB patients. There was no significant difference between the length of follow-up between both groups ($p = 0.506$). Additional information on follow-up attendance is displayed in **Table 2**.

Table 2

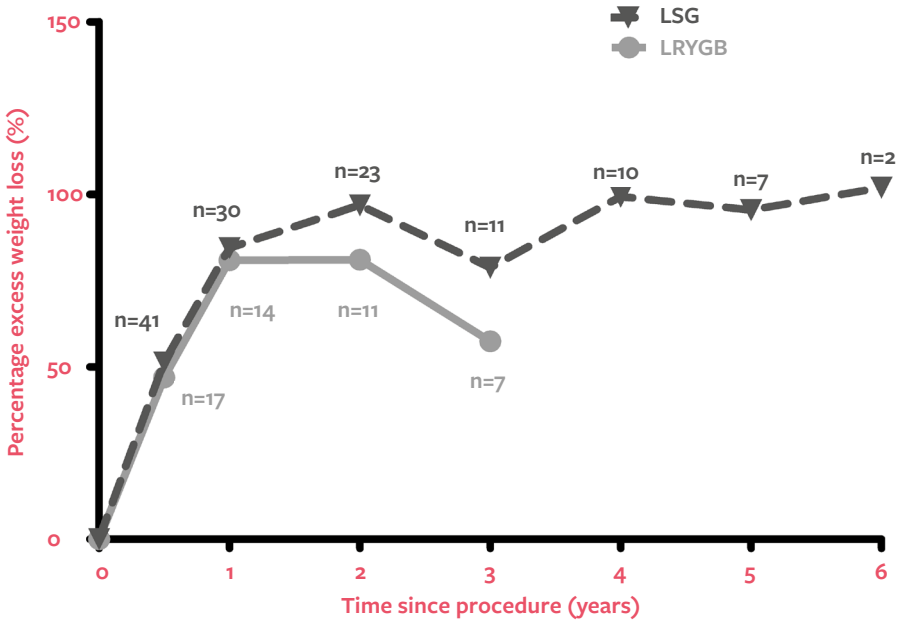
Number of subjects attending follow up in absolute numbers with its percentage presented within brackets

	Total (n=65)	Sleeve gastrectomy (n=45)	Gastric bypass (n=20)
Follow up 1 yr	45 (69.2%)	30 (66.7%)	15 (75.0%)
Follow up 2 yrs	34 (52.3%)	23 (51.1%)	11 (55.0%)
Follow up 3 yrs	18 (27.7%)	11 (24.4%)	7 (35.0%)

The parameter %EWL showed a significant difference between both groups after 2 years of follow-up. Median %EWL was 81.0% [IQR 36.3–85.0] in the LRYGB group (n = 11) and 96.8% [IQR 85.2–111.2] in the LSG patients (n = 23), $p = 0.007$. Furthermore, a significant difference in BMI was observed after 2 years of follow-up, with a BMI of 29.7 kg/m² [IQR 27.0–33.6] after LRYGB and 25.7 kg/m² [IQR 23.3–27.9] after LSG ($p = 0.012$). Additional follow-up results are displayed in Figure 1 and Table 3.

Figure 1

Comparison of percentage excess weight loss in 18- to 20-year-old late adolescents after laparoscopic Roux-en-Y gastric bypass (LRYGB) and laparoscopic sleeve gastrectomy (LSG) during follow-up.



Fourteen patients presented preoperatively with obesity-related comorbidities, such as hypertension, type 2 diabetes and dyslipidemia; none of them had more than one comorbidity. All comorbidities were resolved one year postoperatively.

Table 3

Follow-up in absolute numbers or median value, with its percentage or interquartile range, respectively, presented within brackets

	Total (n=65)	LSG (n=45)	LRYGB (n=20)	*p* -value*
Duration of surgery (min)	51 (40-67)	47 (37-57)	71 (51-86)	*p* < 0.001
Hospital stay (days)	3 (2-4)	3 (2-4)	2 (2-3)	*p* = 0.013
BMI (kg/m2)				
Baseline	44.8 (41.8-49.4)	44.8 (40.8-48.8)	45.0 (42.8-49.7)	*p* = 0.363
1 yr follow-up	28.7 (26.8-31.4)	28.3 (25.2-30.8)	29.7 (27.1-35.1)	*p* = 0.125
2 yr follow-up	26.9 (24.1-30.8)	25.7 (23.3-27.9)	29.7 (27.0-33.6)	*p* = 0.012
3 yr follow-up	30.6 (27.5-37.7)	29.4 (24.7-35.9)	33.2 (28.0-45.6)	*p* = 0.247
EWL (%)				
1 yr follow-up	81.6 (70.2-90.9)	84.4 (71.6-99.4)	80.9 (55.9-88.2)	*p* = 0.165
2 yr follow-up	89.8 (75.7-105.7)	96.8 (85.2-111.2)	81.0 (51.5-88.1)	*p* = 0.007
3 yr follow-up	75.1 (52.2-90.0)	78.7 (64.6-103.2)	57.4 (36.3-85.0)	*p* = 0.165
Complications				
Early re-admission	8 (12.3%)	5 (11.1%)	3 (15.0%)	*p* = 0.693
Early re-intervention	2 (3.1%)	1 (2.2%)	1 (5.0%)	*p* = 1.000
Late re-admission	11 (16.9%)	8 (17.8%)	3 (15.0%)	*p* = 1.000
Late re-interventions	9 (13.8%)	7 (15.6%)	2 (10.0%)	*p* = 0.491
Revisional procedure	3 (4.6%)	2 (4.4%)	1 (5.0%)	*p* = 1.000
Cholecystectomy	7 (10.8%)	5 (11.1%)	2 (10.0%)	*p* = 0.693

* group differences were tested using nonparametric tests

Approximately 86% of all subjects did not report any postoperative complaints. The most commonly reported complaints were fatigue (n = 4) and reflux (n = 4). Of all subjects reporting reflux postoperatively, one LRYGB patient already experienced reflux preoperatively. The other three patients underwent LSG and developed reflux afterwards.

Failure of bariatric surgery, defined as %EWL < 50% or BMI > 35 kg/m², occurred in one patient in each group; the LRYGB patient underwent distalization of the bypass 35 months after the primary procedure, the LSG patient underwent revision into a LRYGB 36 months after the first procedure.

Discussion

Bariatric surgery in adolescents is thought to be the cornerstone of obesity treatment,[1,2,15] but data on adolescents bariatric surgery is scarce.[16] This study investigated the results of the gold standard LRYGB,[1,9,10] which is most commonly described in adolescents, with the relatively newer LSG.[17] Only few studies evaluated the effects of LSG in adolescents, but these results are promising, not only in terms of weight loss, safety and comorbidity resolution,[18] but also in terms of self-esteem improvement.[19] However, most studies describing LSG in adolescents have small study samples,[19,20] short follow-up,[10,19–22] or did not compare results of LSG with results of the gold standard LRYGB.[10,19,20] An overview of all studies is given in Table 4. Furthermore, a recent review and meta-analysis on different bariatric procedures in adolescents,[3] showed good results for LSG in terms of weight loss, complication rate and resolution of comorbidities.

In this patient cohort, LSG showed significant better results than LRYGB in terms of %EWL 2 years after the procedure; weight loss is approximating 100% %EWL 2 years after LSG. Unfortunately, long-term results in the LRYGB group are lacking in this study, due to small numbers and a short follow-up. However, our results on %EWL and BMI changes in LRYGB are comparable with other studies[23] (Table 4).The results of LSG in terms of %EWL appear to be better in this cohort than most of the other studies and are similar to the results of Raziel et al.[19] However, conclusions on superiority cannot be drawn on results in %EWL alone, since this is influenced by the preoperative weight and the definition of ideal weight.[24] Concerning the studies with lower %EWL, in our hospital relatively small gastric bypass pouches and narrow gastric sleeves are created. Although data on exact pouch and sleeve volume are not available, it can be hypothesized that there is reluctance to create a small pouch or sleeve in this young population, in order to prevent complications,[25] such as leakage, stenosis and deficiencies. As a result, the procedure may become less successful in terms of weight loss.

Table 4

BMI and excess weight loss changes in adolescents LSG in different studies

	Baseline characteristics					1 year follow-up		
Article	No. of subject	No. of Procedures	Control intervention	Mean age	Preoperative BMI	BMI	%EWL	No. of subject
Al-Sabah[32], 2015	135	135	none	19 (12-21)‡	48.5	32.0	75.2%	54 (40%)
Aldaqal [22], 2013	64	32	healthy subjects	15.2 (13-17)	49.6	29.3	78.8%	32 (100%)
Alqahtani [4], 2012	108	108	none	13.9 (5-21)	49.6	32.4	61.3%	41 (38.0%)
Boza [33], 2012	51	51	none	<19	38.5	25.2	96.2%	40 (78.4%)
Cozacov [34], 2014	18		LRYGB					
LRYGB		8		18.1	48.5	28.9	87.9% †*	6 (75%)
LSG		10		17.1	46.2	32.5	64.9% †*	9 (90%)
Lennerz [23], 2014	365		LRYGB, LAGB, GB, GP and BPD					
LRYGB		116		19.6 (16-21)	49.7	33.3	69.8% *	50 (43.1%)
LSG		78		18.5 (8-21)	50.8	35.4	61.8% *	37 (47.4%)
Nadler [20], 2012	23	23	none	17.3 (14-19)	52.0	39.0	40%	9 (39.1%)
Nocca [35], 2014	61	61	none	19.5 (18-20)	46.7	unknown	66.7%	50 (81.9%)
Raziel [19], 2014	32	32	none	16.7 (14-18)	43.2	unknown	81.7%	15 (46.8%)
van Mil, 2014	65		LRYGB					
LRYGB		20		19 (18-20)	45.0	29.7	80.9%	14 (70.0%)
LSG		45		19 (18-20)	44.8	28.3	84.5%	30 (66.7%)

† no data available on 1 year follow-up. Data shown for median follow-up of 4 years

** calculated using the 85th percentile on the CDC growth charts*

‡ *median and range*

LSG; laparoscopic sleeve gastrectomy. LRYGB; laparoscopic Roux en Y gastric bypass. LAGB; laparoscopic adjustable gastric banding. GB; gastric balloon. GP; gastric pacemaker. BPD; biliopancreatic diversion.

The number of comorbidities at baseline was very small, and therefore no statement can be made on the difference between LSG and LRYGB in terms of resolution of comorbidities. However, other studies have described good results of LSG on comorbidity resolution in adolescents,[19] as well as in LRYGB.[26] It is generally accepted that weight loss in itself can provide metabolic improvements and various theories are suggested to cause these changes.[27,28]

Our study results complement other studies on the conclusion that LSG is a safe procedure with a similar[10,20,23] or even reduced[9] complication rate compared to LRYGB. Additional advantages of LSG, compared to LRYGB, may be the easier application of single port techniques, with cosmetically better results and possible positive effects on feelings of shame towards peers, as well as the opportunity to revise the procedure to LRYGB after failure in terms of weight loss or GERD.

2 year follow-up			3 year follow-up			Maximum follow-up	
BMI	%EWL	No. of subject	BMI	%EWL	No. of subject	Duration of follow-up	No. of subjects at maximum follow-up
30.8	78.6%	46 (34.1%)	---	---	---	24+	46 (34.1%)
---	---	---	---	---	---	12	32 (100%)
31.8	62.3%	8 (7.4%)	---	---	---	24	8 (7.4%)
26.3	92.9%	34 (66.7%)	---	---	---	24	34 (66.7%)
---	---	---	---	---	---	60	2 (25%)
---	---	---	---	---	---	60	1 (10%)
---	---	---	---	---	---	30	10 (8.6%)
---	---	---	---	---	---	30	8 (10.3%)
---	---	---	---	---	---	12	9 (39.1%)
unknown	78.4%	32 (52.4%)	---	---	---	48	unknown
unknown	71.0%	8 (25.0%)	unknown	75.9%	4 (12.5%)	60	2 (6.3%)
29.7	81.0%	11 (55.0%)	33.2	57.4%	7 (35.0%)	45	2 (13.3%)
25.7	96.8%	23 (51.1%)	29.4	78.7%	11 (24.4%)	72	1 (2.5%)

Within this cohort, only a small fraction of subjects reported postoperative complaints, such as fatigue and reflux. Gastro-esophageal reflux de novo only occurred in subjects who underwent LSG (n = 3). However, due to small numbers, especially in the LRYGB group, no significant differences between both groups were found. Current literature[29] expresses concerns on the development or aggravation of reflux, although data in different studies are contradictory. Concerning both reflux as well as other postoperative complaints, data may be missing in this cohort, since this is a retrospective cohort study. Ideally, data on subjective outcomes should be objectified by the use of standardized questionnaires, such as the GerdQ for gastro-esophageal reflux, in order to make statements on the extend of the complaints.

In general, nutritional complications, dumping and chronic diarrhea are commonly described after LRYGB, but not after LSG. However, micronutrient deficiencies are observed after both procedures,[12,30] even though more profoundly

after LRYGB. These results emphasize the need for long-term follow-up results after bariatric surgery and it may be even more important in adolescents than adults, since they are dependent on micronutrients for their development and growth.

Unfortunately, follow-up in adolescent bariatric patients is poor. In general, Stefater et al.[30] expressed their concerns in the follow-up of adolescents. In our clinic, patients are expected to attend follow-up at 6 months, 1 year and annually thereafter. In our cohort, 12.7% of all adolescents never attended any face-to-face follow-up after the procedure, compared to 3.6% of all other bariatric patients, aged ≥ 20 years. An eventual lost-to-follow-up rate of 5.5% in this cohort was reached by telephonic consultations. However, data collected by telephone may be less reliable. Since bariatric support group attendance can positively influence the long-term outcome of bariatric surgery and increase follow-up attendance,[31] group counseling may be even more effective and important in adolescents.

Obviously, the small sample size and the imbalanced number of subjects at baseline are limitations of this study. In the LRYGB group only seven subjects attended follow-up three years postoperatively. Furthermore, allocation to a specific procedure, based on patient characteristics, can bias the results of this study. Approximately 10% of all subjects were allocated to a specific procedure based on patient characteristics. Once these subjects were excluded from analyses, results of the study did not change. Therefore, it can cautiously be concluded that the allocation procedure did not influence the results in these older adolescents. Nevertheless, since this study is a non-randomized and retrospective study, this selection bias cannot be completely excluded.

In conclusion, bariatric surgery seems to be an effective method for weight loss in morbidly obese late adolescents. Considering the weight loss results of LSG in our patient cohort as well as in other studies and the additional theoretical advantages of LSG (improved quality of life and preservation of an intact gastrointestinal tract), LSG may be an appropriate bariatric technique to perform in obese adolescents. Unfortunately, since results of LSG in adolescents have only

been described in small numbers worldwide, more prospective data are needed on long-term effects and safety, resolution of morbidity, improvement in quality of life and total costs. When results of LRYGB and LSG in adolescents would be compared in a randomized controlled trial and results in terms of weight loss, complications and comorbidity resolution would be equal, the theoretical advantages of the LSG would make this procedure the procedure of preference in this young age group.

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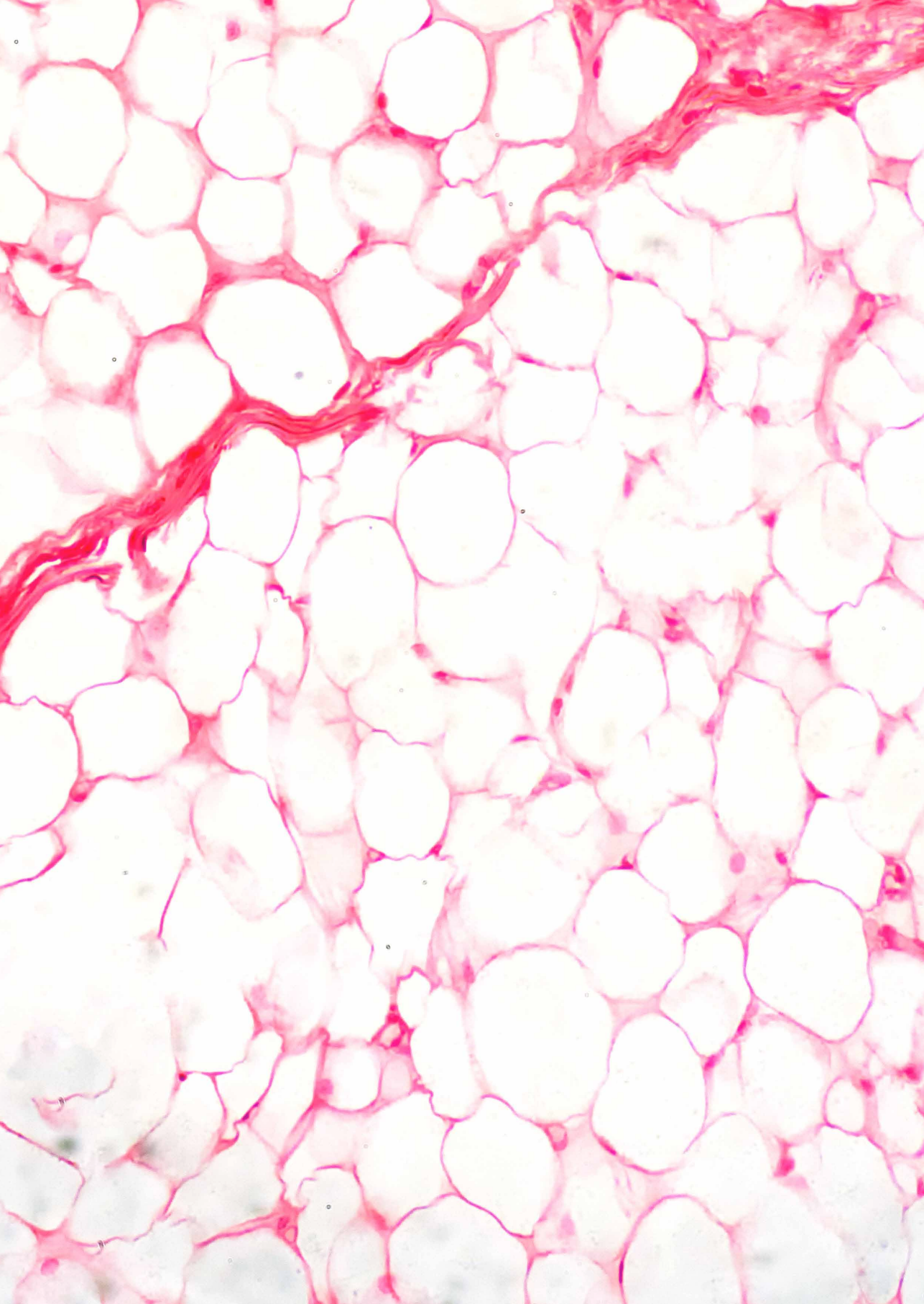

Chapter 7

Results of implementing an enhanced recovery after bariatric surgery (ERABS) protocol

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Abstract

Background

With the increasing prevalence of morbid obesity and healthcare costs in general, interest is shown in safe, efficient and cost-effective bariatric care. This study describes an enhanced recovery after bariatric surgery (ERABS) protocol and the results of implementing such protocol on procedural times, length of stay in hospital (LOS) and the number of complications, such as readmissions and reoperations.

Materials and methods

Results of implementing an ERABS protocol were analyzed by comparing a cohort treated according to the ERABS protocol (2012–2014) with a cohort treated before implementing ERABS (2010–2012). Differences between both cohorts were analyzed using independent T-tests and chi-squared tests.

Results

A total of 1,967 patients (mean age 43.3 years, 80% female) underwent a primary bariatric procedure between 2010–2014, of which 1,313 procedures were performed after implementation of ERABS. A significant decrease of procedural times and a significantly decreased LOS, from 3.2 to 2.0 nights ($p < 0.001$) were seen after implementation of ERABS. Significantly more complications were seen post-ERABS (16.1% versus 20.7%, $p = 0.013$), although no significant differences were seen in the number of major complications.

Conclusions

Implementation of ERABS can result in shorter procedural times and a decreased LOS, which may lead to more efficient and cost-effective bariatric care. The increase in complications was possibly due to better registration of complications.
The main goal of an ERABS protocol is efficient, safe and evidence-based bariatric care, which can be achieved by standardization of the total process.

Introduction

With the rising prevalence of obesity[1] and obesity-related diseases,[2-3] the obesity-related healthcare costs have become a considerable economic burden.[4] Bariatric surgery is the most effective treatment for morbid obesity,[5-7] resulting in sustainable weight loss and effective treatment of obesity-related diseases.[6-8] In search of efficient and cost-effective healthcare, enhanced recovery after surgery (ERAS) protocols (or fast-track protocols) have been developed for different types of abdominal procedures.[9-11] More recent interest has been shown in enhanced recovery after bariatric surgery (ERABS) protocols, although data in the literature is currently scarce.[12-17] The combination of the increasing number of bariatric procedures worldwide and the specific perioperative difficulties and risks for this particular population[13,15] makes this type of surgery highly eligible for ERAS protocols. Implementation of evidenced based interventions and standardization of bariatric care can increase efficiency and cost-effectiveness in these procedures,[14] without the loss of safety.

