Perioperative physiology and optimalisation in bariatric and metabolic surgery

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PERIOPERATIVE PHYSIOLOGY *and* OPTIMALISATION *in* BARIATRIC *and* METABOLIC SURGERY

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PERIOPERATIVE PHYSIOLOGY AND OPTIMALISATION IN BARIATRIC AND METABOLIC SURGERY

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PARANIMFEN

Ben Verkerk
Sanne Tolk

‘So that one may walk in peace’

Imi Lichtenfeld (Founder of Krav Maga)

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PART II: METABOLIC PHYSIOLOGY

1. GENERAL INTRODUCTION

The obesity pandemic is reaching epic proportions (1) and bariatric surgery is the most effective long-term intervention for obesity. The National Institutes Of Health (NIH) consensus statement published 22 years ago largely governed the use of bariatric surgery worldwide. (2) Patients with a Body Mass Index (BMI) greater than 40 kg/m^2, or greater than 35 kg/m^2 with obesity related comorbidities such as type 2 diabetes, are eligible for bariatric surgery. Although these recommendations were carefully written and based on evidence (available at that time), they are outdated and have important limitations. (3, 4)

Anno 2016 this NIH statement is still used as guideline, but bariatric surgery is shifting to a more metabolic approach. Even the name 'bariatric surgery' might have to be changed to metabolic surgery. Nowadays there is more and more evidence present that the metabolic profile of patients need a selection criterion for surgery. It has become increasingly apparent that bariatric surgery exerts powerful, beneficial effects on metabolic diseases, such as type 2 diabetes mellitus (T2DM) (4-8), but also pulmonary and cardiac diseases, like asthma (9, 10) and heart failure. (11, 12) The only landmark study in bariatric and metabolic surgery, the Swedish Obese Subjects study has shown that bariatric surgery is capable of major reductions in cardiovascular risk factors, events and even mortality. (13)

The curiosity about the physiological mechanisms of bariatric and metabolic surgery is not a new phenomenon. The notion that rerouting of the gastro-intestinal tract alters glycaemia was first described in 1930 after surgery for peptic ulcer disease. (14) Bariatric surgical procedures were developed in the 1950's for weight loss primarily, but several reports showed that there was a rapid reduction of T2DM. (14) Pories et al. reported a T2DM reversal in 78% patients who underwent gastric bypass surgery, and proposed that T2DM might even be a surgical disease. (5, 15) Historically, bariatric surgery was meant to promote weight loss by causing gastric restriction and malabsorption. (5, 15) However, newer mechanistic/physiological studies, in parallel with the establishment that the gastro-intestinal tract is a primary regulator of the glucose homeostasis, showed that there is 'more than meets the eye'. Discrete parts of the gastro-intestinal tract have unique physiological functions; hence, the underlying mechanisms contributing to improved glucose homeostasis, clinical outcomes and physiological changes differ among anatomical procedures. (5, 7, 8, 15) Indeed, T2DM remission rates differ according to the type of surgery, with the lowest remission rates in purely restrictive procedures (such as laparoscopic gastric banding (LAGB)) and the highest rates in malabsorptive procedures, as reported by Buchwald et al. (8)

With increasing understanding of the physiology of the T2DM remission, more insights were also created regarding other physiological changes. One of those is the prevalence of nutrient deficiencies and how to optimise a patient prior to specific bariatric surgical procedures (16-18), but also the body of literature regarding cardiac (19) and pulmonary physiology (9, 10, 20) after bariatric surgery is growing. Moreover, the physiological mechanisms of the bariatric surgery on the amelioration of type 2 diabetes, cardiovascular and pulmonary diseases are thought to be weight-dependent but also weight independent (13) The thesis presented here will give insights about some aspects of cardiopulmonary and metabolic physiology following bariatric and metabolic surgery.

1.1 THESIS OUTLINE

In this thesis, several aspects of physiology following bariatric and metabolic surgery are described. It contains both clinical and literature-based research. The content of this thesis is divided in two parts. *The first part* describes the cardiopulmonary physiology after bariatric and metabolic surgery. *The second part* elaborates on two aspects of metabolic physiology: nutrient deficiencies and their treatment, and the remission of type 2 diabetes.

