Bariatric surgery: studies on its consequences with emphasis on thrombotic and bleeding complications
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General Introduction and Outline of the thesis

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Chapter 1

GENERAL INTRODUCTION

Obesity is a steadily growing problem that is associated with several diseases such as diabetes type 2, hypertension and dyslipidemia [1]. Large scale studies have shown that mortality rates are also increased in obese people [2]. The WHO estimates that at least 500 million adults (more than 10%) are obese [3]. The main treatment for obesity consists of adjustments of diet, physical exercise, and/or psychological interventions [4]. Several studies have been performed on the outcomes of diet programs and lifestyle interventions, however, for the majority of participants the long-term efficacy is limited [5]. For morbidly obese persons who have failed to achieve weight loss after several weight loss interventions, bariatric surgery is at this moment the only long-lasting, effective treatment [6].

Bariatric surgery includes a variety of procedures that can be grouped in three main categories: predominantly malabsorptive (biliopancreatic diversion), restrictive (sleeve gastrectomy, adjustable gastric banding) or mixed procedures that apply malabsorptive and restrictive techniques simultaneously (gastric bypass (GBP)). Mason and Ito initially developed the GBP procedure in 1969 [7]. Over several decades, the gastric bypass has been modified into its current form, the Roux-en-Y-gastric bypass (RYGBP). The RYGB is the most commonly performed operation. This procedure creates a small gastric pouch via stapling (10-30 ml), and a limb of the jejunum is attached to the pouch. Bariatric procedures have been able to achieve loss of more than 50% of excess weight [8].

Bariatric surgery is not only an effective option to lose weight. It is also associated with significant improvement or remission of diabetes, cardiovascular risk factors and reduction in mortality [9]. The surgery delivers structural and hormonal changes which can potentially cure diabetes. Further studies are still needed to get better insight in the pathogenesis of these metabolic changes after surgery. However, there is a variation in success in terms of weight loss and improvement of obesity associated comorbidities between patients, even with the same procedure. This might largely depend on the degree to which patients succeed in adopting healthy dietary behavior. Biological, psychological, genetic, and socio-economic factors have all been suggested to play a role. However, more studies are needed to explore these determinants.

While the efficacy of this treatment modality is often expressed as postoperative weight loss and improvement of comorbidities, an important outcome is also the impact of surgery
on psychological health. Although most previous research suggests that weight loss surgery leads to an increase in quality of life for the majority of patients, findings suggest that not everyone experiences mental health gains from weight loss surgery [10].

However, bariatric surgery is not without risk. Different complications can occur thereafter like anastomotic leak, infection or abdominal abscess and gastro-intestinal stenosis [11]. Besides the postoperative complications, diverse adverse effects have been reported after bariatric surgery. A common physical complaint after surgery is gastric dumping syndrome in about 20% of cases (bloating and diarrhea after eating, necessitating small meals or medication) [12]. Nutritional derangements due to deficiencies of micronutrients are common after malabsorptive bariatric procedures [13]. Patients have to take multivitamins every day. Metabolic bone disease manifesting as osteopenia and secondary hyperparathyroidism have been reported after RYGB due to reduced calcium absorption [14]. Rapid weight loss after bariatric surgery can also contribute to the development of gallstones [15].

There is also a higher risk of venous thromboembolism (VTE) [16] and bleeding complications after bariatric surgery leading to a higher rate of re-interventions and risk of mortality [17]. The incidence of VTE after bariatric surgery varies in the literature. There is a decreasing trend over years. Several factors might account for this trend, including increased surgical experience, improved equipment, more procedures done in high-volume centers, dedicated multidisciplinary bariatric teams, and patient selection. Nevertheless, VTE remains a concern in obese patients. The dramatic rise in the prevalence of obesity and bariatric surgery will also bring new challenges for healthcare. Severe obesity complicates the diagnostic process at the radiology department, because of size limitations or imaging quality limitations [18]. The alteration in the anatomy of the gastro-intestinal tract can cause difficulties in the diagnostic and therapeutic process. Another challenge is the limited experience with anticoagulant therapy in very obese patients. In the treatment and prevention of VTE it is necessary to find the right balance between the anticoagulant efficacy and risk of bleeding complications. Low molecular weight heparins are used to prevent thrombosis and to treat thrombosis in very obese patients after bariatric surgery. Obesity has an impact on the dosing of low molecular weight heparins, however, optimal dose and duration of thromboprophylaxis are uncertain [19]. More studies are needed to overcome this issue. Also, more information is needed about the impact of bariatric surgery on the pharmacokinetics of medication.
In short, we are learning more about the consequences of bariatric surgery, but many questions are still unanswered in different areas on the short and longer term after bariatric surgery.

**OUTLINE OF THE THESIS**

This thesis examines different consequences of bariatric surgery. In part I, we focus on venous thrombosis and bleeding complications after bariatric surgery. The aim is to explore the incidence and risk factors of these complications, to evaluate the effect of severe obesity and bariatric surgery on low molecular weight heparin and vitamin K antagonists, and to explore the problems that we encounter in diagnosing pulmonary embolism in these patients.

In part II, we describe other consequences of bariatric surgery. We investigate the longer term effects of bariatric surgery on sodium excretion which reflects dietary salt intake, and change of metabolic stress after surgery. In addition, we evaluate whether there is an influence of ethnic background on weight loss after bariatric surgery.

Chapter 2 describes the findings of an observational study on the overall incidence and risk factors of venous thrombosis in (morbidly) obese patients after bariatric surgery. In the same patients we analyzed the incidence and risk factors of major bleeding complications after bariatric surgery (Chapter 3).

We performed two studies on anticoagulant treatment after bariatric surgery. To evaluate the effect of total and lean body weight on the effect of low molecular weight heparin we performed an observational study after bariatric surgery in patients receiving fixed dose enoxaparin. This is described in Chapter 4. In Chapter 5 we show the effect of bariatric surgery on treatment with vitamin K antagonists and the chance of vitamin K deficiency after bariatric surgery.

We also pay attention to the limitations of CT and nuclear scans used for the diagnosis of pulmonary embolism in obese patients. The aim of Chapter 6 is to examine how often internists and radiologists encounter the problem of non-fitting in the CT scan because of size limitations and whether they have protocols about adjusting the radiation dose of the CT scan.
The first study in the second part of this thesis addresses urinary sodium excretion after bariatric surgery, which reflects salt intake. High salt intake may cause an important risk in the development of hypertension and kidney dysfunction. Many patients are still overweight or obese after surgery, despite considerable weight loss. The aim of Chapter 7 is to examine the mean sodium intake on the longer term after surgery and the relationship with weight loss and blood pressure.

To get more insight in the change of metabolic stress with weight loss, we performed a study with the Age Reader. Advanced glycation end products, as a measure of metabolic stress, were measured before and after bariatric surgery. This is described in Chapter 8.

It has been postulated that weight loss after bariatric surgery varies between ethnic groups. Chapter 9 is a meta-analysis on the ethnic differences in weight loss after bariatric surgery.

In addition, we describe in Chapter 10 a retrospective study on ethnic differences in weight loss after bariatric surgery in the Netherlands.
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