This study describes the ERABS protocol for both laparoscopic Roux-en-Y gastric bypass (LRYGB) and laparoscopic sleeve gastrectomy (LSG) in a large volume teaching hospital in Rotterdam, the Netherlands and the results of implementing an ERABS protocol on procedural times, length of stay in hospital and number of complication and reoperations.

Materials and methods

The Sint Franciscus Gasthuis in Rotterdam, the Netherlands, has a bariatric clinic, which performs mainly LSG and LRYGB procedures and has been a European training location for ERABS programs since 2013. The ERABS protocol was introduced in this clinic at the beginning of 2012.

Prospectively collected outcome data of all consecutive cases that underwent primary LRYGB or LSG from January 2010 to June 2014 in the Sint Franciscus

Gasthuis were collected and analyzed. Since the ERABS protocol was introduced in 2012, all patients treated between January 2010 and December 2011 are considered "pre-ERABS". This pre-ERABS protocol has previously been published by Elte et al.[18] All patients treated from January 2012 until June 2014 are considered "post-ERABS".

The primary outcome parameter is length of stay in hospital (LOS) and secondary outcomes are procedural times, such as surgical time, the number of readmissions and reoperations within 30 days and number of complications within 30 days. Thirty-day complications were recorded and graded according the Clavien–Dindo classification.[19,20]

All analyses were performed using SPSS (PASW) 18.0 software (SPSS Inc., Chicago, Illinois, USA). Categorical data were described as percentage of the total cohort. Continuous variables were presented as mean ± standard deviation (SD). Differences between pre-ERABS and post-ERABS in continuous data were analyzed using independent T-tests. The differences in categorical data were analyzed using the chi-squared test. 95% confidence intervals were calculated of all procedural times. All results were evaluated at a significance threshold of $p < 0.05$.

The Sint Franciscus Gasthuis ERABS protocol

The team

In order to achieve standardization of the treatment process, the ERABS protocol has been composed by a multidisciplinary team, that consisted of delegates from all involved departments.[21] The protocol and possible adjustments to this protocol are discussed within this team on a monthly basis. Decisions are made on an evidence-based, cost-effective basis and consensus on all aspects needs to be reached within the team. All patients are treated according the ERABS protocol; there is no preselection.

Workup for bariatric surgery

Eligibility for bariatric surgery is assessed using the European IFSO criteria.[22] When patients meet the criteria and attended the mandatory bariatric information

evening, they will be scheduled for one-stop-shop workups. These workups are divided into several grouped appointments. The first workup is called intake day, on which the patient is screened by the bariatric nurse and the psychologist. The second workup is analysis day. This day includes screening by the internist, the dietician, the physiotherapist and, when necessary, the pulmonologist. After approval for surgery, the patients are scheduled for the third one-stop-shop workup, called planning day. During this day, the patient will be screened by the surgeon and the anesthesiologist and the operation will be planned by the responsible nurse. This structure ensures comprehensive provision of information.

Mandatory weighing is performed one week prior to surgery. Since weight loss can decrease perioperative risks, weight gain prior to surgery is prohibited and weight loss is stimulated. Surgery will be postponed when patients do not lose any weight.

Type of surgery

LRYGB is recommended to patients, who suffer from severe gastro-esophageal reflux disease (GERD) or type 2 diabetes (T2DM) or patients who show extreme sweet eating behavior. In patients with a BMI > 60 kg/m², large incisional hernias, expected severe small bowel adhesions, Crohn's disease or patients listed for kidney transplantation the LSG is the recommended procedure. Otherwise, the procedure of the patient's preference will be performed.

Preoperative care

Patients will be trained to self-administer a daily dose of low molecular weight heparin (LMWH) subcutaneously (i.e. 5,000 IE dalteparin), starting on the evening before surgery and continued to 4 weeks postoperatively. Intake of solid food is allowed up to 6 hours prior to surgery and intake of clear fluids up to two hours prior to surgery. All patients are admitted to the hospital on the day of surgery.

In case of a history of deep venous thrombosis (DVT) or pulmonary embolism (PE), anti-embolism stockings are provided before transportation to the OR. Patients are required to urinate before transportation to the OR to abandon need for urine catheters. Patients receive an intravenous line on the holding.

No sedative premedication is given to allow each patient to make transfers from his own bed onto the operation table and vice versa. High-risk patients (i.e. patients with obstructive sleep apnea syndrome, DM or superobese patients) are scheduled first on the OR to allow longer postoperative monitoring at recovery.

Perioperative management

Fifteen minutes before surgery, the patient receives intravenous antibiotics, analgesia and anti-emetics (**Figure 1**).[23] The patient is connected to a blood pressure cuff, EKG leads and a pulse oximeter, which remain connected throughout all preoperative procedures to assure maximum efficiency.

Positioning on the OR table is done while the patient is awake, in order to prevent pressure ulcers or neural injuries.[24] The legs are fixed with soft reusable leg fixator bands. The patients head is positioned on a special head elevated laryngoscopy position cushion[25] to maximize sniffing position and facilitate mask ventilation and intubation.

Throughout the procedure, patients are monitored using a Bispectral Index, applied to the patient's forehead.[26] Anesthetic induction and surgical preparation of the patient are performed simultaneously. After preoxygenation[27] for 3 minutes, the protocol, depicted in **Figure 1**, is followed for induction of anesthesia. Rocuroniumbromide (30–40 mg) is administered after the patient is sufficiently anesthetized, using the wink reflex to confirm the sleeping state. Patients are intubated 2–3 minutes after administration and anesthesia is maintained according to the flow-chart (**Figure 1**). Since desflurane and remifentanil are non-lipophil anesthetic agents,[28] quick washout and awakening after termination can be ensured in this particular population.

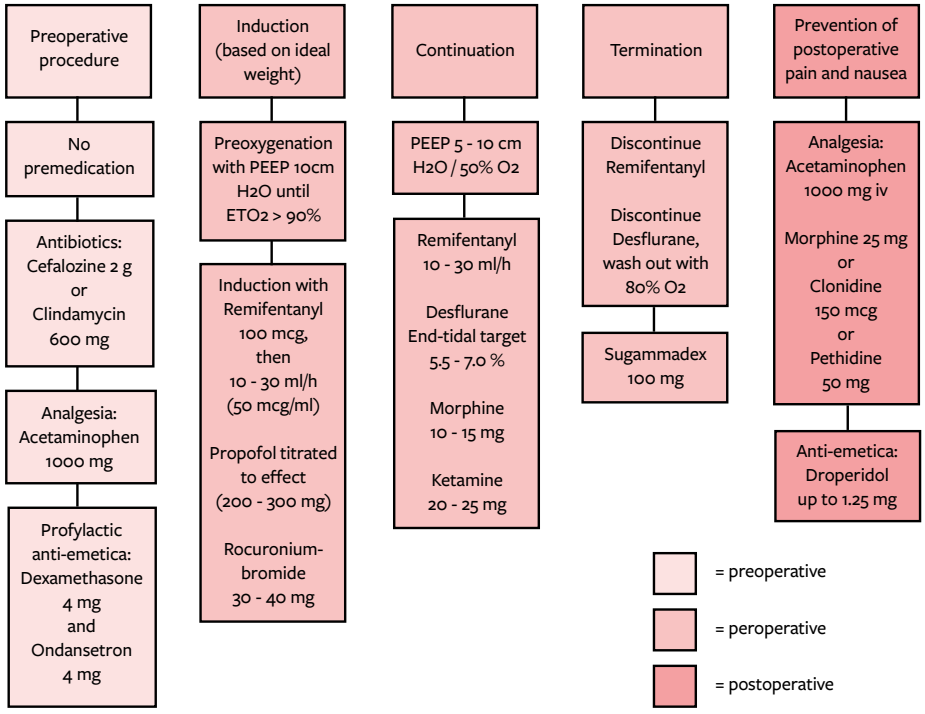
Both surgical procedures are standardized in detail; the LRYGB procedure was previously described by Leiffson et al.[29] and the LSG by Gadiot et al.[30] Intraoperative blood loss is managed with clips with a low threshold, since intra- and postoperative bleeding prolongs recovery.

Termination of anesthesia is achieved by discontinuing desflurane and remifentanil and administrating sugammadex to reverse residual neuromuscular block.[31] The tube is removed after opening the eyes and adequate respiration is assured. The patient is asked to slide over from the operation table into their bed in order to achieve early ambulation.[32]

All patients are transferred to the recovery room for postoperative monitoring and will be treated for pain and nausea[23] according the protocol (**Figure 1**). The patients are discharged to the wards, preferably within 2 hours postoperatively. Standardized pain protocol includes four times daily 1,000 mg acetaminophen and six times daily 10–15 mg morphine intramuscular, when required, for maximally 24 hours.

Figure 1

The ERABS anesthesia protocol



Postoperative care at the ward

None of the patients is routinely admitted to the ICU, since it increases the risk of DVT/PE, as patient's mobility is compromised due to extra lines and catheters.[33] When patients return to the ward, they are directly encouraged to drink full liquid diet and to ambulate, since early mobilization decreases the incidence of DVT.[34,35]

Within 24 hours postoperatively, the standardized postoperative analgesia protocol will be changed into four times daily 1,000 mg of acetaminophen and three times daily 50 mg of tramadol, if necessary. Caution is advised in prescribing NSAIDs, due to the gastrointestinal side effects.[36] Adequate analgesia is highly important for enhanced recovery, since it supports early mobilization and thereby decreases the incidence of DVT/PE and atelectasis.[37] Postoperative nausea is preferably treated with a single dose of 4 mg ondansetron.

All patients with drug dependent T2DM can decrease the dosage of the anti-diabetic medication by 50% immediately after surgery. Blood glucose levels are monitored closely. Intravenous fluid administration is calibrated on urine production, with an accepted minimum average production of 50 ml per hour. An overload of intravenous fluids can delay gut function activation and thereby prolong hospital stay.[38]

When patients meet all discharge criteria (Table 1), they will be discharged one day postoperatively. The bariatric nurse specialist provides the patients with information on diet, exercise, medication, vitamin and mineral supplements, LMWH, proton pump inhibitors and alarm symptoms, prior to discharge. Additionally, the patient will receive written instructions.

Table 1

Discharge criteria	
Anamnesis	
Pain	VAS-score < 4
Nausea	No complaints of nausea or vomiting
Intake	> 1 L of fluids within 24 h
Mobilization	Adequate mobilization
Calf pain	No complaints of calf pain
Well being	Patient feels confident about discharge
Physical examination	
Abdomen	No abdominal tension
Fever	Body temperature < 38°C
Heart rate	Frequency < 100 bpm
Oxygen saturation	O2Sat > 95%
Drain production	Production < 30 ml/24h
Laboratory results	
Hemoglobine	Postoperative decrease < 2mmol/L
Leucocyte count	Leucocytes < 14 x 10^9/L
CRP	CRP < 100 mg/L

Outpatient follow-up

Patients are advised to maintain on a full liquid diet for two weeks, postoperatively. Proton pump inhibitors, in a daily dose of 40 mg esomeprazole, are continued for 6 weeks. One week postoperatively, the bariatric nurse will contact all patients to monitor their recovery. Follow-up visits with the surgeon are scheduled 8 weeks and 1 year postoperatively. Follow-up visits with the internist are scheduled after 4 months and then annually.

Results

Between January 2010 and June 2014, 2,126 consecutive patients received bariatric surgery in our bariatric unit. Ten patients were excluded from analysis because the bariatric procedure was performed simultaneously with a different major procedure. Of the remaining 2,116 patients, 1,967 (93.0%) were primary procedures and 149 (7.0%) were revisions. In all primary procedures, 917 (46.6%) LRYGB procedures were performed, against 1,050 (53.4%) LSG procedures. The number of patients in the pre- and post-ERABS period is specified in **Table 2**.

Table 2

No. of procedures between January 2010 and June 2014

	Total	Pre-ERABS	Post-ERABS
No. Of procedures	2116	721	1395
Primary procedures	1967 (93.0%)†	654 (90.7%)†	1313 (94.1%)†
Primary LSG	1050 (53.4%)*	417 (63.8%)*	633 (48.2%)*
Primary LRYGB	917 (46.6%)*	237 (36.2%)*	680 (51.8%)*
Revisional procedures	149 (7.0%)†	67 (9.3%)†	82 (5.9%)†

† percentage of total no. of procedures

* percentage of no. of primary procedures

Table 3

Baseline characterictics in mean (±SD) or absolute number (percentage)

	Before ERABS (n=654)	After ERABS (n=1313)	*p* -value
Age*	44.2 (±11.0)	42.9 (±10.8)	$p = 0.015$
Sex† Female	524 (80.1%)	1064 (81.0%)	$p = 0.628$
Height*	1.69 (±0.09)	1.69 (±0.09)	$p = 0.212$
BMI*	45.6 (±5.89)	44.3 (±5.45)	$p < 0.001$
Waist circumference*	132 (±14.8)	135 (±13.3)	$p < 0.001$
Medical History			
Type 2 Diabetes†	163 (24.9%)	307 (23.4%)	$p = 0.450$
Hypertension†	226 (34.6%)	366 (27.9%)	$p = 0.002$
Hyperlipemia†	124 (19.0%)	220 (16.8%)	$p = 0.225$
COPD†	27 (4.1%)	57 (4.3%)	$p = 0.826$
OSAS†	34 (5.2%)	115 (8.8%)	$p = 0.005$
GERD†	70 (10.7%)	298 (22.7%)	$p < 0.001$
Abdominal surgery†	213 (32.6%)	433 (33.0%)	$p = 0.856$
Current smoker†	147 (23.0%)	335 (25.8%)	$p = 0.186$

* p-values were measured using independent T-tests

† p-values were measured using Chi-squared tests

The prevalence of hypertension, age and BMI were significantly higher in the pre-ERABS group, while obstructive sleep apnea syndrome and GERD were more frequently present in the post-ERABS patients. Other baseline characteristics are described in Table 3.

Complications and readmissions

During admission, 93 subjects (4.7%) developed a complication of any kind, of which 48 subjects (2.4%) developed major complications, with a Clavien–Dindo classification of 3a or higher. Three hundred and two patients (15.4%) revisited the outpatient or emergency department within 30 days postoperatively. One hundred and forty-seven patients (7.5%) were readmitted due to complications. Of all readmissions, 50 patients (2.5%) required reoperation. Detailed information on complications, readmissions and reoperations is listed in Tables 4 and 5. The number of early readmissions, within 48 hours after surgery, were not statistically significant different between both cohorts.

Table 4
Complications during admission

	Before ERABS n = 654	After ERABS n = 1313	*p* -value*
Complication rate during hospital stay	32 (4.9%)	65 (5.0%)	*p* = 0.956
Wound infection	1 (0.2%)	2 (0.2%)	*p* = 0.998
Abces or hematoma	4 (0.6%)	8 (0.6%)	*p* = 0.995
Bleeding which required transfusion or intervention	14 (2.1%)	24 (1.8%)	*p* = 0.632
Perforation	1 (0.2%)	6 (0.5%)	*p* = 0.286
Anastomotic leakage	2 (0.3%)	9 (0.7%)	*p* = 0.288
Anastomotic stenosis	0 (0%)	1 (0.1%)	*p* = 0.480
Sepsis	2 (0.3%)	9 (0.7%)	*p* = 0.288
Cardiac complications	0 (0%)	5 (0.4%)	*p* = 0.114
Renal dysfunction	4 (0.6%)	3 (0.2%)	*p* = 0.179
Pneumonia	3 (0.5%)	7 (0.5%)	*p* = 0.827
Lung embolism	0 (0%)	2 (0.2%)	*p* = 0.318
Urinary tract infection	1 (0.2%)	2 (0.2%)	*p* = 0.998
Other	13 (2.0%)	22 (1.7%)	*p* = 0.622

* p-values were measured using Chi-square tests

Table 5

Complications, readmissions and reinterventions in absolute numbers with its percentage within brackets

	Before ERABS n = 654	After ERABS n = 1313	*p* -value*
Revisit ER/OPD within 30 days	82 (12.5%)	220 (16.8%)	*p* = 0.015
Readmission within 30 days	48 (7.3%)	99 (7.5%)	*p* = 0.859
Reoperation† within 30 days	13 (2.0%)	37 (2.8%)	*p* = 0.204
Clavien-Dindo classification complications within 30 days	105 (16.1%)	272 (20.7%)	*p* = 0.013
Minor	79 (12.1%)	198 (15.1%)	*p* = 0.071
Grade I	45 (6.9%)	160 (12.2%)	
Grade II	34 (5.2%)	38 (2.9%)	
Major	26 (4.0%)	74 (5.6%)	*p* = 0.596
Grade IIIa	4 (0.6%)	7 (0.5%)	
Grade IIIb	8 (1.2%)	33 (2.5%)	
Grade IVa	13 (2.0%)	30 (2.3%)	
Grade IVb	0 (0%)	4 (0.3%)	
Grade V	1 (0.2%)	0 (0%)	

† including reoperations during primary admission
*p-values were measured using Chi-square tests

Operation room logistics

All procedural times, such as surgical time, were significantly decreased after implementation of ERABS. Procedural times are specified in Table 6. As a result the mean (±SD) amount of surgical procedures in one OR increased significantly from 5.2 (±1.6) procedures to 6.1 (±1.3) procedures per day when performing LRYGB ($p < 0.001$) and from 7.0 (±1.9) procedures to 8.0 (±1.7) procedures per day when performing LSG ($p < 0.001$; Figure 2).

Table 6

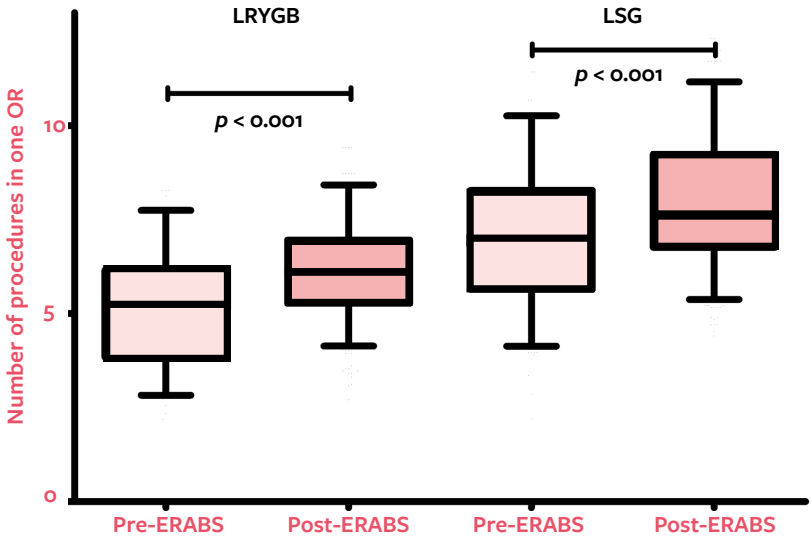
Mean (95% confidence interval) operation times before and after implementation of ERABS

	Before ERABS (n=652)	After ERABS (n=1321)	*p* -value
Induction	17.9 (17.4-18.4)	14.6 (14.4-14.8)	$p < 0.05$
Surgical time	57.8 (55.7-59.9)	50.5 (49.6-51.5)	$p < 0.05$
Bypass	76.6 (72.6-80.6)	59.6 (58.3-60.9)	$p < 0.05$
Sleeve	47.1 (45.3-48.8)	40.8 (39.8-41.7)	$p < 0.05$
Emergence time†	8.9 (8.5-9.3)	7.6 (7.5-7.8)	$p < 0.05$
Time at recovery	89.6 (86.9-92.3)	79.9 (78.3-81.5)	$p < 0.05$
Total time in OR	84.6 (82.1-87.0)	72.8 (71.7-73.8)	$p < 0.05$
Bypass	103.5 (98.8-108.1)	82.2 (80.8-83.6)	$p < 0.05$
Sleeve	73.8 (71.6-76.0)	62.6 (61.6-63.7)	$p < 0.05$

† Time between end of surgery and transport to recovery area

Figure 2

Number of procedures in one operation room in one day



With the implementation of ERABS the mean length of stay reduced from 3.0 to 2.1 nights ($p < 0.001$). Before introduction of ERABS, 39.4% of all subjects were discharged on the first postoperative day. Since the introduction, this percentage is increased to 74.2% of all subjects, with 91.7% of all subjects being discharged within two days postoperatively.

Discussion

ERAS protocols have shown that optimizing and standardizing perioperative care results in a significant reduction in hospital stay and postoperative morbidity. This resulted in an increased interest in such protocols for bariatric surgery (ERABS protocols). In this study, the mean length of stay decreased from 3.0 to 2.1 nights after introduction of ERABS care, respectively allowing 39.4% and 74.2% of the patients to be discharged on the first postoperative day. This decrease in length of stay is mainly caused by the clarification of the discharge criteria with the introduction of ERABS. Although discharge before the ERABS protocol was also determined on clinical parameters, such as temperature, pulse and CRP, no clear thresholds for the different parameters were defined and patient discharge was probably more conservative. Clear thresholds were first introduced with ERABS (Table 1), and patients who met all criteria on the first postoperative day were discharged directly on that day.