PART I: CARDIAC AND PULMONARY PHYSIOLOGY

Chapter 2 gives an overview of the cardiac structure and function changes before and after bariatric surgery. In chapter 3, the Nexfin® noninvasive continuous hemodynamic monitoring device was validated against blood pressure measurement according to Riva-Rocci/Korotkoff in obese patients scheduled for bariatric surgery. The results of a prospective cohort study investigating hemodynamic changes before and after surgery using the Nexfin® device are described in chapter 4.

The pulmonary physiology in patients with obesity and its considerations for perioperative care in bariatric surgery are described in chapter 5. Changes in maximal inspiratory muscle strength are one of the important pulmonary function alterations after bariatric surgery (chapter 6), but are very difficult to predict with the current available predictive equations. Chapter 7 gives a critical appraisal of the available predictive equations. In the final chapter of part I (chapter 8), the current evidence regarding perioperative exercise in bariatric surgery was systematically reviewed and this chapter an exercise advice was given.

PART II: METABOLIC PHYSIOLOGY

In chapter 9, the variations in supplementation regimes to treat perioperative vitamin B12 deficiencies were systematically reviewed and analysed. Chapter 10 is a retrospective matched cohort study to assess the effectiveness of three different intramuscular vitamin B12 supplementation regimes. Nowadays, nutrient deficiencies are quite common after bariatric surgery, but there seems to be differences in the deficiencies after several surgical procedures. In Chapter 11, we aimed to develop an algorithm to improve and optimize the screening for nutrient deficiencies after bariatric surgery. The final chapter of part II (chapter 12) assessed the time to glycemic control after several bariatric surgical procedures.

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PART I: CARDIAC AND PULMONARY PHYSIOLOGY

2. CARDIAC STRUCTURE AND FUNCTION BEFORE AND AFTER BARIATRIC SURGERY; A NEW PERSPECTIVE

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ABSTRACT

Obesity, defined as a body Mass Index of ≥30 kg/m2, is the most common chronic metabolic disease worldwide and its prevalence has been strongly increasing. Obesity is associated with various diseases such as cardiovascular disease, type 2 diabetes, hypertension, obstructive sleep apnoea syndrome, rheumatoid arthritis and neoplasms. Obesity has deleterious effects on cardiac function. The purpose of this review is to evaluate the cardiac function and structure changes and hemodynamic responses to obesity before and after excessive weight loss. Secondly, to elucidate the possible clinical implications of cardiac remodelling after bariatric surgery for perioperative and anesthesiological care.

2.1 INTRODUCTION

Obesity, defined as a Body Mass Index (BMI) of ≥30 kg/m2, is the most common chronic metabolic disease worldwide and its prevalence has been strongly increasing. (1) Obesity is associated with various diseases such as cardiovascular disease, type 2 diabetes, hypertension, obstructive sleep apnoea syndrome (OSAS), together called the metabolic syndrome (2)

Obesity has physiological effects on several organ systems, like pulmonary and cardiac function. Obesity induces pulmonary and cardiac changes that can result in right and/or left heart failure. (3) Basically, the pathophysiological mechanism is multifactorial. With moderate or severe obesity, significant increments in blood volume are found (this reflects an increased size of the vascular bed) and this paralleled with an increase in cardiac output. (3) Under this state of increased cardiac output, renal and cerebral blood flow remains roughly the same (compared to 'ideal body weight'). (3) Results from inert gas washout studies showed that excess body fat incorporates an extra blood flow of 2-3ml/min/100g. This means that 100 kg of excess body fat would require as much as 3L/min blood flow, that implicates an increase in cardiac output. (3) Actually, the blood volume and cardiac output of an individual of 170 kg are roughly twice those of a subject of 70 kg. (3) It is a clinical observation that obese patients do not suffer tachycardia; per physiology there must be an increase in stroke volume to reach the high cardiac output. (3, 4)

This basically means that obesity results in augmented left ventricular preload (volume) and often increased afterload (hypertension), with maintenance of a high output state at the expense of elevated right and left ventricular filling pressures. (3, 4)

Some of the cardio-pulmonary changes to obesity are associated with obstructive sleep apnoea (OSA) and obese hypoventilation syndrome (OHS). OHS is characterised by chronic hypoxia, hypercapnia and respiratory acidosis. (3) This chronic hypoxia and hypercapnia result mainly in pulmonary vasoconstriction. (3) The presence of high pre-existing pulmonary blood flow in conjunction with pulmonary vasoconstriction lead to pulmonary hypertension and a significant trans-pulmonary diastolic pressure gradient in addition to elevated left ventricular filling pressures. (3, 4)

A large amount of information on obesity and cardiac function is available. In this review, we will evaluate the cardiac function, structural changes and hemodynamic responses to obesity by integrating the influence of volume and pressure on both the left and the right ventricles. Secondly this review aims to elucidate the possible clinical implications of cardiac remodelling after excessive weight loss by bariatric surgery for perioperative and anesthesiological care.