There was no significant difference in the number of complications during admission in both cohorts. However, within 30 days postoperatively, significantly more complications occurred in the post-ERABS group (20.7% versus 16.1%, $p = 0.013$). On the other hand, this increase did not result in a significant difference in the number of major complications, with a Clavien–Dindo score of 3a or higher (4.0% pre-ERABS versus 5.6% post-ERABS, $p = 0.596$), or the number of reoperations (2.0% pre-ERABS versus 2.8% post-ERABS, $p = 0.204$). Although not significant, we have to take a critical view on the percentage increase in complications and reoperations. First of all, due to increasing demands on health care and perioperative care in the Netherlands, hospitals are increasingly encouraged to register the perioperative course of their patients. As a result, the registration of complications has been improved in recent years. Furthermore, our clinic has made a transition from paper patient charts to digital charts in the same period in which ERABS was introduced. In the era of paper charts, hospitals were unfortunately confronted with loss of patient information throughout the hospital, while patient data is now centrally stored causing a minimized loss of data. However, in this cohort, we cannot differentiate between an increased number of

complications due to better registration or due to decreased safety caused by the introduction of ERABS, for example caused by the pursuit of high numbers of procedures and short turnover times. Possibly, there is a maximum efficiency in which we can guarantee patient safety and therefore it is of major importance to register complications thoroughly and adjust the protocol, when necessary, to achieve the most safe and efficient bariatric care.

In current literature, very low rates of perioperative complications after ERABS[13,39,40] have been described, but it remains unclear how and which complications are scored in these studies. One study[16] described their scoring system in detail and also used the Clavien–Dindo classification. Results of our study are comparable with their results, with an increase in complications after implementation of ERABS, although it did not cause an increase in serious adverse events. In our cohort, most major complications requiring invasive treatment occurred more than 48 hours after the primary procedure. These complications were not likely to be prevented by extending the length of stay to 3 nights, as in the pre-ERABS group.

After the implementation, patients were more likely to revisit the emergency department within 30 days. However, early readmission rates (7.5%) and reoperation rates (2.5%) did not change significantly and were similar to rates in previous ERABS studies.[15,16] This ERABS protocol includes intensive monitoring of patients by telephone by the obesity nurse, with a low threshold to reassess patients in the emergency department and to readmit the patients for observation. This monitoring may explain the higher number of early revisits.

Additionally, ERABS allows the performance of a higher volume of bariatric procedures, which, as a result, improves the quality of surgery,[42-47] without increasing perioperative morbidity.[13,32,39,47,48] As a result, ERABS protocols may increase cost-effectiveness of bariatric surgery.[14,39] In the future, bariatric surgery will consume an increasing part of limited health economic and surgical resources of our already burdened health care system. In this study, all procedural times were significantly reduced after implementation of ERABS. This efficiency enabled us to

currently perform seven LRYGB procedures or eight LSG procedures per surgeon within 8 hours in one OR. Nonsurgical times within the operation room improved by working efficient and parallel to each other and decreased average time in the OR from 103 to 82 minutes in LRYGB and from 74 to 63 minutes in LSG. The use of dedicated bariatric teams and standardization of the protocol is probably the main cause of this reduced procedural duration and it improves teamwork, without having an adverse effect on patients' outcome.[49]

In conclusion, implementation of ERABS can result in shorter procedural times and a decreased LOS, which may lead to more efficient and cost-effective bariatric care. Even though the number of complications increased after implementation of ERABS, the number of major complications, readmissions and reoperations did not change. Therefore, by implementing an ERABS protocol, you can achieve efficient and safe bariatric care, as well as a substantial reduction in operation time, LOS and costs. It is of major importance to intensively monitor results and complications after introduction of ERABS and update the protocol regularly.

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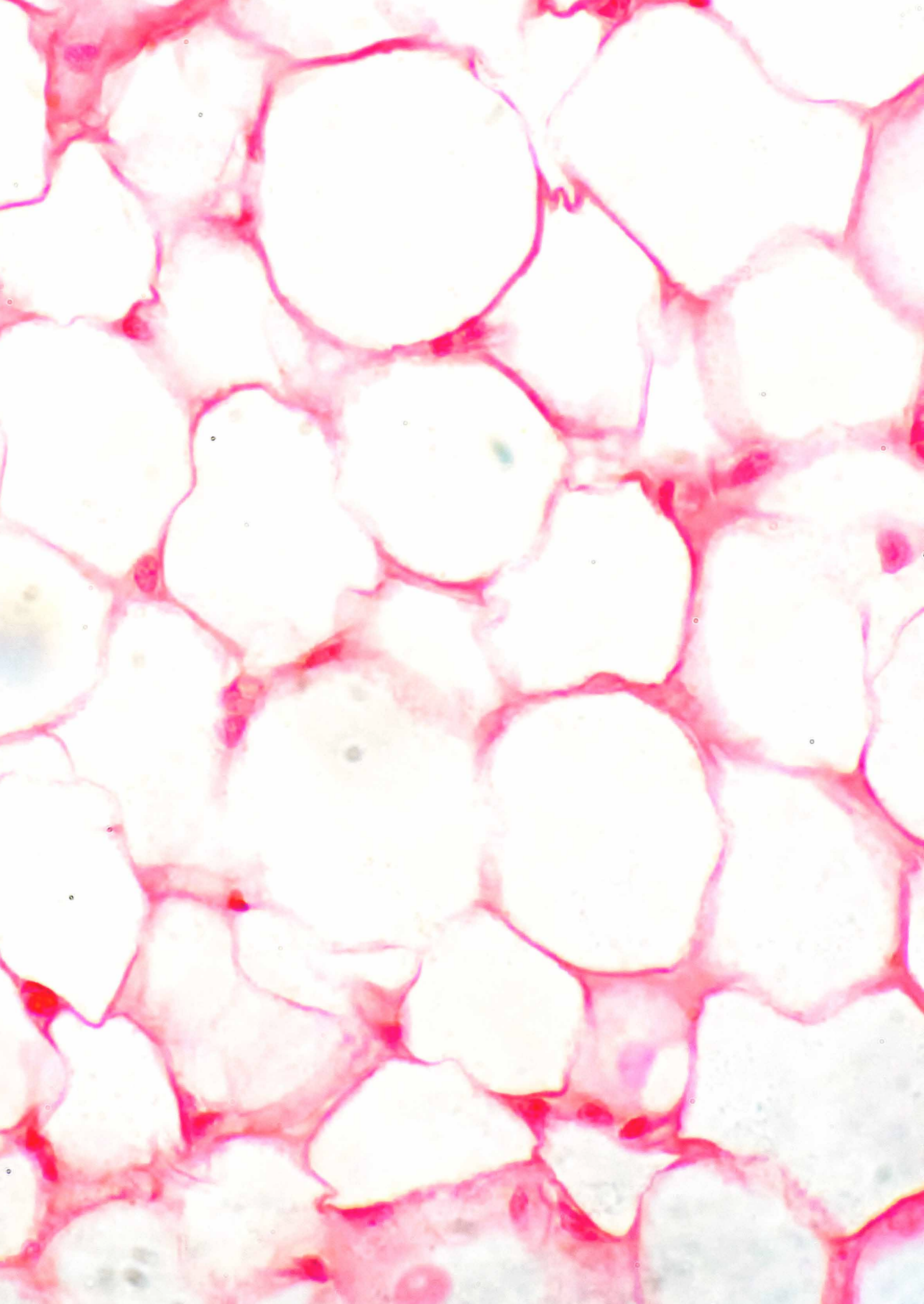

Chapter 8

The standardized postoperative checklist for bariatric surgery; what are the predictors of complications?

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Abstract

Background

Morbidly obese patients are at higher risk of complications after surgery. In bariatric surgery, pre- and intraoperative checklists are commonly used to identify high-risk patients preoperatively, to decrease the number of postoperative complications. This pilot study evaluates the effect of a postoperative checklist in bariatric surgery, addressing regularly measured parameters, on the occurrence and early recognition of complications.

Materials and methods

An in-house-developed postoperative checklist was used on the first postoperative day after bariatric surgery and included information on nausea, pain, temperature, heart rate and laboratory markers. Complications were scored using the Clavien–Dindo (CD) classification and three groups were formed: no complications (CD0), minor complications (CD1 and 2) and major complications (≥CD3a). Differences between groups were analyzed using nonparametric tests.

Results

694 subjects were included (79.5% female, age 42.6 [±10.8] years, BMI 43.8 [±5.8] kg/m^2). 29 subjects developed major complications within 30 days postoperatively. There were no significant differences in baseline characteristics between groups. Subjects with major complications were less willing to be discharged due to complaints, compared to subjects with no or minor complications (14.8% versus 3.6% and 4.6%, respectively) and had a higher decrease of hemoglobin level (0.8 versus 0.6 and 0.65 mmol/l, respectively).

Conclusions

The patients' willingness for discharge, in combination with hemoglobin decrease, may be the best early predictors of major complications after bariatric surgery. This postoperative checklist may be an adequate instrument to identify patients who can be safely discharged home on the first postoperative day and thereby play a part in patient management after bariatric surgery.

Introduction

Bariatric surgery is the most effective long-term treatment option for patients suffering from morbid obesity and its related diseases.[1-4] However, patients with morbid obesity are at higher risk for intraoperative and short- and long-term postoperative complications compared to lean patients,[5] which can result in prolonged hospital stay, readmission, reoperation and even death.[6]

Pre- and intraoperative checklists are becoming increasingly commonplace as a safety tool in standardized surgical treatment programs and these checklists are increasingly seen as best practice. It is known that proper use of these checklists results in a lower rate of postoperative complications.[7] In addition, the use of postoperative checklists to structurally monitor signs of possible complications and subsequent early intervention could contribute to better patient care. However, in current literature, information on the use of postoperative checklists, addressing generally used postoperative parameters, such as heart rate, C-reactive protein (CRP) and hemoglobin values, is scarce. This pilot study presents the results of an in-house developed postoperative checklist for bariatric surgery based on these parameters and evaluates the different components of this checklist. To our knowledge, this is the first study that addresses the use of a postoperative checklist and its effect on complication management in bariatric surgery.

Materials and methods

Study population

All patients who underwent laparoscopic sleeve gastrectomy (LSG)[8] or laparoscopic Roux-en-Y gastric bypass (LRYGB)[9] within our bariatric clinic after the introduction of the checklist in February 2014 until December 2014 were included in this retrospective cohort study. Inclusion criteria for bariatric surgery are in accordance to international IFSO criteria.[10] All patients were treated according to the enhanced recovery after bariatric surgery protocol[11] and expected to be discharged on the first postoperative day. The choice of operation was made according to the patient's and doctor's preference based on comorbidity, age, the presence of gastro-esophageal

reflux disease (GERD) and dietary pattern. Since this is the first study to describe a postoperative bariatric checklist, no formal power calculation was performed.

Baseline characteristics

Baseline characteristics were collected during the initial outpatient preoperative screening and included gender, age, medical history and smoking habit. Weight (in kg) and BMI (in kg/m^2) were the main measurements for anthropometry. Baseline laboratory tests were performed approximately two months before surgery. The postoperative laboratory measures are performed on the first postoperative day.

Postoperative checklist

An in-house-developed, computerized postoperative checklist was used during the ward rounds on the first postoperative day. Cutoff points were determined based on clinical experience. Pain was scored using a visual analog scale (VAS).[12] Willingness for discharge was defined by asking the patient explicitly whether they agree to be discharged and was not influenced by the outcome of the other parameters in the checklist or the judgment of the clinician. Parameters and their cutoff points are shown in Table 1. Based on the outcome of the checklist, using the predetermined cutoff points, it was determined whether patients were ready for discharge or had to stay for further observation. An experienced bariatric surgeon determined further patient management, which could include patient discharge, further evaluation or reintervention.

Complications

Any abnormal course within 30 days postoperatively was scored as a complication. The severity of this complication was scored using the Clavien–Dindo (CD) classification.[13,14] For statistical and clinical considerations, patients were divided into three groups: no complications, minor complication (CD1 and CD2) and major complications (CD3a or higher).

Table 1

Parameters presented in the postoperative checklist for bariatric surgery.

Parameter	Score	Cut-off points
History		
VAS for pain	0 – 10	≥ 4
Nausea score	1 – 4	≥ 4
Ate liquid food?	Yes / No	No
Mobilizing?	Yes / No	No
Patient consent with going home?	Yes / No	No
Physical examination		
Abdominal guarding?	Yes / No	Yes
Heart rate		≥ 120 bpm
O2 saturation		≤ 90 %
Drain production in 24 hours		≥ 30 ml
Lab findings		
Hemoglobin decrease		≥ 1 mmol/l, or ≥ 1.6 g/dl
White blood cell count post-operative		≥ 14 x10^9/l
C-reactive protein post-operative		≥ 79 mg/l

VAS visual analogue scale

Statistical analysis

All analyses were performed using SPSS (PASW) 18.0 software (SPSS Inc., Chicago, Illinois, USA). Outcomes of the checklist were described as median with interquartile range (IQR) or absolute number with percentage. Subjects without a completed checklist were excluded from analysis. Differences between the three groups, based on the CD classification, were analyzed using nonparametric tests. In order to determine the absolute differences in the parameters within the checklist, these parameters were considered to be continuous variables. Additionally, to determine the appropriateness of the different cutoff points for these parameters, all variables were transformed into dichotomous variables ("patient meets criterion" versus "patient fails criterion") using these predefined cutoff points. Results were evaluated at a significance threshold of $p < 0.05$.

Results

After implementation of the checklist a high compliance to complete the checklist on the first postoperative day was achieved; after 2 months, in more than 95% of all bariatric patients the checklist was completed and this percentage remained stable over time.

Baseline characteristics

A total of 694 patients were included between February and December 2014. The majority of patients were female (79.5%) and the mean age was 42.6 (±10.8) years. The mean BMI was 43.8 (±5.81) kg/m^2 with a mean waist circumference of 131 (±12.2) cm or 51.6 (±4.8) inches. Medical history included earlier abdominal surgery (33.3%), hypertension (33.0%), type 2 diabetes mellitus (21.3%), GERD (18.0%) dyslipidemia (15.4%), sleep apnea (10.1%) and chronic obstructive pulmonary disease (3.6%). Additional baseline characteristics are shown in Table 2.

Surgical techniques

From the total of 694 procedures performed in this period, 630 procedures (90.8%) were primary procedures, while 64 procedures were revisional procedures after previous bariatric surgery, such as laparoscopic adjusted gastric banding or sleeve gastrectomy. Of all primary procedures the most frequently performed surgery was the laparoscopic Roux-en-Y gastric bypass (LRYGB), with 350 procedures (55.6%), followed by the laparoscopic sleeve gastrectomy (LSG), with 278 procedures (44.1%). In only two cases was a primary mini-gastric bypass performed.

Complications

In 147 patients a complication occurred within 30 days postoperatively, of which there were 118 minor complications (17%) and 29 major complications (4%). Baseline characteristics of patients, who developed a complication within 30 days, were not significantly different from the baseline characteristics of patients without complications, except for the preoperative occurrence of GERD. Further details are shown in Table 3.

Table 2

Baseline characteristics in absolute numbers or mean value, with its percentage or standard deviation, respectively, presented within brackets

	Total (n=694)
Sex (%)	
female	552 (79.5%)
Age	
(years)	42.6 (±10.8)
Height	
(meters)	1.69 (±0.09)
(foot)	5.5 (±0.30)
BMI	
(kg/m2)	43.8 (±5.81)
Waist circumference	
(cm)	131 (±12.2)
(inch)	51.6 (±4.8)
Medical history	
Type 2 diabetes	148 (21.3%)
Hypertension	229 (33.0%)
Dyslipidemia	107 (15.4%)
OSAS	70 (10.1%)
GERD	125 (18.0%)
Abdominal surgery	231 (33.3%)
Smoking	
Yes	142 (20.5%)
Quit smoking	182 (26.5%)
Characteristics procedure	
Primary procedure	630 (90.8%)
Re-do procedure	64 (9.2%)
Gastric bypass	398 (57.3%)
Sleeve gastrectomy	290 (41.8%)
Minibypass	6 (0.9%)

BMI body mass index; OSAS obstructive sleep apnea syndrome;

Within the group of minor complications 17 subjects developed a minor complication during their initial stay in the hospital and 104 subjects developed a minor complication after discharge. Only 16 of the 118 subjects required medical treatment of their complication (CD2), the rest were treated conservatively. Within this group, the major complaints were abdominal pain, nausea, surgical site problems and reduced oral intake with risk of dehydration.

Within the group of major complications 13 of 29 subjects developed the complication after they were discharged. In 7 of these 13 subjects, the initial stay in hospital was extended due to a negative checklist outcome. However, the complications only occurred 7 or more days after the procedure. The most frequently occurring complications within 7 days postoperative were bleeding, anastomotic leakage and perforation. After 7 days, the most frequently occurring complication was stenosis.

Table 3

Baseline characteristics in absolute numbers or median value, with its percentage or IQR, respectively, presented within brackets

	No complications n=547	Minor complications (CD 1 or 2) n=118	Major complications (≥ CD 3a) n=29	*p* -value
Sex (female)	437 (79.9%)	92 (78.0%)	23 (79.3%)	$p=0.895^{\lozenge}$
Age (years)	44 (36-51)	42 (31-50.8)	46 (40-50.5)	$p=0.528^{\dagger}$
Height				
(meter)	1.68 (1.62-1.74)	1.67 (1.62-1.74)	1.66 (1.59-1.74)	
(foot)	5.5 (5.3-5.7)	5.5 (5.3-5.7)	5.4 (5.2-5.7)	$p=0.612^{\dagger}$
BMI (kg/m2)	42.9 (40.2-46.6)	42.4 (40.6-46.9)	42.3 (39.3-46.3)	$p=0.756^{\dagger}$
Waist circumference				
(cm)	130 (122-138)	130 (123-140)	128 (118-138)	
(inch)	51.2 (48.0-54.3)	51.2 (48.4-55.1)	50.4 (46.5-54.3)	$p=0.592^{\dagger}$
Systolic blood pressure (mmHg)	135 (122-146)	135 (120-149)	133 (124-153)	$p=0.919^{\dagger}$
Diastolic blood pressure (mmHg)	75 (69-83)	76 (70-81)	80 (74-89)	$p=0.158^{\dagger}$
Current smoker	108 (19.7%)	29 (24.6%)	5 (17.2%)	$p=0.466^{\lozenge}$
Quited smoker	140 (25.6%)	33 (28.0%)	9 (31.0%)	$p=0.685^{\lozenge}$
Medical history				
Type 2 diabetes	112 (20.5%)	26 (22.0%)	10 (34.5%)	$p=0.196^{\lozenge}$
Hypertension	179 (32.7%)	37 (31.4%)	13 (44.8%)	$p=0.368^{\lozenge}$
Hypercholesterolemia	83 (15.2%)	19 (16.1%)	5 (17.2%)	$p=0.932^{\lozenge}$
COPD	20 (3.7%)	4 (3.4%)	1 (3.4%)	$p=0.989^{\lozenge}$
OSAS	51 (9.3%)	15 (12.7%)	4 (13.8%)	$p=0.430^{\lozenge}$
GERD	84 (15.4%)	34 (28.8%)	7 (24.1%)	$p=0.002^{\lozenge}$
Previous bariatric surgery	54 (9.9%)	14 (11.9%)	3 (10.3%)	$p=0.811^{\lozenge}$
Previous abdominal surgery	181 (33.1%)	41 (34.7%)	9 (31.0%)	$p=0.910^{\lozenge}$
Completed checklits	512 (93.6%)	109 (92.4%)	26 (89.7%)	$p=0.656^{\lozenge}$

IQR interquartile range; CD Clavien Dindo classification; BMI body mass index; COPD chronic obstructive pulmonary disease; OSAS obstructive sleep apnea syndrome; GERD gastro esophageal reflux disease

† Independent samples Kruskal-Wallis test

◊ Chi squared test

Outcome of checklist

The checklist was completed in 648 subjects within this cohort. On all different parameters included in the checklist, only the hemoglobin decreased, and the patients' willingness for discharge were significantly different between the three complication groups (Table 4). Within the group of patients who developed a major complication the median hemoglobin decrease was 0.8 mmol/l (1.18 g/dl), compared to 0.6 mmol/l (0.96 g/dl) in the group without any complications and 0.65 mmol/l (1.04 g/dl) in the group with a minor complication (p = 0.009). Within the minor complication group and the group without complications, approximately 95% of all patients felt confident to be discharged on the first day postoperatively, while 14.8% of all subjects with major complications were not confident to be discharged.

Table 4

Baseline characteristics in absolute numbers or median value, with its percentage or IQR, respectively, presented within brackets

	No complications n=512	Minor complications (CD 1 or 2) n=109	Major complications (≥ CD 3a) n=27	p -value
VAS for pain	3 (2 - 4)	3 (2 - 4)	3 (2 - 5.5)	p =0.087†
Nausea scale	1 (1 - 2)	1 (1 - 2)	1 (1 - 2)	p =0.459†
Oral intake				
Yes	487 (95.1%)	100 (91.7%)	25 (92.6%)	p =0.638*
No, per surgeons order	4 (0.8%)	2 (1.8%)	0 (0.0%)	p =1.000*
No, due to complaints	18 (3.5%)	6 (5.5%)	2 (7.4%)	p =0.298*
Ambulation	505 (98.6%)	107 (98.2%)	27 (100.0%)	p =1.000*
Willingness for discharge				
Yes	486 (94.9%)	101 (92.7%)	23 (85.2%)	p =0.036*
No, per surgeons order	3 (0.6%)	1 (0.9%)	0 (0.0%)	p =1.000*
No, due to complaints	18 (3.5%)	5 (4.6%)	4 (14.8%)	p =0.023*
Body temperature				p =0.067†
degrees Celsius	37.3 (36.9 - 37.6)	37.2 (36.8 - 37.4)	37.5 (37.0 - 37.8)	
degrees Fahrenheit	99 (98 - 100)	99 (98 - 99)	100 (99 - 100)	
Heart rate (bpm)	78 (70 - 87)	78 (69 - 86)	79 (72 - 95)	p =0.185†
Oxygen saturation (%)	97 (95 - 98)	96 (95 - 98)	96 (94 - 97)	p =0.311†
Abdominal distension	504 (98.4%)	106 (97.2%)	26 (96.3%)	p =0.083*
Drain				
No drain	408 (79.7%)	85 (78.0%)	20 (74.1%)	p =0.366◊
Drain production < 30 ml	72 (14.1%)	14 (12.8%)	6 (22.2%)	p =0.243◊
Drain production > 30 ml	23 (4.5%)	6 (5.5%)	1 (3.7%)	p =1.000*
Hemoglobin decrease				p =0.009†
(mmol/l)	0.6 (0.3 - 0.9)	0.65 (0.2 - 1.0)	0.8 (0.5 - 1.5)	
(g/dl)	0.96 (0.48 - 1.44)	1.04 (0.32 - 1.60)	1.28 (0.80 - 2.40)	
Leukocyte count (x10^9/l)	11.9 (10.1 - 13.6)	12.0 (9.8 - 13.7)	13.0 (11.2 - 15.1)	p =0.203†
CRP (mg/l)	18 (12 - 32)	20 (12 - 34)	27 (17 - 45)	p =0.172†

IQR interquartile range; CD Clavien Dindo classification; VAS visual analogue scale

* Fisher's exact test

† Independent samples Kruskal-Wallis test

◊ Chi squared test

Patient discharge is dependent on the outcome of the checklist, using predefined cutoff values, as described in Table 1. Independent analysis of the different parameters in the checklist, after transformation to dichotomous variables, showed a significant difference in the rate of major complications between patients who did or did not meet the criterion of VAS for pain, white blood cell count and the willingness of the patient for discharge.

There was no significant difference in the occurrence of major complications, using the current cutoff values for hemoglobin decrease, heart rate and CRP. Further details are shown in Table 5. Using these cutoff points, the positive predictive value of this checklist on development of a major complication is 6%, while the negative predictive value is 98%.

Table 5

Incidence of major complications* based on the predefined cut off point in the computerized checklist

	No major complications n=512	Minor complications n=109	Major complications n=26	*p* -waarde
VAS > 4	66 (12.9%)	19 (17.4%)	8 (30.7%)	*p* =0.025
Nausea scale ≥ 4	28 (5.5%)	5 (4.6%)	3 (11.5%)	*p* =0.383
Diet no intake	22 (4.3%)	8 (7.3%)	2 (7.7%)	*p* =0.354
Mobilisation not mobilized	5 (1.0%)	1 (0.9%)	0 (0.0%)	*p* =0.874
Willingness for discharge not willing	21 (4.1%)	6 (5.5%)	4 (15.4%)	*p* =0.039
Abdominal distension present	1 (0.2%)	0 (0.0%)	1 (3.8%)	*p* =0.083
Heart frequency ≥ 120 bpm	1 (0.2%)	0 (0.0%)	0 (0.0%)	*p* =0.873
Oxygen saturation ≤ 90%	2 (0.4%)	0 (0.0%)	0 (0.0%)	*p* =0.759
Drain production ≥ 30 ml	23 (4.5%)	6 (5.5%)	1 (3.8%)	*p* =0.864
Hemoglobine decrease ≥ 1 mmol/l or ≥ 1.6 g/dl	109 (21.3%)	25 (22.9%)	10 (38.5%)	*p* =0.126
Leukocyt count ≥ 14 x10^9/l	108 (21.1%)	23 (21.1%)	12 (46.2%)	*p* =0.012
C-reactive protein ≥ 79 mg/l	20 (3.9%)	7 (6.4%)	1 (3.8%)	*p* =0.427

VAS visual analogue scale

* All parameters were transformed into dichotomous variables based on the predefined cutoff points

Discussion

With the increasing prevalence of bariatric surgery, in combination with the high risk of intra- and postoperative complications, there is an emerging demand for bariatric safety tools. The use of pre- and intraoperative checklists has been proven to decrease the rate of postoperative complications. Even though many clinics will use the same postoperative parameters to evaluate the risk of postoperative complications, it has not been investigated which parameters are most reliable in predicting the complication risk in bariatric patients.

Analyzing the differences in patient characteristics between patients without complications, with minor complications and with major complications, patients with preoperative complaints of GERD were more likely to develop a complication, either minor or major. This effect was not restricted to a specific surgical procedure or influenced by smoking habit. The largest effect of GERD on the occurrence of complications was seen in the group of minor complications. This may be caused by the synergetic effect of GERD on complaints of nausea and abdominal discomfort, which leads to an increased frequency of emergency room visits, without a requirement of additional treatment.

However, the main focus of this study was to early identify symptoms of complications, using a postoperative discharge checklist. Interestingly, the patients who developed major complications were less willing to be discharged on the first postoperative day, even though these patients expected to be discharged on that day. There was no difference in oral intake and ambulation between the three groups, which may be explained by the protocol in which patients are required en encouraged to start early refeeding and mobilization.[11] Additionally, there were no significant differences in the experienced pain and nausea between the three different groups. Therefore, the VAS and nausea score may not be appropriate measures to estimate the possibility of a major complication. However, after analysis of the appropriateness of the cutoff point for VAS, it had been found that subjects with a VAS score of 4 or higher were more likely to develop a major

complication compared to subjects with a lower VAS score. Therefore, a high VAS score should alert the clinician, while low VAS scores do not exclude the possibility of development of a complication.

There was no difference in the physical exam findings of the two groups. While the parameters were measured at an early stage, and therefor fever might not be expected to have developed, it is interesting that even in the major complication group there was no difference in heart rate or abdominal distension.

Within laboratory evaluation of postoperative subjects, most interest is shown in the decrease of hemoglobin, indicating postoperative bleeding, and inflammatory markers CRP and leukocyte count. Within this cohort, only the level of hemoglobin decrease was different in subjects with major complications compared to all other subjects. Therefore, the level of hemoglobin decrease may be a predictive factor in the development of complications. Unfortunately, the considerable overlap in hemoglobin decrease levels between the three groups makes it difficult to differentiate between subjects prone to develop a major complication and those who are not, purely based on the hemoglobin decrease. It can be concluded that a high hemoglobin decrease should alert for a major complication, although major complications cannot be excluded in subjects with small hemoglobin decreases. The lack of differences in the inflammatory markers can be explained by the fact that inflammatory complications, such as anastomotic leakage and abscesses will usually not occur within 24 hours postoperatively. It is important to realize, that not all complications occur within this first postoperative day and may therefore not be identified in the first 24 hours. However, early discharge after bariatric surgery, as applied in enhanced recovery after bariatric surgery protocols, does not increase the risk of complications and therefore early discharge is considered safe.[15-16]

Overall, significant differences were only seen in the level of hemoglobin decrease and the patient's willingness to be discharged. However, the computerized checklist uses certain cutoff point for each parameter. In addition to the patient's unwillingness to be discharged, subjects with major complications were more

likely to meet the VAS criterion and the leukocyte count criterion, and therefore, these two parameters may have an additional value in the early recognition of complications. Other cutoff points, such as a heart rate of 120 bpm or higher, occurred seldom and appeared to be inadequate. With the current cutoff points of the different parameters in the checklist a negative predictive value of 98% was reached, which means that most patients who were sent home on the first postoperative day based on the outcome of the checklist did not develop major complications. However, the positive predictive value was only 6%, which means that 94% of all reevaluations and additional investigations during hospital admission could have been avoided. It can be concluded from this pilot study that the checklist, in its current state, is not a good tool to identify subjects who will develop a major complication, but it can identify subjects who can safely be discharged on the first postoperative day. The next step in the development of this postoperative checklist is to increase the positive predictive value by determining better cutoff values and omitting unnecessary parameters. A prospective study should demonstrate whether the use of this checklist would eventually promote early recognition of complications and decrease the severity of these complications.

In conclusion, the patient's willingness to be discharged home and the level of hemoglobin decrease appear to be the most discriminating parameters within this checklist, although the VAS score and leukocyte count may have a role as well. Overall, a postoperative checklist may be a useful tool to identify bariatric patients that can be safely discharged home on the first postoperative day. The current checklist has a very low positive predictive value and should therefore be optimized with critical evaluation of the necessary parameters and determination of the best cutoff values.

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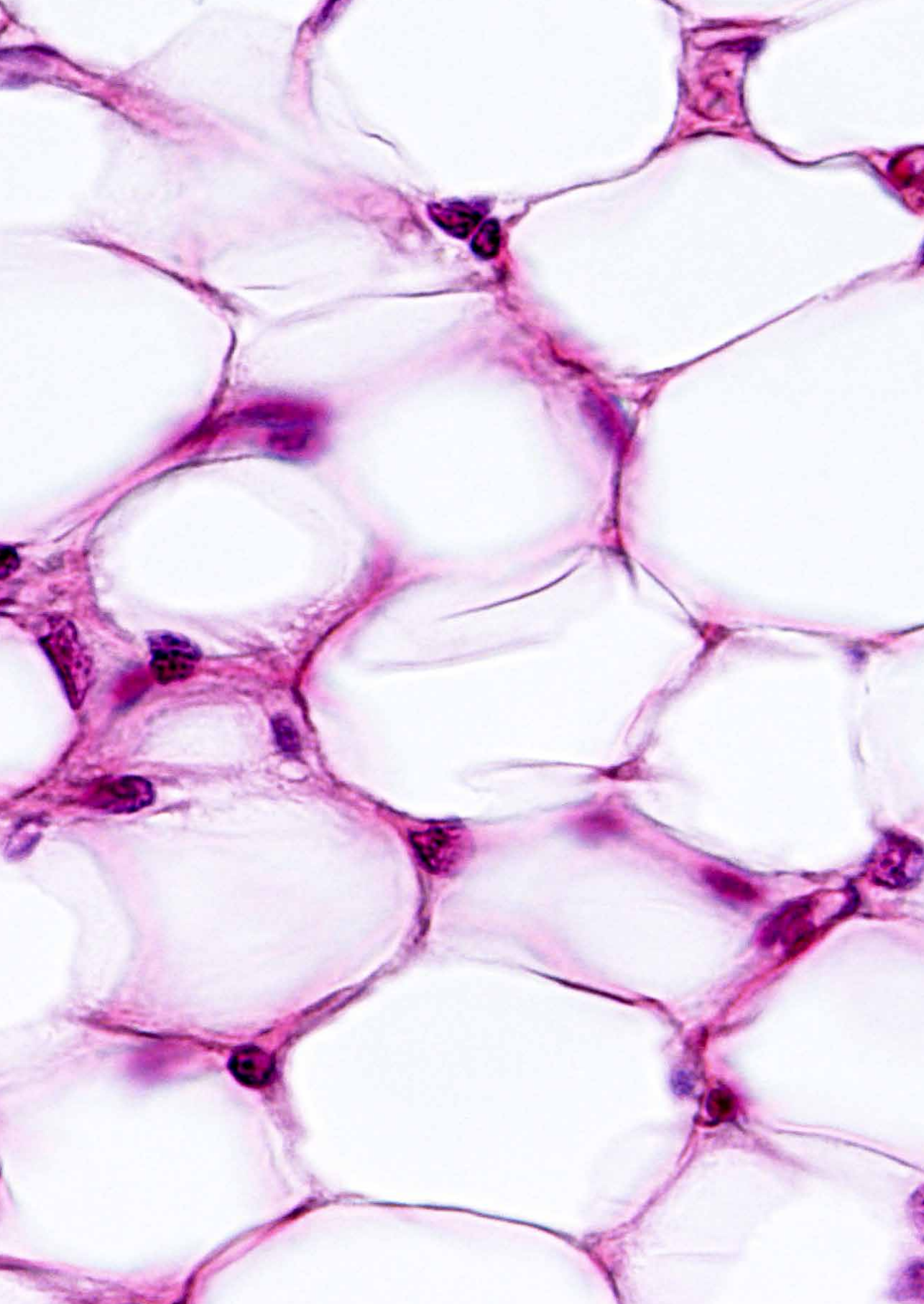
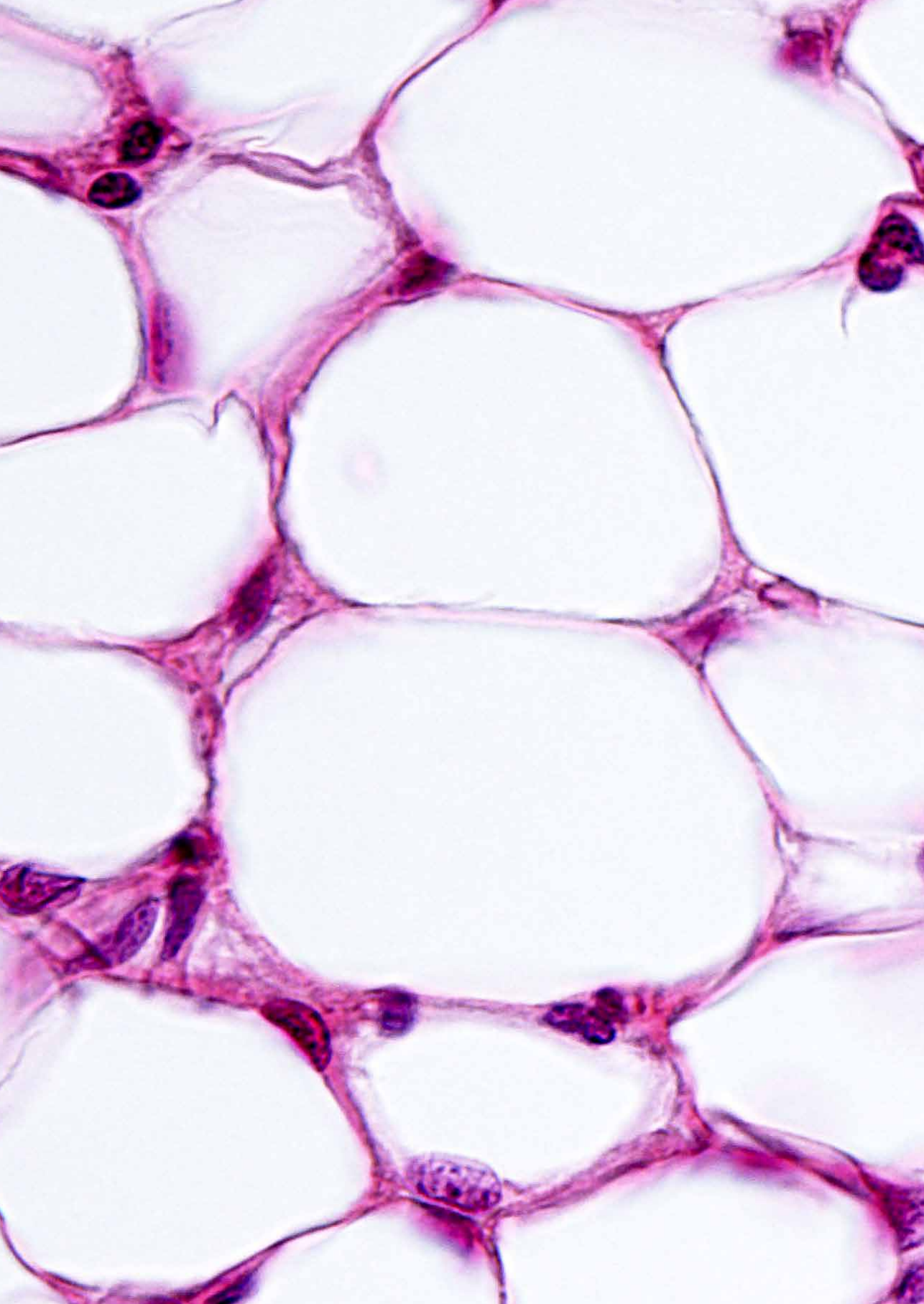


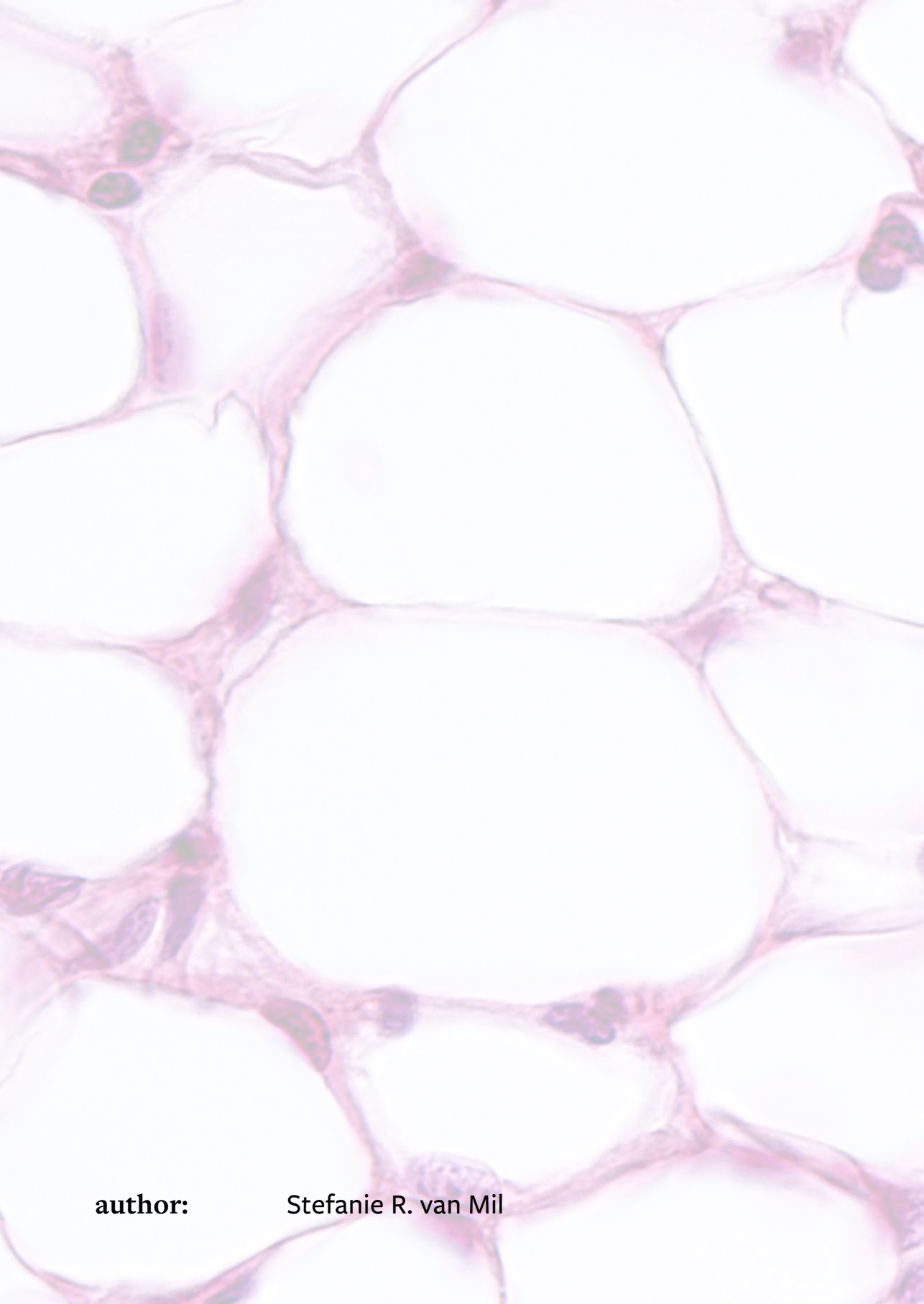
Conclusion

Discussion, future perspectives, Nederlandse samenvatting



Chapter 9

General discussion and future perspectives



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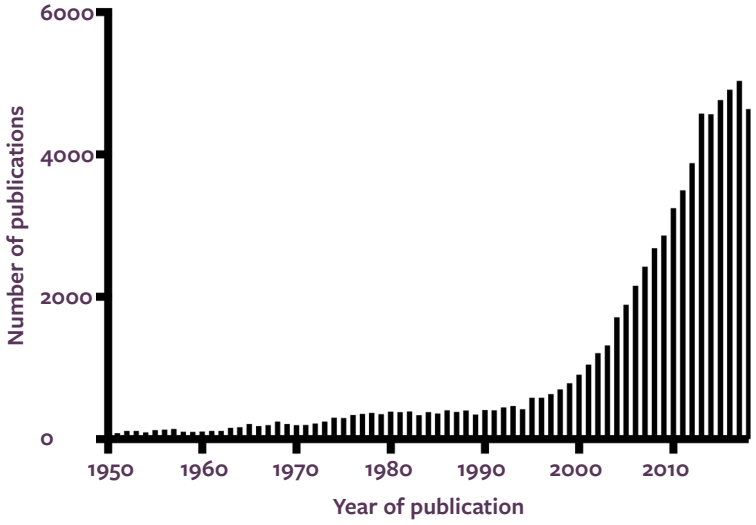
Introduction

Today, obesity is a major health problem that impacts both individual patients and public health. With the increasing prevalence of obesity, the number of patients suffering from obesity-related diseases, as well as the number of patients seeking obesity treatment, continues to rise. Over the past two decades, interest in obesity has rapidly increased, as is clearly depicted by the number of publications outlined in Figure 1. While the oldest publication on PubMed with the term "obesity" in the title dates to 1880 and describes an autopsy of a morbidly obese man,[1] it was not until 1945 that the annual number of publications on obesity entered the dozens and 2001 that the number entered the thousands; the ongoing exponential rise of published research has continued ever since.[2] This thesis reflects the broad range of interests in terms of obesity research today, from epidemiology, etiology and pathophysiology to treatment modalities involving effectiveness, safety, costs and patient satisfaction.