2.2 PRIOR TO BARIATRIC SURGERY: 'THE OBESE'

2.2.1 CARDIAC GEOMETRY

Left ventricle

The chronic volume overload (preload) and hypertension (afterload) in obesity, lead to compensatory mechanisms as left ventricular enlargement and hypertrophy. To determine the degree of hypertrophy, the thickness of the basal interventricular septum (IVST) and posterior wall (PWT) are measured by echocardiography; a mathematical formula is used to estimate left ventricular mass (LVM) from these measurements. (Figure 2.1). (5) An increase in wall thickness (IVST, PWT) with normal LVM is defined as concentric remodelling as opposed to concentric hypertrophy (in which LVM is also increased).(5)

Both volume-overload induced by the increased blood volume and hypertension induce left ventricular remodelling in the obese. (4, 6-8) Indeed, it has been observed that the left ventricle dilates in the obese, resulting in increased diastolic and systolic volumes compared to lean. (9) On the other hand, it is also reported that obesity is frequently associated with either concentric or eccentric remodelling (2.6-74%). Figure 2.2 gives an overview of the pathophysiological changes induced by obesity on the cardiac and hemodynamic function.

Right ventricle

Although right ventricular dysfunction is more common in the obese, right ventricular (RV) function has gained much less attention than left ventricular function. One study showed an increase in right myocardial performance index, as well as isovolumetric contraction and relaxation time together with reduction RV ejection time compared to lean subjects.(10) These observations indicate both systolic and diastolic dysfunction in obese patients.

Another study showed a significant greater RV mass in obese, as well as RV end-diastolic and end-systolic volumes, and RV stroke volume (as measured by MRI), however without differences in RV ejection fraction between obese and lean.(7) This suggests a mechanism where a reduction in stroke volume (and ejection fraction) is compensated by the Frank-Starling mechanism. As a result, ejection fraction remains constant at the expense of ventricular dilation.