Figure 1

The anual number of publications on Pubmed with 'obesity' in the title since 1950



Part I:
Cardiovascular consequences of obesity

The relationship of cardiovascular risk and the level of obesity

Even though most people are quite aware of the health hazards of overweight and obesity, especially for cardiovascular health,[3,4] the relationship between level of obesity and severity of cardiovascular derangement remains unclear. It is generally accepted that obese individuals have an increased risk for overall mortality in general, and cardiovascular mortality in particular.[4,5] Moreover, it has been well established that these mortality rates rise with increasing BMI. **Chapter 2** investigated the relationship between BMI and cardiovascular risk factors. In accordance with previous studies, we found that obese subjects have significantly increased levels of certain cardiovascular risk factors, such as blood pressure, LDL-cholesterol and glucose. However, the severity of obesity, in terms of BMI, was not found to be associated with the levels of these cardiovascular risk factors. For example, systolic and diastolic blood pressure, as well as LDL- and HDL-cholesterol, gradually worsen up to a BMI of approximately 35–40 kg/m^2 and then plateau, as if a limit to the effect of progressive weight gain on the deterioration of cardiovascular risk factors exists. We have proposed an effect of differences in adipose tissue distribution in different levels of obesity, since central adiposity is known to be metabolically more unhealthy and is associated with hypertension, insulin resistance and dyslipidemia, as well as both cardiovascular and overall mortality.[6–8] We performed CT-volumetry of subcutaneous abdominal and visceral adipose tissue in a small subgroup of the obese subjects; the increase in BMI was primarily explained by an increase of subcutaneous adipose tissue volumes rather than an increase in visceral fat. We believe that a maximal expansion capacity of the visceral adipose tissue may exist and that further deterioration of cardiovascular risk factors with increasing BMI may be limited. The expansion ability of visceral adipose tissue in relation to increasing levels of BMI should be further evaluated to determine the role of visceral adipose tissue expansion in the deterioration of cardiovascular risk and disease. A more thorough understanding of this process may be useful in the development of better treatment modalities.

Nevertheless, one may question what the specific cause of increased mortality is, since cardiovascular risk factors do not further deteriorate with a BMI over 40 kg/m^2. In contrast to cardiovascular risk factors, a clear relationship exists between BMI and markers for systemic inflammation and atherosclerosis, which suggests the presence of a chronic low-grade inflammatory disease.[9] The expansion of adipose tissue may be related to the excessive production and release of pro-inflammatory markers, such as interleukin 6 and adipokines, and may contribute to the process of atherosclerosis. Another hypothesis lies in the versatility of cardiovascular mortality; existing mortality studies do not distinguish between cardiovascular death caused by atherosclerotic or non-atherosclerotic heart disease, such as hypertensive heart disease, cardiomyopathies or heart failure. The increased cardiovascular mortality risk may be caused not by atherosclerotic diseases but by non-atherosclerotic causes such as, for example, diastolic and systolic dysfunction leading to heart failure caused by mechanical changes in obesity. In addition, obesity is closely associated with an increased risk of atrial fibrillation, which by itself impairs left ventricle function.

Gender differences in cardiovascular disease and obesity

Women are known to be relatively protected for cardiovascular disease,[10] particularly before menopause.[11] Despite obesity being associated with the increased risk of cardiovascular disease, **Chapter 3** has demonstrated that morbidly obese women are still relatively protected when compared to their male counterparts. This advantage is reflected by both cardiovascular risk factors and cardiovascular outcome measures, in terms of carotid intima media thickness and pulse wave velocity. As previously described, in lean women, the advantage diminishes post menopause, and the prevalence of cardiovascular disease approaches similar rates for women and men in the seventh decade of life.[10,11] For obese women, a postmenopausal state, compared to a premenopausal state, also has negative effects on cardiovascular health, although the disadvantage is subtler than in lean women. It has been suggested that hormonal imbalances affect the development of cardiovascular disease. In premenopausal women, the incidence of ischemic heart disease is low,[11] and estrogen is thought to have both anti-atherosclerotic and anti-inflammatory properties. While the ovaries are the most important source for estrogen in premenopausal years, after menopause, the primary source for estrogen is estrone, which can be produced

from the conversion of androgens in adipose tissue.[11] Even though the levels of estrogen decrease after menopause, the excessive amount of adipose tissue may cause a subtler decrease in estrogen levels and thereby attenuate the effect of the postmenopausal state in women suffering from morbid obesity.

The effect of type 2 diabetes mellitus and inflammation on cardiovascular disease

A major health problem associated with obesity is type 2 diabetes mellitus (T2DM), which causes micro- and macrovascular complications; subjects suffering from T2DM are more likely to develop atherosclerosis[12] and cardiovascular disease.[13,14] Additionally, low-grade systemic inflammation is thought to be a major contributor to the development of these cardiovascular complications,[15] and obesity is considered a form of low-grade inflammation.[16] Therefore, the increased risk of cardiovascular disease and mortality in obese subjects may be partially explained by both the increased inflammatory state and the increased occurrence of T2DM.

Chapter 4 demonstrated that the occurrence of T2DM in obese patients negatively affects vascular health in terms of carotid intima media thickness and pulse wave velocity. However, these two parameters are primarily influenced by age, gender, blood pressure and lipid profile, and not by the occurrence of T2DM itself. This result suggests that not T2DM, but other cardiovascular risk factors linked to T2DM, have the greatest impact on vascular health in obese subjects.

Additionally, it has been suggested that increased cardiovascular risk and disease in obese diabetes patients, when compared to their non-diabetic counterparts, may be explained by differing levels of systemic inflammation. Despite obese patients suffering from T2DM having increased inflammatory markers when compared to non-diabetics, this did not result in differences in cardiovascular outcomes, as described in Chapter 5.

Part II:
Treatment strategies for obesity

Bariatric surgery in adolescents

Obesity is a major health problem not only in adults but also in children and adolescents, with an increasing prevalence in these age groups in recent decades.[19–21] Unfortunately, the health risks of obesity also exist for these young patients.[22–24] Even if they achieve normal weight in adulthood, their cardiovascular risk will remain increased when compared to children with normal weight.[25] Bariatric surgery is thought to be the only long-term effective treatment for morbid obesity and morbid obesity-related diseases, with substantial and long-term weight loss. However, much discussion is ongoing regarding the ethics of bariatric surgery in children and adolescents. Can young patients make informed decisions on such chronic interventions? Can they estimate the consequences, both in the short and long term, of such operations? On the other hand, are we allowed to withhold from them the best effective treatment, knowing the risks they will encounter in both their current and future lives when untreated? A high need for information remains on the most effective and safest bariatric procedure in children and adolescents, including information on long-term results and patient satisfaction. **Chapter 6** has reported the encouraging results of both the laparoscopic Roux-en-Y gastric bypass (LRYGB) and the laparoscopic sleeve gastrectomy (LSG) in a group of young adults. We recommend the LSG for young adults and adolescents due to its theoretical advantages, including the lack of dumping, with improved quality of life, less malnutrition and vitamin disturbances, the possibility of normal endoscopy after surgery and options for revisional surgery. A primary concern in these young patients is the lack of long-term follow-up; a special follow-up program may need to be implemented to increase follow-up attendance and thus increase patient safety.

Increasing efficiency and monitoring safety of bariatric surgery

With the increasing number of morbidly obese subjects, the number of bariatric procedures performed worldwide is also increasing. In the search for safe and efficient treatment, enhanced recovery after bariatric surgery (ERABS) protocols have been developed,[26–30] as described in **Chapter 7**. Implementation of this protocol

has significantly decreased the length of stays in the hospital. Furthermore, operation times have become significantly shorter after implementation, from which the patient benefits in term of risk of thrombosis, infection and other postoperative complications. The implementation of an ERABS protocol does not result in an increase of major complications and is therefore considered safe. The majority of minor complications in the post-ERABS group were complaints of nausea in patients who did not stick to the prescribed diet. With more extensive education, particularly postoperatively, the number of minor complications can likely be reduced. Overall, ERABS is thought to be a safe method to perform bariatric surgery in high volumes, and it may actually lead to a reduction in healthcare costs.

Even though the length of stay in the hospital has significantly decreased after the implementation of ERABS, it is essential to differentiate patients who can be discharged early from those who may develop complications. Although pre- and intraoperative checklists are becoming a standard safety tool in many surgical treatment programs, a postoperative checklist to identify patients prone to complications was first described in **Chapter 8**. The checklist in its current form had a very high negative predictive value, and patients who met the criteria of the checklist could be sent home safely. However, the positive predictive value was very low, indicating a high percentage of unnecessary reevaluation and investigation in this group. The current checklist is being reevaluated annually to adjust its cutoff points and increase its positive and negative predictive values.

Future perspectives

A new insight emerging from this thesis relates to the finding that the extent of obesity, in terms of BMI, does not appear to influence the risk of cardiovascular disease. We assume that the distribution of adipose tissue may be influential in this finding. Data from a small subgroup analysis described in **Chapter 2** suggests that the expansion capacity of visceral adipose tissue in morbid obesity may be limited. Importantly, visceral adipose tissue is known to be more metabolically unhealthy

than the other adipose tissue compartments. Body composition analysis should be performed using DEXA scans, which are low in radiation exposure to the patient and relatively inexpensive. In a large group of subjects with a wide BMI range, from normal weight to morbidly obese, the differences in volumes of adipose tissue depots will be measured and correlated to the cardiovascular risk and disease to test our hypothesis. Furthermore, in collaboration with the department of cardiology in our hospital, a clinical study is being conducted to investigate the pathophysiology of subclinical cardiac dysfunction in morbid obesity; first results are currently being analyzed, and first publications are to be expected in 2020.

A primary task in the field of bariatric surgery is to define which patients have the highest profit of bariatric surgery. Can we, preoperatively, identify the patient who will have the best results of bariatric surgery in terms of weight loss and resolution of comorbidity? Based on the current thesis, BMI should likely not be the primary criterion for performing bariatric surgery. As previously described in the SOS study,[31] bariatric surgery leads to a clear decrease in the number of cardiovascular events and cardiovascular mortality. However, no relationship was observed between preoperative BMI and the extent of decrease in cardiovascular events and mortality postoperatively. This thesis further shows that BMI is not a good predictor of metabolic or cardiovascular health in obese subjects. Therefore, we believe that international guidelines for bariatric surgery should be adjusted. They should not only focus on BMI; the primary focus should be on the metabolic and cardiovascular characteristics of the individual patient. Previous studies[31–32] showed that preoperative BMI did not influence the resolution or new development of metabolic and cardiovascular disease after bariatric surgery. However, subjects with high fasting glucose or insulin levels show more resolution of metabolic and cardiovascular disease and a higher decrease in mortality after bariatric surgery. Furthermore, subjects suffering from obstructive sleep apnea syndrome (OSAS) have a higher risk of developing cardiovascular disease, and bariatric surgery gives a clear resolution of OSAS.[31] Additionally, in the majority of bariatric studies, the study population consists primarily of female subjects, while premenopausal women are relatively protected against cardiovascular disease when compared to men. The effects of bariatric surgery may be more relevant for men in terms of the

resolution of comorbidity and prevention of cardiovascular disease and mortality. Currently, no clear profile exists of the obese subjects with the highest risk of cardiovascular disease or the greatest presumed benefit from bariatric surgery. We believe that new international guidelines should focus more on the already known factors that can predict an increased risk of cardiovascular disease or increased benefit of bariatric surgery. Within the obese population, treatment should be more aggressive in men, people with increased fasting glucose or insulin levels and people suffering from OSAS, since the greatest gains in both personal and public health can be achieved in these specific groups. These factors may also be crucial in decision-making on the type of surgical procedure. The LRYGB is known to have better results in terms of the resolution and prevention of cardiovascular and metabolic disease when compared to the LSG[33] and may therefore be the most appropriate bariatric procedure in these specific adult subgroups.

Bariatric treatment should provide not only significant and long-lasting effects on both weight loss and comorbidity resolution and prevention but also a low level of maintenance in which intensive and long-lasting follow-ups are unnecessary. Unfortunately, this is still a future perspective. Some patients experience weight regain after bariatric surgery. More importantly, metabolic deterioration is also regularly described in long-term follow-ups. For example, even though glycated hemoglobin (HbA1c) levels significantly decrease after weight loss, in the long term, they may slowly increase again, even though weight is not regained.[34] In the long term, up to 50% of all bariatric patients experience a relapse of T2DM or cardiovascular disease, and therefore, their risk of cardiovascular events and death is still increased, when compared to non-obese people.[31,35] These results can be compared with the long-term follow-up results of so-called "metabolically healthy" obese subjects. For now, we cannot completely eliminate the increased risk of metabolic and cardiovascular disease in obese subjects, but bariatric surgery may decrease their occurrence and subsequently slow the progression of these diseases. Current bariatric procedures should be adjusted or combined with, for example, medical treatment to achieve lifelong effects on metabolic and cardiovascular risk factors and disease. Until such treatments have been developed, lifelong follow-up is strictly recommended for all bariatric patients.

These follow-ups can be transferred to the general practitioner after the stabilization of weight and comorbidity. At least an annual follow-up of blood pressure, lipid profile and glucose metabolism should be performed to identify early changes. Even though revisional bariatric surgery is not extremely effective in terms of weight loss, it does have significant effects on comorbidity[36] and may therefore be considered in these patients.

Based on the results described in **Chapter 6**, first steps have been taken to develop a randomized controlled trial on the LSG and the LRYGB in adolescents aged 16–18 years. However, due to low compliance among these young patients, our primary concerns are the safety of such procedures and of participation in a surgical trial. We believe that intensive support by all involved specialties is an obligation, including not only the surgeon, internist and pediatrician but also the dietician, psychologist and physiotherapist. Even though bariatric surgery is an effective method to achieve substantial weight loss in both adults and adolescents, the treatment of obesity must comprise more modalities than surgery alone. Programs focusing on the prevention of obesity and weight regain after bariatric surgery should be improved and intensified, particularly for these young subjects, who are known to show low compliance and short follow-up.

Based on the results of the postoperative checklist in bariatric surgery, as described in **Chapter 8**, the current checklist should be optimized and finetuned. An annual reevaluation of the checklist, its cutoff points and the occurrence of complications is required to optimize the current checklist. The goal will be to increase the positive predictive value of the checklist, without loss of the negative predictive value.

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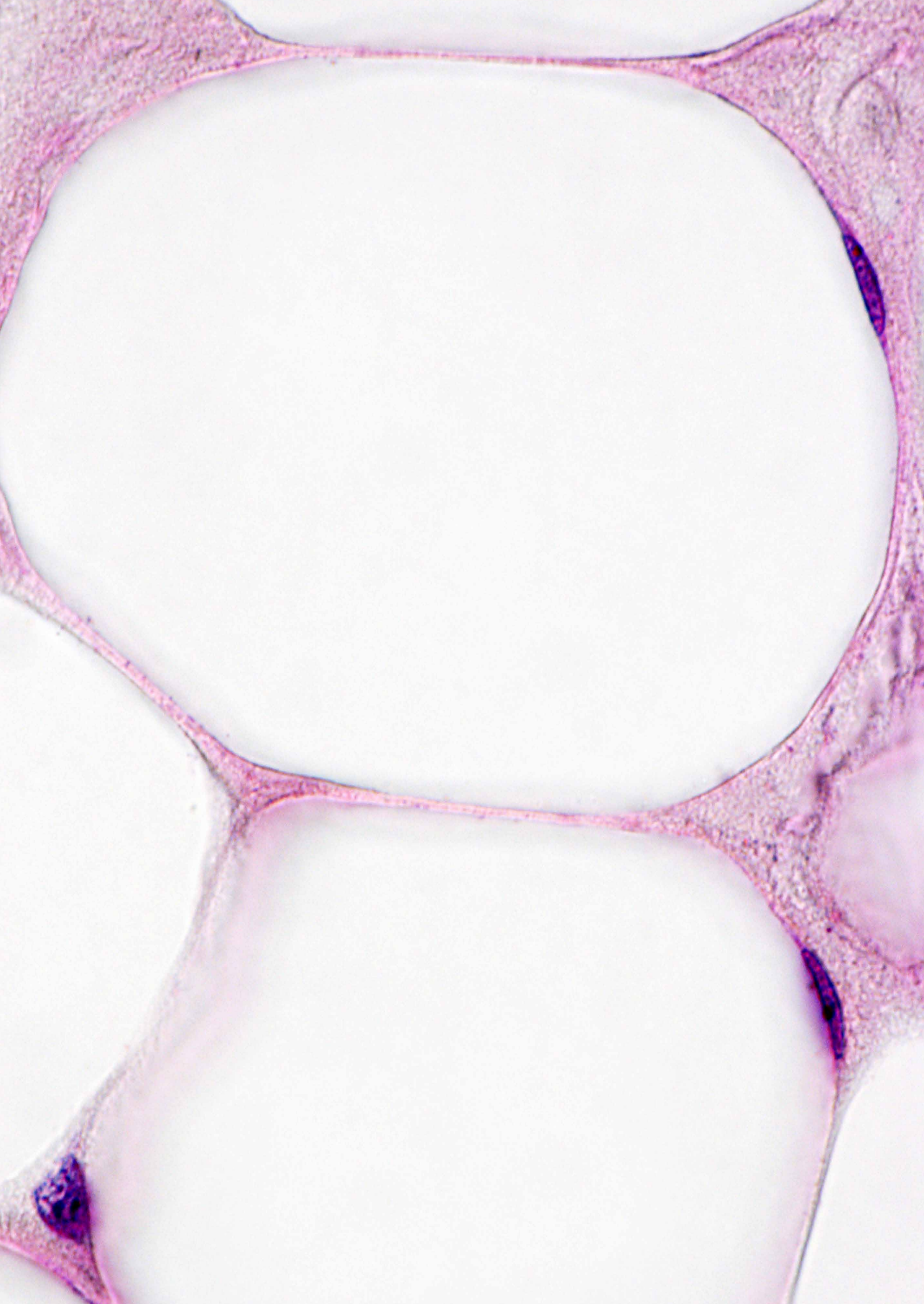
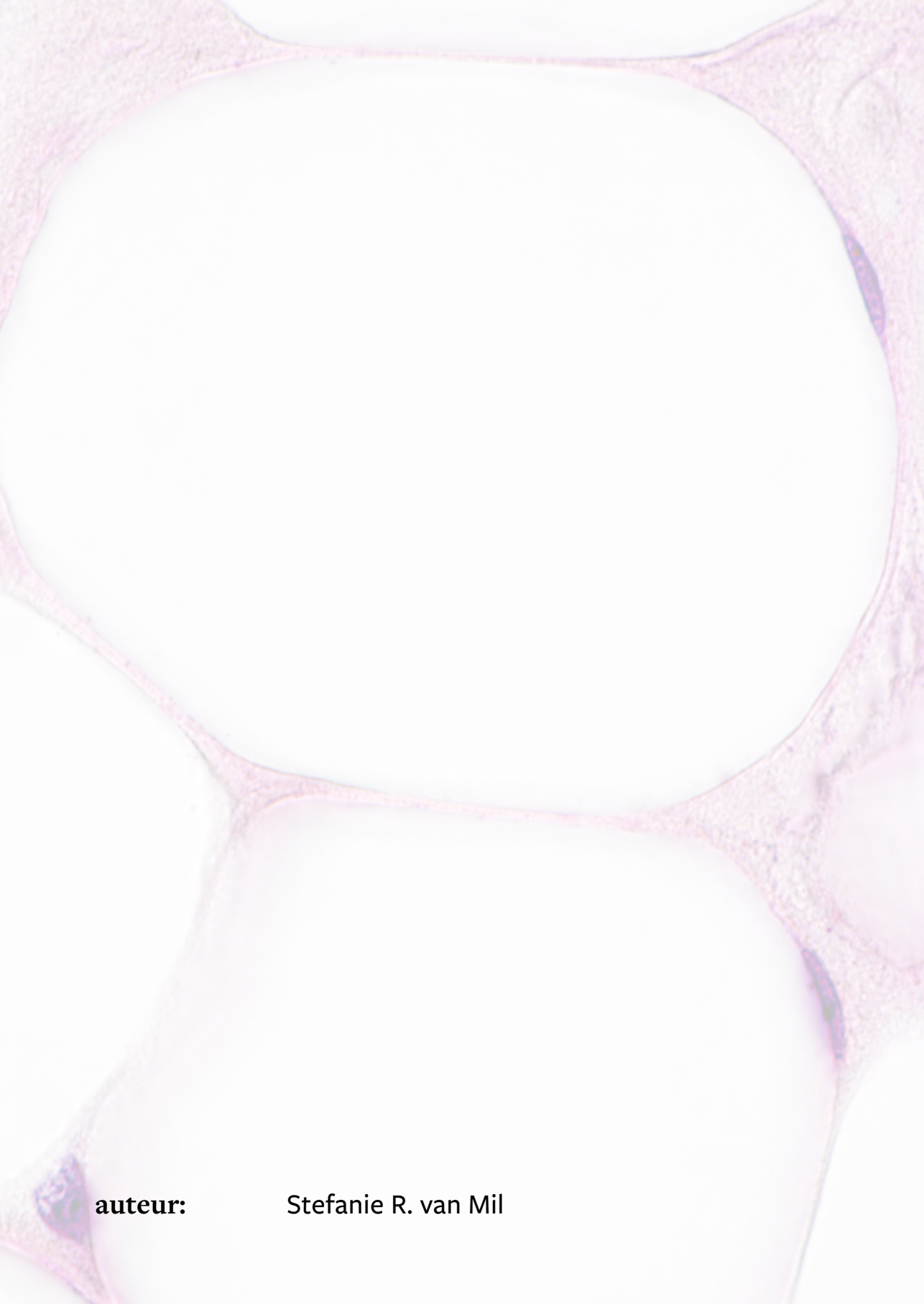