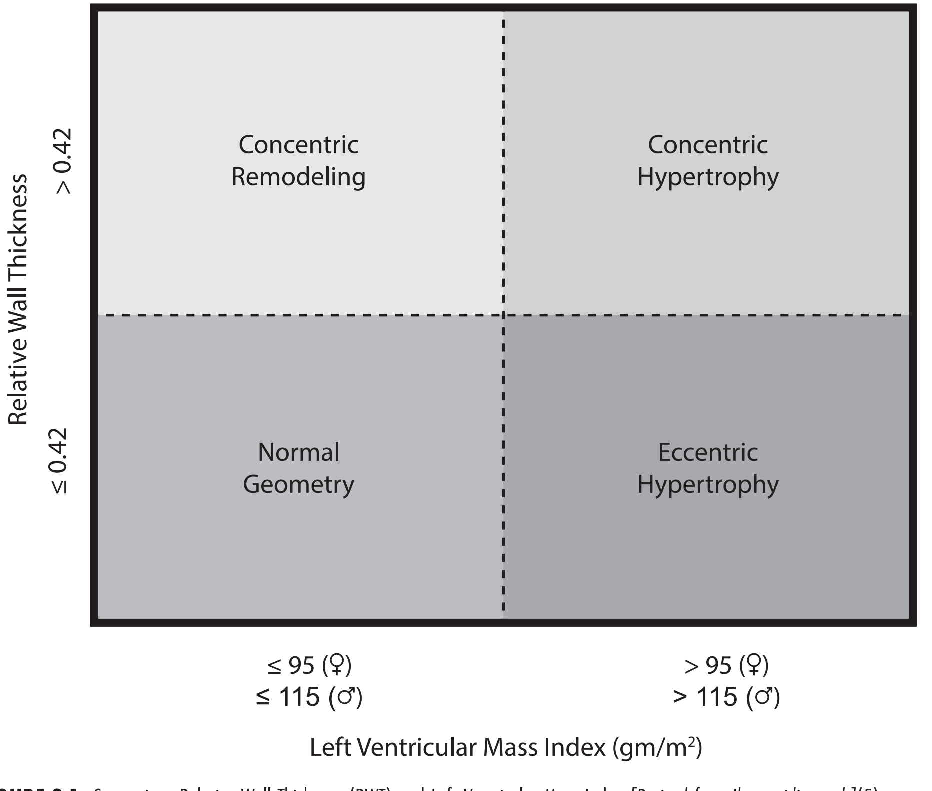

FIGURE 2.1: Comparison Relative Wall Thickness (RWT) and Left Ventricular Mass Index *[Derived from Ikonomidis et al.]*(5)

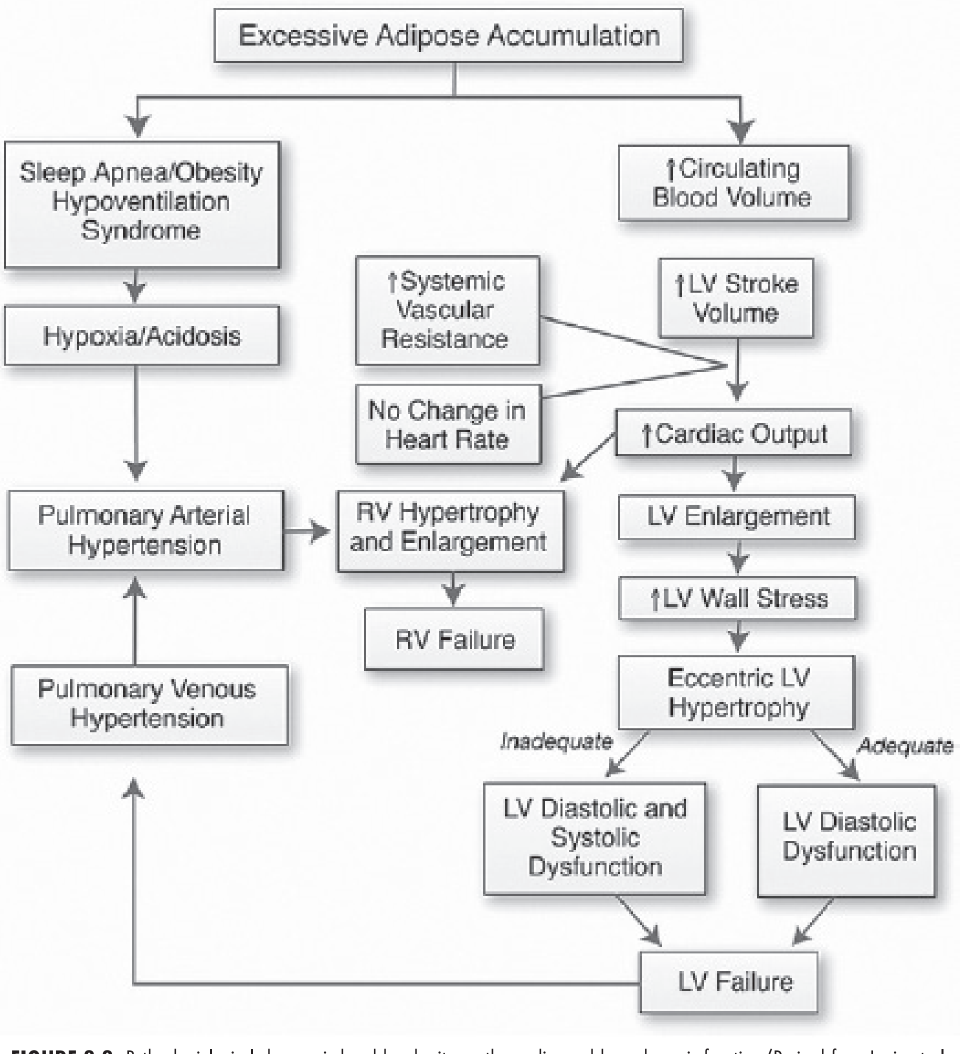

FIGURE 2.2: Pathophysiological changes induced by obesity on the cardiac and hemodynamic function (Derived from Lavie et al. (59) and Adams et al. (60))

2.2.2 SYSTOLIC AND DIASTOLIC FUNCTION

Most people with obesity have normal to normal-high hemodynamic function, in terms of heart rate and blood pressure.(6, 7, 11-14) However, obese often suffer hypertension compared to lean, frequently as part of the metabolic syndrome. Also, a significant greater stroke volume and cardiac output (6, 7) (or an increasing trend (10)) is observed.