Chapter 10

Nederlandse samenvatting



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Inleiding

Het woord 'obesitas' is afkomstig uit het Latijn en betekent 'gezet' of 'dik'. Het is een samenvoeging van het voltooid deelwoord van eten 'ēsus' en het woord 'ob', dat 'te veel' betekent. Obesitas is de medische term die overgewicht of zwaarlijvigheid beschrijft.

Obesitas is wereldwijd een groot probleem en het aantal mensen met obesitas neemt steeds verder toe. Er zijn verschillende gradaties van overgewicht en obesitas, die worden beschreven aan de hand van de Body Mass Index (BMI). De BMI wordt berekend aan de hand van de volgende formule:

BMI (kg/m^2) = gewicht / $lengte^2$

Een BMI tussen de 18,5 en 25 kg/m^2 wordt gezien als een gezond gewicht. Zodra de BMI boven de 25 kg/m^2 komt, wordt gesproken van overgewicht. Er is sprake van obesitas bij een BMI van 30 kg/m^2 of hoger. In dit proefschrift komt de term 'morbide obesitas' veelvuldig voor: dit is obesitas met een BMI van 40 kg/m^2 of hoger. De term 'morbide' impliceert ernstige gevolgen van deze mate van overgewicht op de gezondheid en de levensverwachting van de patiënten. Vanwege deze gezondheidsgevolgen wordt obesitas sinds enkele jaren niet enkel gezien als een persoonskenmerk, maar ook als een ziekte. De erkenning van obesitas als een ziekte heeft ervoor gezorgd dat er steeds meer aandacht is voor het ontstaan, de preventie en de behandeling van obesitas.

Inmiddels zijn de uitgebreide gevolgen van obesitas steeds beter bekend. Patiënten met obesitas hebben een groter risico op onder andere een hoge bloeddruk, een verhoogd cholesterol, hart- en vaatziekten, suikerziekte (diabetes mellitus), leververvetting, astma, slaapapneu, (invaliderende) gewrichtsklachten, verschillende vormen van kanker en psychische problemen. Dit zorgt ervoor dat personen met obesitas gemiddeld minder lang leven dan personen met een gezond gewicht.

Vanwege deze uitgebreide gevolgen van obesitas op de gezondheid wordt al lange tijd gezocht naar de beste behandeling voor obesitas. Helaas blijkt een levensstijlaanpassing, zoals diëten of sporten, of een behandeling met medicijnen, onvoldoende effectief in de behandeling van obesitas en het verbeteren van de gezondheid van de patiënt met obesitas. Al sinds de jaren 50 van de 20e eeuw wordt nagedacht over de operatieve behandeling van obesitas. Heden ten dage worden obesitas-operaties, zogenaamde 'bariatrische chirurgie', gezien als de enige effectieve behandeling met goede resultaten op de lange termijn. Daarbij treedt niet alleen een substantieel gewichtsverlies op, maar ook een verbetering van de aandoeningen die met de obesitas verband houden, zoals hoge bloeddruk en diabetes mellitus.

Deel I:
De gevolgen van obesitas op hart- en vaatziekten

Hart- en vaatziekten en obesitas

Wereldwijd zijn hart- en vaatziekten nog steeds een van de belangrijkste oorzaken van overlijden. Er zijn verschillende entiteiten van hart- en vaatziekten, zoals aderverkalking (atherosclerose) die kan leiden tot een hartinfarct, een herseninfarct of een verstopping van de bloedvaten van armen of benen, en aneurysmatisch vaatlijden, wat betekent dat een bloedvat een potentieel gevaarlijke verwijding van zijn diameter heeft. De vijf belangrijkste risicofactoren voor hart- en vaatziekten zijn roken, verhoogd cholesterol, een hoge bloeddruk, diabetes mellitus en obesitas. De relatie tussen hart- en vaatziekten en obesitas is complex; obesitas geeft niet alleen op zichzelf een verhoogd risico op hart- en vaatziekten, maar geeft ook een verhoogd risico op de andere risicofactoren voor hart- en vaatziekten. Het is bekend dat het risico op hart- en vaatziekten en op vroegtijdig overlijden groter wordt op het moment dat de BMI hoger is. Dit betekent dat hoe ernstiger de obesitas is, des te ernstiger de gevolgen voor de algehele gezondheid zijn. Soms wordt gesuggereerd dat dit toenemende risico op hart- en vaatziekten bij een hoger BMI komt, doordat deze patiënten ook een hogere bloeddruk hebben of een hoger cholesterol dan patiënten met een lager BMI. Deze relatie tussen de BMI en de ernst van de risicofactoren was echter nog nooit grondig onderzocht.

In **Hoofdstuk 2** wordt het verband beschreven tussen de BMI en de ernst van de risicofactoren op hart- en vaatziekten in een groep patiënten met een BMI variërend van een gezond gewicht tot zeer ernstige morbide obesitas. Zoals verwacht, blijkt dat mensen met obesitas meer risicofactoren hebben om hart- en vaatziekten te ontwikkelen dan personen met een gezond gewicht. Zo hebben zij gemiddeld een hogere bloeddruk, een hoger cholesterol en meer aanwijzingen voor diabetes mellitus. Echter, wat opvalt is dat de mate van obesitas, uitgedrukt in BMI, weinig invloed lijkt te hebben op de ernst van de risicofactoren. Een voorbeeld hiervan is: de bloeddruk neemt steeds verder toe bij een oplopend BMI tot een BMI van 35-40 kg/m^2. Boven deze waarde neemt de bloeddruk niet verder toe. Een patiënt met een BMI van 55 kg/m^2 heeft gemiddeld genomen een vergelijkbare bloeddruk als een patiënt met een BMI van 40 kg/m^2. In de zoektocht naar een verklaring voor deze bevinding is het huidige onderzoek gericht op de vetverdeling in de verschillende gradaties van obesitas. Het is algemeen bekend dat de zogenaamde 'vrouwelijke vetverdeling' met voornamelijk vetophoping op de billen en de heupen gezonder is dan de 'mannelijke ververdeling' met vet ter plaatse van de buik. In een kleine subgroep van de obese patiënten is met behulp van CT-scans gemeten hoe de vetverdeling is in relatie tot de hoogte van de BMI. Hierbij is te zien dat de hoeveelheid orgaanvet (in de buik) bij mensen met obesitas niet per se groter wordt bij een oplopend BMI, maar dat het met name het onderhuids gelegen vetweefsel is dat verder toeneemt naarmate de BMI hoger is. De mogelijkheid bestaat dat de mate waarin het orgaanvet kan toenemen, beperkt is en dat mensen daarna vet gaan stapelen op andere plekken, zoals onderhuids. Aangezien juist de hoeveelheid orgaanvet samenhangt met het risico op hart- en vaatziekten, is voor te stellen dat de genoemde risicofactoren voor hart- en vaatziekten niet erger worden als dit orgaanvet niet verder kan toenemen. Het blijft dan wel de vraag waarom een hoger BMI, ondanks gelijke waarden van de risicofactoren van hart- en vaatziekten, toch leidt tot een hoger risico om vroegtijdig te overlijden. Wellicht dat deze vroegtijdige sterfte niet zozeer verklaard wordt door atherosclerotisch vaatlijden, maar bijvoorbeeld door een overbelasting van het hart, hartritmestoornissen en hartfalen.

Geslachtsverschillen in hart- en vaatziekten en obesitas

Het is bekend dat vrouwen relatief beschermd zijn tegen het ontwikkelen van hart- en vaatziekten in vergelijking met mannen. Dit is met name het geval bij vrouwen voor de overgang. Pas vanaf het zeventigste levensjaar wordt het risico op hart- en vaatziekten bij mannen en vrouwen ongeveer gelijk. In **Hoofdstuk 3** is beschreven dat bij een groep patiënten met morbide obesitas, vrouwen nog steeds relatief beschermd zijn tegen hart- en vaatziekten en dat dit voordeel ten opzichte van mannen verdwijnt na de overgang. Daarbij is wel te zien dat de gevolgen van de overgang op vroege tekenen van aderverkalking minder uitgesproken zijn bij vrouwen met obesitas, in vergelijking met vrouwen met een gezond gewicht. Waarschijnlijk speelt de hormoonhuishouding een belangrijke rol in het ontstaan van hart- en vaatziekten bij vrouwen. Oestrogenen zouden zowel beschermend kunnen zijn voor aderverkalking als voor chronische ontstekingsprocessen in het lichaam die weer kunnen bijdragen aan aderverkalking. Terwijl de eierstokken de belangrijkste bron van oestrogenen zijn bij vrouwen in de vruchtbare leeftijd, worden oestrogenen na de overgang met name gevormd vanuit het vetweefsel. Bij een overmaat aan vetweefsel, zoals bij morbide obesitas, daalt het oestrogeengehalte mogelijk minder hevig na de overgang dan bij vrouwen met een gezond gewicht. Op die manier kan obesitas bij vrouwen na de overgang mogelijk bescherming bieden tegen de negatieve gevolgen van een lage oestrogeenspiegel op het ontstaan van hart- en vaatziekten.

De gevolgen van diabetes mellitus en chronische ontsteking op hart- en vaatziekten

Diabetes mellitus is een van de belangrijke risicofactoren voor hart- en vaatziekten. Diabetes mellitus zorgt voor schade aan de bloedvaten en kan hierdoor problemen veroorzaken in verschillende orgaansystemen, waaronder hart- en vaatziekten. Het is algemeen bekend dat personen met obesitas een groot risico hebben om diabetes mellitus te ontwikkelen. In **Hoofdstuk 4** is aangetoond dat obese patiënten die lijden aan diabetes mellitus, meer tekenen hebben van beginnende aderverkalking dan obese patiënten zonder diabetes. De mate van deze beginnende aderverkalking wordt echter vooral bepaald door de leeftijd, het geslacht, de bloeddruk en het cholesterol van de patiënt en niet zozeer door de aanwezigheid van de diabetes

mellitus zelf. Het lijkt dus niet specifiek de diabetes mellitus te zijn die het verschil in aderverkalking veroorzaakt, maar juist andere risicofactoren die frequenter lijken voor te komen bij patiënten met diabetes mellitus.

In de afgelopen decennia is gebleken dat ontstekingsprocessen in het lichaam een belangrijke rol spelen bij het ontstaan van aderverkalking. Het gaat hierbij om een laaggradige ontsteking die in het bloed gemeten kan worden. Mensen voelen zich hier in principe niet ziek bij, zoals bij een hevige longontsteking of een blindedarmontsteking. Gedacht wordt dat een belangrijke rol is weggelegd voor het afweersysteem in het ontstaan van aderverkalking; het afweersysteem zorgt ervoor dat witte bloedcellen zich kunnen ophopen in de vaatwand en daar plaques vormen die de basis zijn van de aderverkalking. Ook bij mensen met obesitas is sprake van een laaggradige ontsteking in het bloed. Waarschijnlijk worden vanuit het vetweefsel hormonen en eiwitten geproduceerd die betrokken zijn bij het afweersysteem. Gedacht wordt dat juist in deze ontsteking de verklaring ligt voor het hogere risico op hart- en vaatziekten bij morbide obesitas. In **Hoofdstuk 5** is naar voren gekomen dat de mate van ontsteking bij obese patiënten met diabetes mellitus hoger is dan bij patiënten zonder diabetes, al leidt dit uiteindelijk niet tot verschillen in de mate van aderverkalking.

Deel II: Behandelstrategieën voor obesitas

Behandelmethodes voor gewichtsverlies

Gewichtsverlies bij personen met obesitas leidt tot een kleiner risico op het ontwikkelen van hart- en vaatziekten en een verbetering van reeds aanwezige hart- en vaatziekten. Bij een gewichtsverlies van 5 tot 10% is reeds een sterke verbetering zichtbaar van de bloeddruk, het cholesterol en de glucosehuishouding bij patiënten met diabetes mellitus type 2. Gewichtsverlies is daarom een van de belangrijkste behandeldoelen voor patiënten met obesitas.

De eerste stap van de behandeling van overgewicht en obesitas is een levensstijlverandering, met gezondere voeding en meer lichaamsbeweging. Met dergelijke levensstijlaanpassingen kunnen mensen gemiddeld 5 tot 7% van hun initiële lichaamsgewicht verliezen. Helaas is het resultaat vaak maar van korte duur. Ook is veel onderzoek verricht naar medicijnen die gewichtsverlies kunnen geven, zoals orlistat, liraglutide en lorcarserine. Hiermee kunnen mensen gemiddeld 4 tot 8% van hun lichaamsgewicht verliezen. Toch worden deze middelen niet veel voorgeschreven, omdat er veel discussie is over de effectiviteit, het risico op misbruik, het risico op bijwerkingen en de kosten. Na het staken van deze medicijnen, komen de meeste patiënten weer aan in gewicht.

Voor personen met obesitas en morbide obesitas worden bariatrische operaties tegenwoordig gezien als de beste behandeling. Deze geven een substantieel gewichtsverlies van wel 60 tot 70% van het overgewicht, wat al snel kan neerkomen op circa 30 tot 35% van het initiële gewicht, met ook goede langetermijnresultaten. Daarbij is een sterke verbetering te zien van de bloeddruk, het cholesterol en de diabetes mellitus, waarbij een deel van patiënten zelfs volledig kan stoppen met de medicamenteuze behandeling. De meest uitgevoerde operaties zijn op dit moment de gastric bypass en de gastric sleeve. De maagband wordt tegenwoordig niet meer veel toegepast vanwege teleurstellende resultaten.

Bariatrische chirurgie in adolescenten

Obesitas wordt wereldwijd een steeds groter probleem. Ook bij kinderen en adolescenten komt obesitas steeds vaker voor. In de Verenigde Staten lijdt op dit moment 17% van alle kinderen aan obesitas. Daarmee hebben de kinderen een verhoogd risico om hart- en vaatziekten te ontwikkelen op latere leeftijd, zelfs als zij op volwassen leeftijd weer een relatief gezond gewicht hebben. Vroege behandeling lijkt het risico op de complicaties van obesitas te verlagen en er wordt steeds meer gedacht dat ook voor adolescenten bariatrische chirurgie overwogen moet worden als behandelstrategie. Op dit moment worden bariatrische operaties bij kinderen in Nederland enkel in studieverband uitgevoerd. Er is veel discussie over het verrichten van dergelijke operaties bij kinderen en adolescenten. De vraag is of jonge patiënten een weloverwogen beslissing kunnen nemen ten aanzien van een

dergelijke ingrijpende behandeling en of zij kunnen inschatten wat de korte- en langetermijngevolgen zijn van deze operaties en daarmee de impact op hun dagelijkse leven. Aan de andere kant is het de vraag of het ethisch verantwoord is om kinderen en adolescenten niet de best beschikbare behandeling te bieden en ze daarbij bloot te stellen aan een verhoogd risico om chronische aandoeningen te ontwikkelen, zoals diabetes mellitus en hart- en vaatziekten, en een verhoogd risico op vroegtijdige sterfte. In de zoektocht naar de beste chirurgische behandeling van obesitas voor adolescenten, inclusief langetermijnresultaten en patiëntentevredenheid, worden in **Hoofdstuk 6** de resultaten vergeleken van de gastric sleeve en de gastric bypass in jonge volwassenen. Beide operaties tonen goede resultaten ten aanzien van de mate van gewichtsverlies. Wel is het opvallend dat de compliantie van deze jonge patiënten teleurstellend is; zij verschijnen minder vaak op de vervolgafspraken, verdwijnen sneller uit de controle en een aanzienlijk deel komt direct na de operatie nooit meer terug voor controle.

Aangezien patiënten na een gastric sleeve minder risico hebben op langetermijn-complicaties, zoals ondervoeding of vitaminetekorten, zou de gastric sleeve als eventuele eerste-keus-operatie bij adolescenten de voorkeur hebben. Daarbij is het van essentieel belang dat een programma wordt opgezet om de therapietrouw van deze specifieke patiëntengroep te verbeteren.

Efficiëntie en veiligheid van bariatrische chirurgie

Aangezien het aantal patiënten met obesitas en obesitas-gerelateerde ziekten nog altijd toeneemt, lopen de gezondheidskosten ten gevolge van obesitas steeds verder op. Ook het aantal bariatrische operaties dat wereldwijd wordt uitgevoerd, neemt steeds verder toe met ruim 600.000 bariatrische operaties in 2014. Het is van belang om in de chirurgie te blijven zoeken naar methodes om de effectiviteit, de veiligheid en de kosteneffectiviteit van bepaalde operaties steeds verder te verbeteren. Zo worden bijvoorbeeld eisen gesteld aan het aantal keren dat een chirurg een bepaalde operatie uitvoert in een jaar; hoe vaker hij een operatie uitvoert, des te kleiner zou het risico op complicaties zijn. Ook in de medische industrie worden continu nieuwe hulpmiddelen en instrumenten ontwikkeld om operaties zo efficiënt en veilig mogelijk te laten verlopen. Voor verschillende soorten buikoperaties zijn in

de afgelopen decennia protocollen ontwikkeld onder de naam 'Enhanced Recovery After Surgery' (ERAS). Met behulp van dergelijke protocollen wordt de zorg rondom een specifieke operatie zoveel mogelijk gestandaardiseerd. De interventies bij deze protocollen zijn wetenschappelijk bewezen effectief om een spoedig herstel te bereiken met een laag risico op complicaties. **Hoofdstuk 7** beschrijft een dergelijk protocol specifiek voor bariatrische chirurgie, namelijk het protocol Enhanced Recovery After Bariatric Surgery (ERABS). Het implementeren van dit protocol heeft geleid tot een kortere opnameduur in het ziekenhuis en een kortere operatieduur, wat leidt tot een lager risico op wondinfecties, trombose en andere postoperatieve complicaties. Bij het gebruik van het ERABS-protocol werd ook geen toename gezien van het aantal ernstige complicaties dat zich voordeed en het lijkt derhalve een veilige manier om de efficiëntie en de kosteneffectiviteit te verbeteren.