Systolic function is often similar between obese and lean.(11, 15, 16) No significant difference, or only a decreasing trend, was found in LV ejection fraction (EF) and LV fractional shortening (FS) (one-dimensional surrogate of ejection fraction).(4, 6, 7, 10, 17)

Diastolic dysfunction is quite common in obese,(4, 7, 12, 15) which is probably a consequence than a cause given the higher incidence of LVH in obese. The ratio of the mitral peak velocity of early filling to late filling (E/A-ratio) is <1 in 17-52.9% of the obese, (11, 13, 16, 17) and significant more reduced compared to lean.(6) Also, increased deceleration time and isovolumetric relaxation time are found in obese,(8) as well as increased LA dimensions. (6, 8) All of them are seen in diastolic dysfunction.

2.2.3 CHRONIC HEART FAILURE

The mean duration of obesity is a significant factor for left and/or right ventricular failure. (18) No direct relationship was found in mean body mass index (BMI), heart rate, and systolic and diastolic blood pressures between obese with and without chronic heart failure. (18)

2.3 AFTER BARIATRIC SURGERY: THE “NOT SO” OBESE

2.3.1 WEIGHT LOSS

Most people with obesity develop significant weight loss after bariatric surgery, however, they remain clinically obese with a BMI around 29-34 kg/m2 after 3-36 months and even after 10 years of surgery. (4, 7, 8, 10-17, 19-38) Most weight loss is seen in the first three months and declines in the months thereafter, with a smaller decrease in weight 6-36 months after surgery. (8, 12, 15-17, 19, 24, 27, 30) In these first three months, the cardiac remodelling must occur.

2.3.2 HEMODYNAMIC FUNCTION

The effect of excessive weight loss on blood pressure varies widely. Several studies found a short and long term significant improvement in systolic and diastolic blood pressure, (13, 15-17, 26, 29, 30, 37) as well as a significant decrease in mean arterial blood pressure.(4,

22) However other studies showed only a long term significant decrease in systolic blood pressure,(8, 14, 21, 36) while others have the opposite results; a significant decrease in diastolic blood pressure.(10, 25, 27) About the same amount of studies found no short and long-term significant differences in systolic or diastolic blood pressure or only a decreasing trend.(7, 8, 10-12, 19, 20, 22, 23, 28, 31, 33) When a (significant) decrease is seen, it is often in obese with high blood pressure and/or LVM before surgery.(20, 35)

A similar effect is seen on heart rate; Several studies found a significant decrease in heart rate 3-24 months, and even 3.6-10 years, after surgery,(6, 10-14, 22, 25-27, 36, 37) but just as much other studies did not found any significant changes in heart rate after 4-24 months, or only a decreasing trend.(4, 7, 19, 20, 28, 31-33, 35) It seems that pre-existing hypertension or LVH is a prerequisite for reverse remodelling after surgery.

More effect of excessive weight loss in systolic function is seen in cardiac output and stroke volume. Cardiac output was the only systolic parameter, in all studies, which reported it, showed a significant decrease after 6-24 months and even after 10 years.(6, 7, 10, 13, 14, 22) A significant reduction, or a decreasing trend, in stroke volume was found after 3-24 months and even after 10 years (by decrease in EDV and ESV) (6, 7, 10, 22, 31) however, one study with a decreasing trend after 3 months, showed a return to baseline after 17 months, while BMI continued to decline.(27) These changes indicate an improvement in volume overload, which can be the start of normalization of cardiac remodelling.

2.3.3 CARDIAC GEOMETRY

Left ventricle

Excessive weight loss can lead to a significant reduction in LV dimensions after 3-36 months and even after 10 years.(7, 8, 10, 15, 16, 22, 23, 32) Sometimes, a significant improvement is only seen in obese with LVH before surgery,(4, 20, 35) and a decreasing, but not significant, trend in obese without LVH before surgery.(20) However, it does not always lead to significant changes, or a decreasing trend after 3-24 months.(4, 6, 13, 14, 21, 26, 28, 29, 31, 33, 37) Some studies even found an increase in LV end-diastolic or end-systolic dimension after 6-36 months.(17, 27)

In almost every study, LVM, LVM/height2.7 or LVM/BSA decreases significantly after 3-36 months and even after 3.6-10 years of excessive weight loss.(6-8, 10, 11, 14-17, 19, 21-27, 29, 30, 32, 36, 37) It continues to decrease linear up to 24-36 months, while most other variables, such as weight loss, plateaus after several months.(12, 13, 17, 19, 28) One study only showed a significant reduction in LVM in obese with LVH before surgery, but not in people without LVH.(35) A significant decrease was not always found in LVM/BSA after 3-36 months,(7, 8, 17, 27, 31) which is probably the result of a proportional decrease in LVM and body surface area after excessive weight loss. Also, no change in LVM/end-diastolic volume ratio is seen and remained higher than in lean people after 12 months.(7) In addition to the decrease in LVM, a significant reduction is also seen in IVST and PWT after 3-36 months and even after 3.6 years of excessive weight loss,(8, 15, 16, 22, 24-26, 28, 36) as well as in RWT.(6, 13, 14, 17, 21, 26, 29) However, not all studies found significant decrease in these parameters after 3-36 months,(12, 17, 23, 37) or only in obese with LVH, but not in obese without LVH before surgery.(35) Improvement in LV geometry is observed after 3-36 months of excessive weight loss. (13, 16, 17, 21, 26)

One study showed a complete normalization in geometry in 36.6% of the obese, 51.2% changed into an improved pattern, 39% showed no changes and 9.8% became worse, after 12 months.(13) However, another group found no mean significant changes in the prevalence of LVH in obese 12 months after surgery; A normalized geometry was seen in 9.6%, though 12.0% developed a new LV geometry anomaly.(23)

Right ventricle

Excessive weight loss causes a significantly decrease in RV mass after 3-24 months.(7, 14, 27) RV dimensions are often not improved after 3-17 months,(15, 25, 27, 37) however, one study found a significant decrease in RV end-diastolic volume, but not in RV end-systolic volume after 12 months.(7)

The RV systolic pressure results vary between no significant changes after 7.6 months,(37) a significant decrease after 22.7 months(31) and a decreasing trend after 3.6 years(25) (Measured with Doppler imaging). The RV ejection fraction and volumes remained unchanged after 3-17 months.(7, 27)

Significant changes were found in RV fractional area,(14) RV isovolumetric contraction time, isovolumetric relaxation, ejection time,(33) and RV myocardial performance index after 12-24 months of excessive weight loss.(25, 33) Also, peak systolic and early diastolic tricuspid annular velocities significantly increased, as well as the ratio of early-to-late diastolic velocities at the tricuspid annulus.(37) All indicators of a better RV function.

2.3.4 SYSTOLIC AND DIASTOLIC FUNCTION

Systolic function was quite similar in obese compared to lean before surgery, and remained this way after 3-36 months of excessive weight loss. (7, 11-14, 17, 26, 28, 31, 32, 37) However, some studies did find a significant increase in LVEF after 6-12 months up to 3.6 years of excessive weight loss, (16, 25, 30, 36) or only a significant increase in LVFS in obese with low pre-operative LVFS after 4.3 months of surgery.(4)

In addition to the improvements in cardiac output and stroke volume, diastolic function improved significant, or showing a trend, in most studies as well, after 3-24 months up to 3.6-10 years of excessive weight loss.(6, 8, 10, 13, 15, 16, 22, 26, 28, 32, 36, 37, 39) A significant increased E/A ratio is was frequently found,(6, 10, 13, 15, 16, 22, 26, 28, 36, 37, 39) even when there was no significant changes in peak E and A velocity,(28, 39) or only in one of them.(6, 13, 15, 36) However, one study did not found a significant change after 22.7 months.(31) Improvements are also seen in LV isovolumetric relaxation time,(6, 8, 10, 17, 22, 26, 28) deceleration time,(8, 10, 12, 13, 31) and left atrial dimensions(6, 10, 13, 16, 21, 22, 26, 30, 32) after 3-36 months and 3.6-10 years. However, improvements in left atrial dimensions are not always observed,(15, 37) some only found a decreasing trend.(14) Also, in a couple of studies, the deceleration time remained the same.(15, 37)