Om patiënten veilig vroegtijdig te kunnen ontslaan uit het ziekenhuis na bariatrische chirurgie, is het van belang om eventuele signalen van complicaties vroegtijdig te kunnen herkennen. **Hoofdstuk 8** beschrijft een checklist die ontwikkeld is, waarin gebruikgemaakt is van standaard postoperatieve klinische parameters, zoals de lichaamstemperatuur, de hartfrequentie en de ontstekingswaarden in het bloed. Met behulp van een algoritme bepaalt de checklist of patiënten veilig kunnen worden ontslagen op de eerste dag na de operatie. De huidige checklist heeft een hoge negatief voorspellende waarde. Dat betekent dat als patiënten naar aanleiding van de checklist ontslagen konden worden uit het ziekenhuis, dat de kans klein was dat zij later alsnog een complicatie zouden ontwikkelen. Daarmee was het ontslag veilig. Helaas was de positief voorspellende waarde van de checklist nog zwak. Van alle patiënten die naar aanleiding van de checklist nog niet klaar waren voor ontslag, ontwikkelde slechts een klein deel een complicatie. Het overige deel moest ten onrechte langer opgenomen blijven in het ziekenhuis of aanvullende onderzoeken ondergaan. Door een jaarlijkse herevaluatie van de checklist met aanpassing van het algoritme, kan de checklist verder geoptimaliseerd worden, met een toename van de positief voorspellende waarde, zonder een verlies van de negatief voorspellende waarde.

Toekomstvisie

Een opmerkelijke bevinding in dit proefschrift is dat de mate van obesitas geen invloed lijkt te hebben op de ernst van de risicofactoren van hart- en vaatziekten. Gezien de vele factoren die een rol spelen bij het ontstaan van morbiditeit bij sterk overgewicht, is het mogelijk dat relaties pas kunnen worden aangetoond wanneer de onderzoeksgroepen voldoende aantallen patiënten bevatten. Het kan zijn dat deze studies daar niet aan voldoen. Derhalve lijkt uitbreiding naar studies met grotere aantallen patiënten noodzakelijk en kan intensivering van de samenwerking van Nederlandse bariatrische klinieken hierbij een unieke mogelijkheid bieden.

Een van de vragen die in dit kader beantwoord kan worden, heeft betrekking op de rol van de vetverdeling in verschillende stadia van obesitas. Bij toenemende obesitas lijkt met name het onderhuidse vetweefsel zich verder uit te breiden. Door de relatie tussen de vetverdelingspatronen en hart- en vaatziekten in kaart te brengen, kunnen wellicht op relatief eenvoudige wijze personen met een verhoogd risico op cardiovasculaire morbiditeit vroegtijdig geïdentificeerd worden. De vetverdeling kan bijvoorbeeld met behulp van DEXA-scans worden vastgesteld en vervolgens kunnen worden gecorreleerd met cardiovasculaire risicofactoren. Het gebruik van een DEXA-scan kent een aantal voordelen boven het gebruik van CT- of MRI-scans, zoals weinig stralingsbelasting voor de patiënt, de snelheid van het onderzoek en de kosten. Derhalve lijkt het een voor de hand liggende keuze om in onderzoek onder grote aantallen patiënten DEXA-scans te gebruiken.

Naast onderzoek naar de anatomische relatie tussen de vetverdeling en het risico op hart- en vaatziekten, is onderzoek naar de mechanismen van het ontstaan van comorbiditeit essentieel om in de toekomst patiënten beter en gerichter te kunnen behandelen. Dergelijk onderzoek dient gericht te zijn op de biologische activiteit van vetweefsel in de verschillende compartimenten en het effect op het metabolisme en het immuunsysteem. Het geeft inzicht in of vetweefsel het metabolisme en het immuunsysteem kan beïnvloeden en op welke wijze dit tot uiting komt bij verschillende vetverdelingen. Samenwerking tussen verschillende disciplines is noodzakelijk om de complexiteit van deze patronen te ontrafelen.

Voor de huidige studie is een samenwerking aangegaan met cardiologen om de kennis van hart- en vaatziekten en veranderingen bij obesitas, waaronder de cardiale functie, te integreren in de analyse van de comorbiditeit van obese patiënten. Onderzoek naar de pathofysiologie van de hartdysfunctie van patiënten met obesitas kan op deze wijze worden uitgebreid door een relatie te leggen met de karakteristieken van obese patiënten in de huidige studies. De eerste resultaten van deze gezamenlijke aanpak worden in 2020 verwacht. Ook hier zal validatie in grotere cohorten waarschijnlijk nodig zijn, hetgeen ook in dit opzicht het belang van een multidisciplinaire samenwerking op nationaal niveau onderstreept.

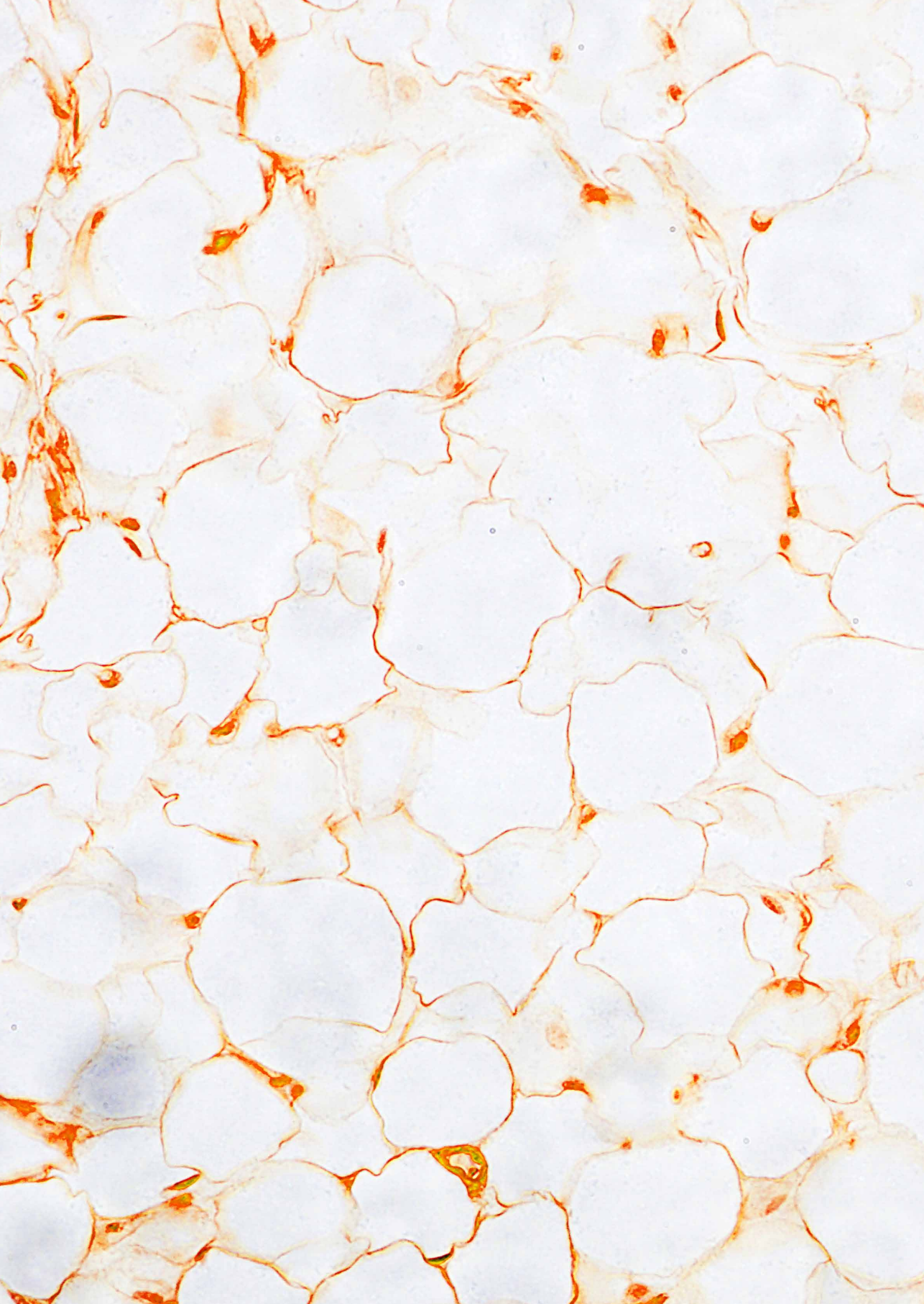
Een belangrijk vraagstuk in de bariatrische chirurgie is gericht op de identificatie van patiënten die het meeste profijt hebben van bariatrische chirurgie. De vraag is of het mogelijk is om voorafgaand aan de operatie die patiënten te identificeren die uiteindelijk het beste resultaat zullen bereiken, zowel op het gebied van gewichtsverlies als op het gebied van het verbeteren van obesitasgerelateerde ziekte. Aan de hand van het huidige proefschrift wordt gedacht dat de BMI van patiënten niet de belangrijkste leidraad moet zijn om de behandelkeuze te bepalen. Eerdere studies laten immers zien dat er geen relatie bestaat tussen de preoperatieve BMI en de kans op vermindering van hart- en vaatziekten na de operatie. Ook is aangetoond dat de BMI geen voorspellende waarde heeft voor de cardiovasculaire gezondheid van morbide obese patiënten. Verder onderzoek dient gericht te zijn op een nadere analyse van verschillende patiëntenkarakteristieken en het risico op hart- en vaatziekten om voorspellende markers te kunnen definiëren. Zo is bijvoorbeeld aangetoond dat patiënten met een hoog nuchter bloedsuikergehalte of hoge insulinespiegels een beter resultaat behalen na bariatrische chirurgie en dan met name een vermindering van het overlijdensrisico ten gevolge van hart- en vaatziekten. Ook is aangetoond dat obese patiënten met slaapapneu meer risico hebben op hart- en vaatziekten en dat bariatrische chirurgie dit risico kan beïnvloeden door het gunstige effect van de ingreep op de ernst van de slaapapneu. Ook de invloed van het geslacht op de uitkomsten van bariatrische chirurgie verdient meer aandacht. Het merendeel van de patiënten in de huidige studies is vrouw, terwijl juist mannen een hoger risico lijken te hebben op hart- en vaatziekten. Nader onderzoek is nodig om aan te tonen of vrouwen en mannen

op gelijke wijze profiteren van bariatrische chirurgie. Tot op heden ontbreekt een voorspellend profiel van patiënten die duidelijk baat hebben bij bariatrische chirurgie. Dergelijke voorspellende karakteristieken dienen uiteindelijk opgenomen te worden in richtlijnen om zowel de patiënten als de artsen juist te informeren. Op dit moment is aan te bevelen om mannen met morbide obesitas, patiënten met hoge bloedsuiker- of insulinespiegels en patiënten met slaapapneu eerder te behandelen. Ten aanzien van het type operatie geeft de gastric bypass een betere afname van hart- en vaatziekten dan de sleeve-resectie en zou derhalve de voorkeur genieten voor deze patiëntengroep.

Bariatrische chirurgie kan leiden tot significant gewichtsverlies en een verbetering van hart- en vaatziekten. Echter, vervolgonderzoek na bariatrische chirurgie toont aan dat tot 50% van de geopereerde patiënten uiteindelijk alsnog diabetes mellitus of hart- en vaatziekten ontwikkelt of terugkrijgt, ook zonder opnieuw aan te komen in gewicht. Behandelde morbide obese patiënten lijken op deze wijze dus nog steeds een verhoogd risico op vroegtijdig overlijden te houden in vergelijking met controlepersonen. Derhalve blijft de noodzaak bestaan om patiënten na succesvolle bariatrische chirurgie te blijven controleren om langetermijnrisico's vroegtijdig op te sporen en te behandelen. In het geval van nieuwe gewichtstoename kan eventueel een tweede bariatrische operatie worden overwogen. De effecten hiervan op het gebied van gewichtsverlies lijken vooralsnog beperkt, maar er worden zeker effecten op het gebied van de reductie van de comorbiditeit gezien. Het effect hiervan dient nader te worden onderzocht voor verschillende subgroepen, zoals mannen en vrouwen en verschillende leeftijden.

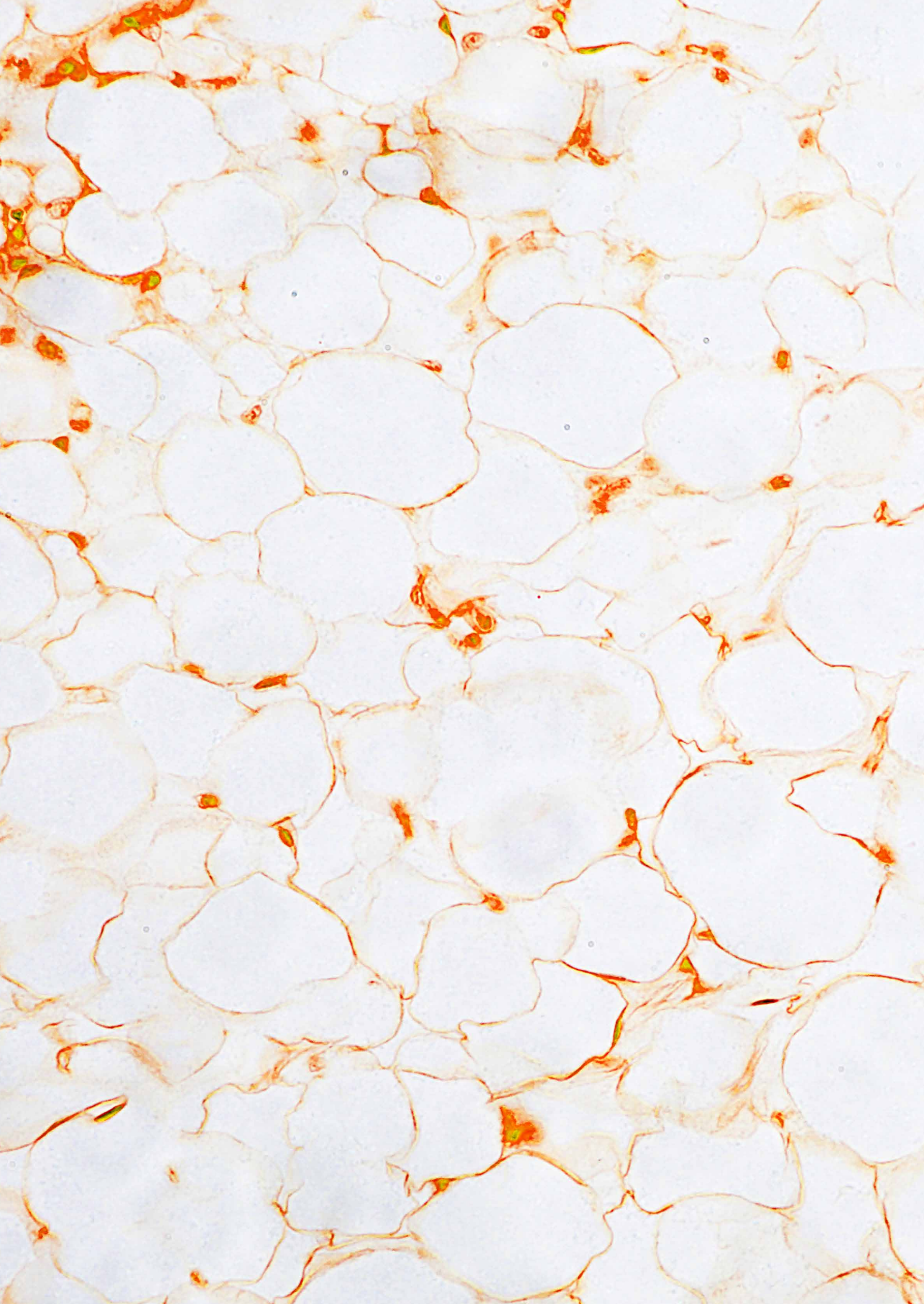
Met deze huidige studies zijn de eerste stappen gezet voor een gerandomiseerd onderzoek naar verschillende operatietechnieken voor morbide obese adolescenten in de leeftijd van 16 tot 18 jaar. Een intensief begeleidingsprogramma met betrokkenheid van de chirurg, de internist, de kinderarts, de fysiotherapeut, de diëtist en de psycholoog is noodzakelijk om een bariatrisch programma onder adolescenten te laten slagen. Met name bij deze jongeren is het essentieel dat de behandeling meer omvat dan de operatie alleen. Onder andere uitgebreide educatie over de preventie van obesitas en de preventie

van gewichtstoename na bariatrische chirurgie dient onderdeel te zijn van het programma om jongeren te helpen om een gezonde levensstijl te ontwikkelen en te behouden. Bariatrische chirurgie zal uiteindelijk met name een plaats krijgen voor de behandeling van patiënten met een hoog risico op complicaties van morbide obesitas. Verder onderzoek, ook in verschillende subgroepen van patiënten met ernstig overgewicht, zal zich uiteindelijk niet alleen richten op het effect van de operatie op het gewichtsverlies en de verbetering van de comorbiditeit, maar ook op de kwaliteit van leven en de levensverwachting van patiënten met morbide obesitas.



Appendices

Portfolio, list of publications, curriculum vitae, dankwoord



Appendix 1

PhD portfolio

name PhD student:	Stefanie Ramona van Mil
Erasmus MC department:	Surgery
PhD period:	2014 - 2019
promotor:	Prof. dr. J.N.M. IJzermans
co-promotor:	Dr. M. Castro Cabezas

1. PhD training

General Courses	year	ECTS
– Scientific Writing in English	2014	1.0
– ICH-GCP	2014	1.0
– Biostatistical Methods 1	2014	5.7
– Course 'Wetenschappelijk Onderzoek'	2015	0.5

Presentations at (inter)national conferences	year	ECTS
– Vitamin D is inversely associated with BMI and inflammatory markers in morbid obesity. Netherlands Association for the Study of Obesity, Oosterbeek, Nederland.	2014	0.5
– Sleeve Gastrectomy versus Gastric Bypass in late adolescents. International Federation for the Surgery of Obesity and metabolic disorders world congress 2014, Montreal, Canada.	2014	0.5
– Complement C3 and vitamin D; a central role in both immunology and metabolism in morbid obesity. Symposium "Dik of dun", Franciscus Gasthuis & Vlietland, Rotterdam, Nederland.	2014	1.0
– Minibattle preoperatief dieet en gewichtsverlies. Roundtable meeting 2015, Feyenoord de Kuip, Rotterdam, Nederland.	2015	1.0
– Results of implementing an Enhanced Recovery After Bariatric Surgery (ERABS) protocol. Wetenschapsdag 2015 Franciscus Gasthuis & Vlietland, Rotterdam, Nederland.	2015	1.0

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		year	ECTS
–	Laparoscopische sleeve gastrectomie versus gastric bypass in late adolescenten; wat is de optimale chirurgische behandelstrategie? Dutch Society of Metabolic and Bariatric Surgery Congres 2015, Doorn, Nederland.	2015	1.0
–	Vitamin D is inversely associated with BMI & inflammatory markers in morbid obesity. Vitamin D Workshop 2015, Delft, Nederland.	2015	0.5
–	Results of implementing an Enhanced Recovery After Bariatric Surgery (ERABS) protocol. International Federation for the Surgery of Obesity and metabolic disorders world congress 2015, Wenen, Oostenrijk.	2015	0.5
–	Discrepancies in the relationship of BMI and traditional cardiovascular risk factors in subjects with different levels of obesity. European Association for the Study of Diabetes annual meeting 2015, Stockholm, Zweden.	2015	0.5
–	The postoperative checklist for bariatric surgery. Obesity Week 2015, Los Angeles, Verenigde Staten.	2015	0.5
–	Discrepancies in the relationship of BMI and traditional cardiovascular risk factors in subjects with different levels of obesity. Obesity Week 2015, Los Angeles, Verenigde Staten.	2015	1.0
–	Acute complement C3 veranderingen ten gevolge van bariatrische chirurgie. Wetenschapsdag 2016 Franciscus Gasthuis & Vlietland, Rotterdam, Nederland.	2016	0.5
–	Discrepanties in de relatie tussen BMI, vetweefsel volume, klassieke cardiovasculaire risicofactoren en vetweefsel inflammatie. Wetenschapsdag 2016 Franciscus Gasthuis & Vlietland, Rotterdam, Nederland.	2016	1.0
–	De postoperatieve checklist voor bariatrische chirurgie; welke parameters zijn zinvol om te meten? Dutch Society of Metabolic and Bariatric Surgery Congres 2016, Doorn, Nederland.	2016	0.5
–	Acute complement C3 veranderingen ten gevolge van bariatrische chirurgie. Dutch Society of Metabolic and Bariatric Surgery Congres 2016, Doorn, Nederland.	2016	1.0
–	Discrepanties in de relatie tussen BMI, vetweefsel volume, klassieke cardiovasculaire risicofactoren en vetweefsel inflammatie. Dutch Society of Metabolic and Bariatric Surgery Congres 2016, Doorn, Nederland.	2016	1.0
–	The postoperative checklist for bariatric surgery; which parameters should be used? International Federation for the Surgery of Obesity and metabolic disorders, European Obesity Summit 2016, Gothenborg, Zweden.	2016	0.5

	year	ECTS
– Acute complement C3 changes after bariatric surgery. International Federation for the Surgery of Obesity and metabolic disorders, European Obesity Summit 2016, Gothenborg, Zweden.	2016	0.5
– Discrepancies in the relation of BMI, adipose tissue volume, classic cardiovascular risk factors and adipose tissue inflammation. International Federation for the Surgery of Obesity and metabolic disorders, European Obesity Summit 2016, Gothenborg, Zweden.	2016	0.5
– Obesitas en cardiovasculaire morbiditeit en mortaliteit. Grensvlak symposium 2016, Olioeducatie, Sint Michielsgestel, Nederland	2016	1.0

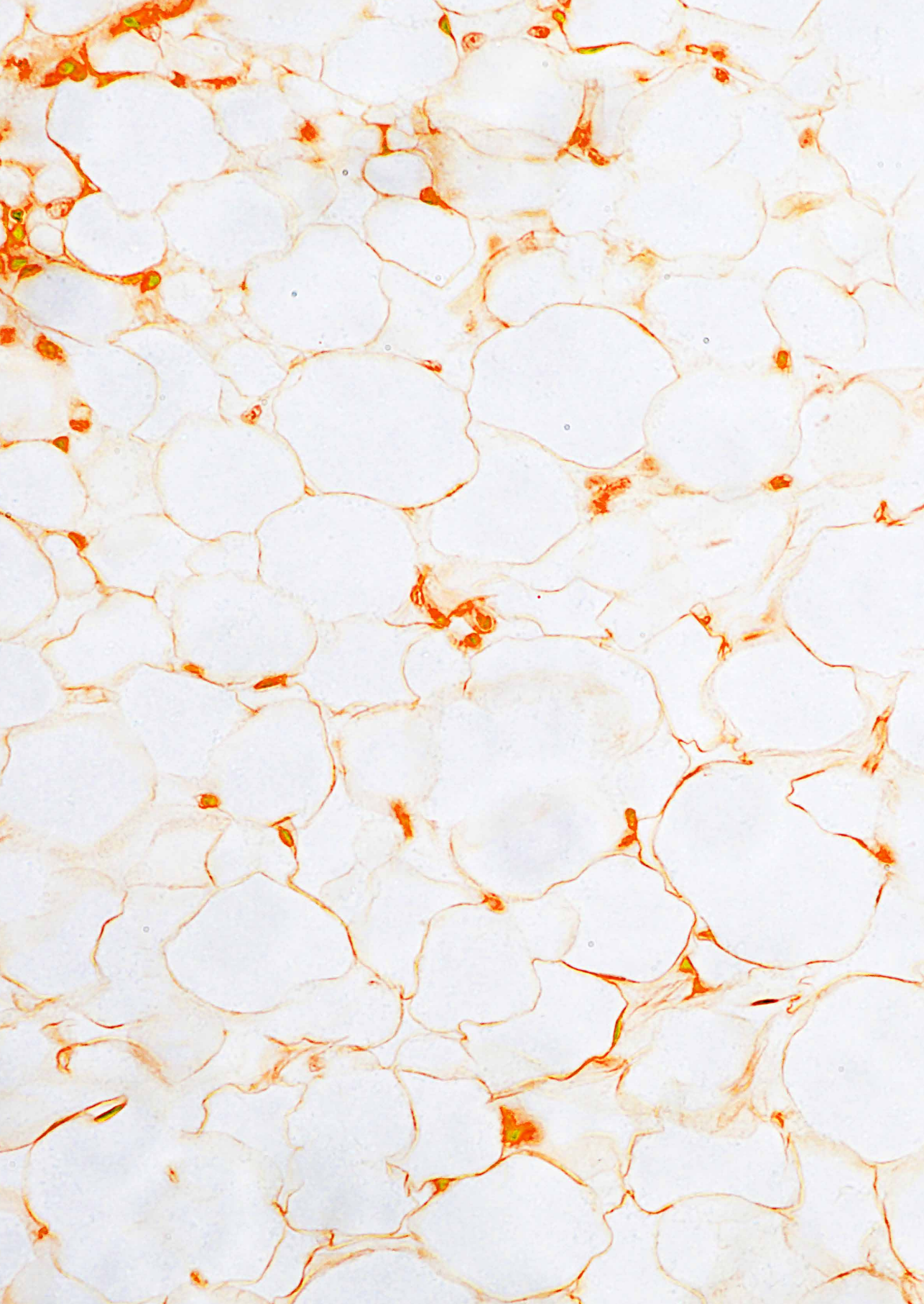
(Inter)national conferences (0.3 points/day)	year	ECTS
– Chirurgendagen	2014–2019	3.6
– International Federation for the Surgery of Obesity and metabolic disorders (IFSO)	2014–2016	3.0
– Dutch Society of Metabolic and Bariatric Surgery Congres (DSMBS)	2015–2016	0.6
– ASMBS Obesity week	2014–2015	2.7

Other	year	ECTS
– Organising committee Franciscus Wetenschapsdag 2016	2015 – 2016	2.0
– Development and implementation of digital QoL questionnaires on the outpatient department	2015	2.0
– Implementation of the DATO registration in the electronic patient system, with verification of the data	2015 – 2016	3.0

2. Teaching

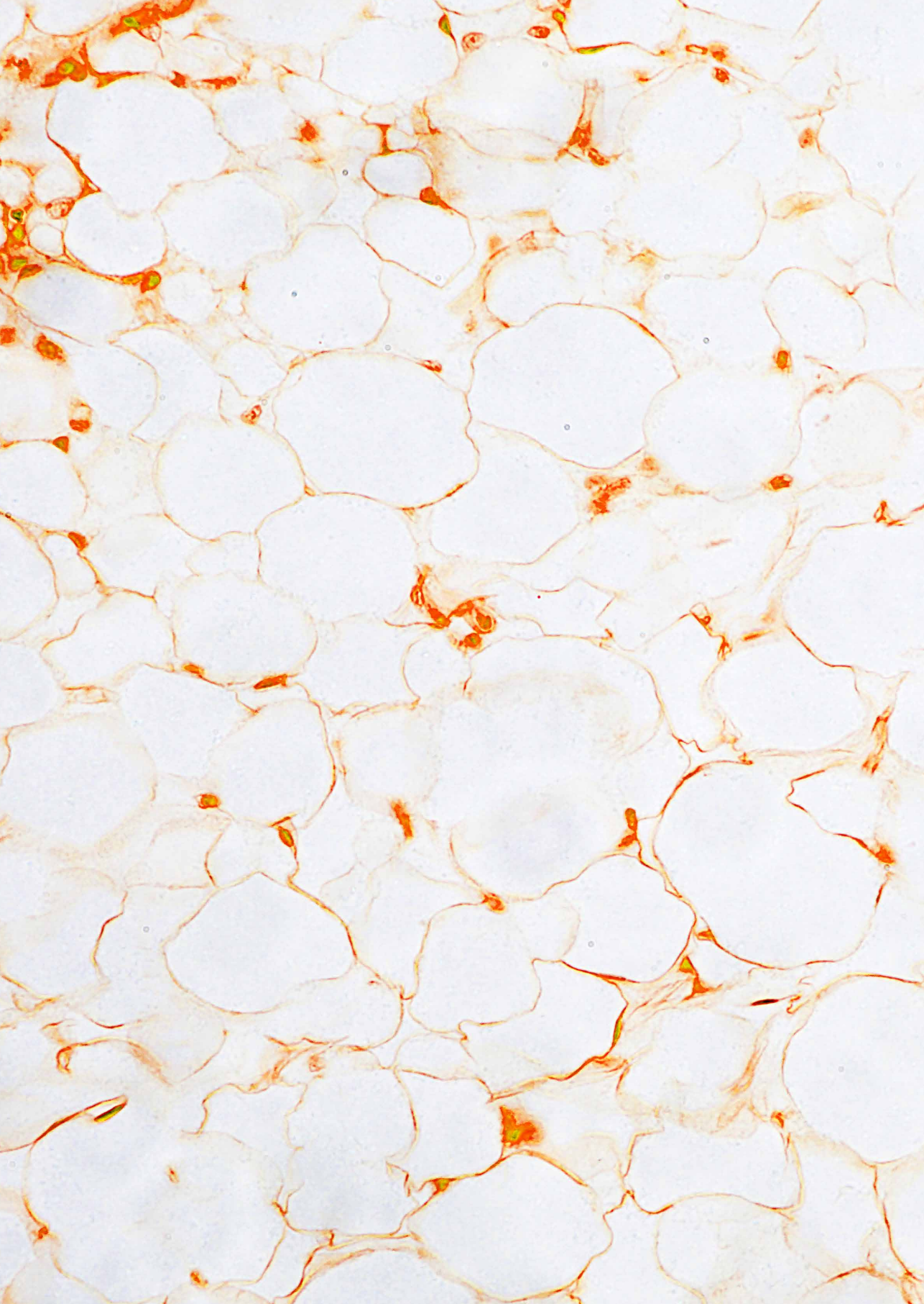
Lecturing	year	ECTS
– Lecturing at Department of Surgery, Internal Medicine and Clinical Chemistry, Franciscus Gasthuis & Vlietland, Rotterdam, Nederland	2015 – 2016	1.5
– Lecturing at Department of Surgery, Amphia ziekenhuis, Breda, Nederland	2017	0.3

Supervising Master's theses	year	ECTS
– Ashnaa Rahman	2016	1.0
– Metin Sahin	2016	1.0



Appendix 2 List of publications

1. Leeman M, van Mil SR, Biter LU, Apers JA, Verhoef K, Dunkelgrun M. Reducing complication rates and hospital readmissions while revising the enhanced recovery after bariatric surgery (ERABS) protocol. Surg Endosc. 2020 Feb 12. Online ahead of print.
2. Leeman M, van Mil SR, Al-Ghanam I, Biter LU, Dunkelgrun M, Castro Cabezas M. Structural and functional vascular improvement 1 year after bariatric surgery: a prospective cohort study. Surg Obes Relat Dis. 2019 Oct;15(10):1773-1779.
3. van Mil SR, Biter LU, van de Geijn GJM, Birnie E, Dunkelgrun M, IJzermans JNM, van der Meulen N, Mannaerts GHH, Castro Cabezas M. The effect of sex and menopause on carotid intima-media thickness and pulse wave velocity in morbid obesity. Eur J Clin Invest. 2019 Jul;49(7):e13118.
4. Walinga AB, van Mil SR, Biter LU, Dunkelgrün M, Vijgen GHEJ. A Stepwise Approach in Learning Surgical Residents a Roux-en-Y Gastric Bypass. Obes Surg. 2019 Feb;29(2):414-419.
5. van Mil SR, Vijgen GHEJ, van Huisstede A, Klop B, van de Geijn GM, Birnie E, Braunstahl GJ, Mannaerts GHH, Biter LU, Castro Cabezas M. Discrepancies Between BMI and Classic Cardiovascular Risk Factors. Obes Surg. 2018 Nov;28(11):3484-3491.
6. van Mil SR, Biter LU, van de Geijn GM, Birnie E, Dunkelgrun M, IJzermans JNM, van der Meulen N, Mannaerts GHH, Castro Cabezas M. Contribution of Type 2 Diabetes Mellitus to Subclinical Atherosclerosis in Subjects with Morbid Obesity. Obes Surg. 2018 Aug;28(8):2509-2516.
7. van Mil SR, Duinhouwer LE, Mannaerts GHH, Biter LU, Dunkelgrun M, Apers JA. The Standardized Postoperative Checklist for Bariatric Surgery; a Tool for Safe Early Discharge? Obes Surg. 2017 Dec;27(12):3102-3109.
8. Gadiot RP, Biter LU, van Mil S, Zengerink HF, Apers J, Mannaerts GH. Long-Term Results of Laparoscopic Sleeve Gastrectomy for Morbid Obesity: 5 to 8-Year Results. Obes Surg. 2017 Jan;27(1):59-63.
9. van Mil SR, Biter LU, Grotenhuis BA, Zengerink JF, Mannaerts GH. Laparoscopic Sleeve Gastrectomy versus Gastric Bypass in Late Adolescents: What Is the Optimal Surgical Strategy for Morbid Obesity? Eur J Pediatr Surg. 2016 Dec;26(6):487-493.
10. Biter LU, Gadiot RP, Grotenhuis BA, Dunkelgrün M, van Mil SR, Zengerink HJ, Smulders JF, Mannaerts GH. The Sleeve Bypass Trial: a multicentre randomized controlled trial comparing the long term outcome of laparoscopic sleeve gastrectomy and gastric bypass for morbid obesity in terms of excess BMI loss percentage and quality of life. BMC Obes. 2015 Aug 26;2:30.
11. Mannaerts GH, van Mil SR, Stepaniak PS, Dunkelgrün M, de Quelerij M, Verbrugge SJ, Zengerink HF, Biter LU. Results of Implementing an Enhanced Recovery After Bariatric Surgery (ERABS) Protocol. Obes Surg. 2016 Feb;26(2):303-12.



Appendix 3 - Nederlands

Curriculum vitae

Stefanie Ramona van Mil werd geboren op 25 januari 1985 te Schiedam als dochter van Peter en Jeanette van Mil. Rond de leeftijd van 6 jaar wilde ze graag veearts worden, maar binnen enkele jaren veranderde deze toekomstdroom in 'mensenarts'. Nadat ze in 2003 haar Vwo-diploma aan S.G. Spieringshoek in Schiedam behaalde, startte ze dan ook datzelfde jaar nog met haar studie Geneeskunde aan de Erasmus Universiteit in Rotterdam.

Tijdens haar studie greep ze iedere mogelijkheid aan om de gezondheidzorg in andere werelddelen te ontdekken, met stages en coschappen in Ecuador, Zuid-Afrika en Tanzania. In eerste instantie werd haar interesse getrokken door de Plastische en Reconstructieve chirurgie, waar zij ook enige tijd als onderzoekstudent werkzaam is geweest onder begeleiding van Dr. J.W. van Neck in het Erasmus MC, Rotterdam. De verschillende stages en coschappen leerden haar echter twee dingen: ze is een liefhebber van de snelle en efficiënte zorg, zoals we die in Nederland aanbieden, en haar hart ligt bij de Algemene Heelkunde.

Direct na het behalen van haar artsdiploma startte zij als ANIOS Chirurgie in het Sint Franciscus Gasthuis in Rotterdam, onder begeleiding van Dr. A.C. van der Ham en Dr. G.H.H. Mannaerts. De laatste was tevens - in samenwerking met dr. M. Castro Cabezas, vasculair internist - de initiator van haar promotieonderzoek binnen de bariatrische chirurgie, waar het huidige proefschrift het resultaat van is.

Sinds 1 januari 2017 volgt zij de opleiding tot chirurg in Onderwijs- en Opleidingsregio Rotterdam onder supervisie van Prof. Dr. L.L.A. van der Laan (Amphia ziekenhuis, Breda) en Dr. B.P.L. Wijnhoven (Erasmus MC, Rotterdam). Binnen deze twee klinieken zal zij zich verder specialiseren tot vaatchirurg.

Appendix 3 - English

Curriculum vitae

Stefanie Ramona van Mil was born on January 25th, 1985 in Schiedam, daughter of Peter and Jeanette van Mil. Around the age of 6 she wanted to become an 'animal doctor', but within a few years this dream changed to 'people doctor'. After she obtained her VWO diploma from S.G. Spieringshoek in Schiedam in 2003, she started studying Medicine at the Erasmus University in Rotterdam that same year.

During her studies she took every opportunity to discover health care in other parts of the world, with internships and clinical rotations in Ecuador, South Africa and Tanzania. Initially her interest was drawn to Plastic and Reconstructive Surgery, a field she worked in for some time as a research student under the supervision of Dr. J.W. van Neck at Erasmus MC, Rotterdam. Her various internships and working experience taught her two things: she thrives best in a fast and efficient working environment, as offered in Dutch healthcare, and her heart lies in General Surgery.

Immediately after obtaining her medical degree, she started as ANIOS Surgery in the Sint Franciscus Gasthuis in Rotterdam, under the supervision of Dr. A.C. van der Ham and Dr. G.H.H. Mannaerts. The latter was also - in collaboration with Dr. M. Castro Cabezas, vascular internist - the initiator of her PhD research in bariatric surgery, of which the current thesis is the result.

Since January 1st, 2017 she is a surgical trainee at Onderwijs- & Opleidingsregio Rotterdam under the supervision of Prof. Dr. L.L.A. van der Laan (Amphia ziekenhuis, Breda) and Dr. B.P.L. Wijnhoven (Erasmus MC, Rotterdam). Within these two clinics she will specialize to become a vascular surgeon.

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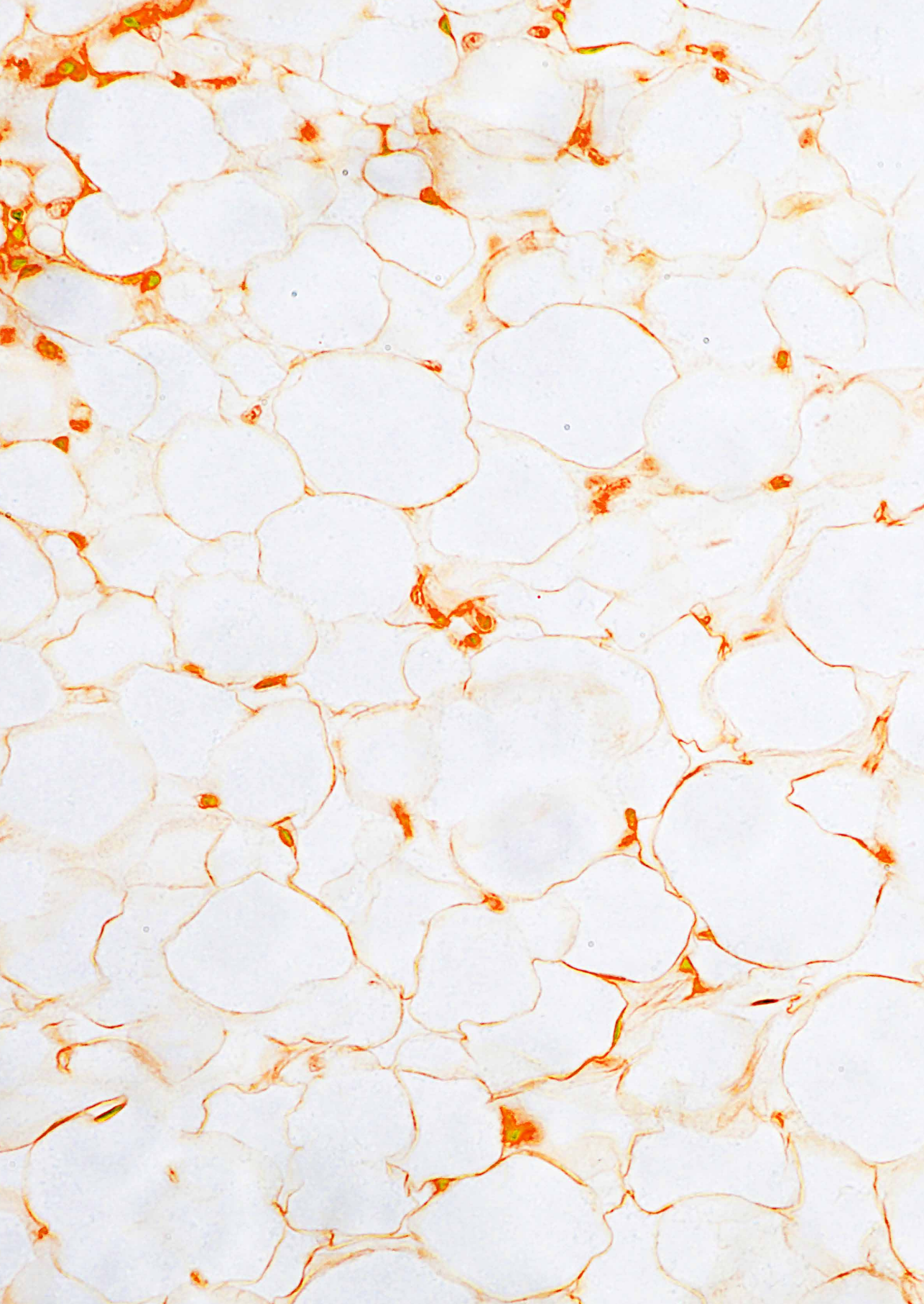

Appendix 4 - Nederlands

Dankwoord

Dat was het dan. Mijn boek is af. De verdediging is nabij. Het heeft even mogen duren, maar ik ben ontzettend blij dat ik dit project heb mogen afronden!
Ik had dit nooit alleen gekund, door de jaren ben ik door heel veel mensen geholpen. Ik wil jullie allemaal ontzettend bedanken voor alle hulp die jullie me gegeven hebben. Er zijn een aantal mensen die ik in het bijzonder wil bedanken.

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