2.3.5 CHRONIC HEART FAILURE

Improvements in CHF symptoms and Assessment of New York Heart Association functional class were observed 6-12 months after surgery,(18, 34, 38) indicating that excessive weight loss has a positive effect on cardiac remodelling. These findings are supported by several case series investigating the effect of bariatric surgery on LVEF in patients with end-stage heart failure and/or patients scheduled for heart transplantation. (34, 38, 40-42)

No difference is found between the amounts of weight loss after 4.5 months between obese with or without CHF, as well as in hemodynamic, systolic and diastolic function. The only significant difference was found in right ventricular internal dimension. All other parameters improved in the same amount as in obese without CHF.(18)

Obese with CHF showed a significant increase in LVEF from an average of 23% to 32% after 6 months and an average of 21.7% to 35.0% after 12 months of excessive weight loss.(34, 38) Also a trend towards normalization in LV size is seen after 12 months.(38) The effect on LV diastolic diameter and left atrial size was a non-significant improving trend after 12 months.(38) Also, no significant changes were found in heart rate, systolic and diastolic blood pressure.(38)

2.4 IMPLICATIONS FOR CLINICAL PRACTICE

In summary, bariatric surgery has beneficial effects on systolic and diastolic function and myocardial structure. (9) Pre-existing hypertension or LVH seems to be a prerequisite for reverse remodelling after bariatric surgery. But there are still questions that remain unanswered:

1) What are the possible mechanisms of these cardiac/hemodynamic function improvements?
2) Should cardiac pathology and obesity be an indication for a surgical procedure? And if so, which bariatric surgical procedure shows the most improvements?
3) Should anaesthesiological care be modified, with special attention for hemodynamic alterations, for patients who had bariatric surgery in the past?

Physiology of the enterocardiac axis

The findings of cardiovascular changes after bariatric surgery are noticeable (9) and may represent a supra-physiological effect of metabolic/bariatric surgical procedures. (43) Basically, the bariatric cardiac effects are considered to be metabolic and hemodynamic, rather than solely hemodynamic. (44) The classical hemodynamic weight-dependent effect of bariatric surgery is no longer thought to be the only one responsible for reverse remodelling seen after bariatric surgery, as the beneficial effects can be independent from changes in blood pressure. (25, 45) This includes that there is a possibility of direct gut hormonal inotropic action on the myocardium through an enterocardiac axis. (9, 43)

Cardiac pathology as indication for bariatric surgery

Strictly taken, according to the guidelines of the International Federation of Surgery for Obesity and Metabolic disorders (IFSO) (46) cardiac pathology solely is not an indication for bariatric surgery. In patients with (end-stage) heart failure, several case series have demonstrated the positive effect of weight loss (due to bariatric surgery) on LVEF and the NYHA functional class (of heart failure). (34, 38, 40-42) Ristow et al. (47) reported on two patients who no longer required heart transplantation after successful weight reduction and improvement of LVEF.

Nowadays there is a shift going from bariatric surgery to metabolic surgery. (2, 48) In our opinion, there is enough evidence to state that obesity increases the risk of getting cardiac pathology, but nevertheless the current IFSO do not state them as comorbidity.

Also there is increasing evidence that the metabolic profile of obese is associated with changes in cardiovascular parameters (4, 18, 20, 35, 49-53) and therefore we think that the current IFSO criteria need to be adjusted incorporating a more 'metabolic approach.' Currently there is no consensus on which bariatric surgical procedures has the most benefits, in terms of cardiovascular hemodynamics.

Modifications of perioperative care for ex-bariatric patients?

As summarised in the recent systematic review by Aggarwal et al. (9) bariatric surgery has beneficial short term effects on cardiovascular physiology in general. Most of the preoperative abnormal cardiac parameters normalise over the course of bariatric surgery. So from an anaesthesiological point of view, ex-bariatric patients might not have to be treated differently than other patients in future (anaesthesiological) care concerning cardiac hemodynamics. However, it is uncertain whether ex-bariatric patients need to be screened before any future surgical procedure, because there is a wide variety in cardiovascular physiological changes between the different ex-bariatric patients. (9) Also, most cardiovascular changes are seen in obese with the greatest abnormalities before bariatric surgery. (4, 18, 20, 35, 49-53) Even that they now can have normal cardiovascular physiology, it is important to realise that their cardiovascular system has had much to endure for years, which might make them less responsive in alterations during surgery than patients who have never been obese. As mentioned by Alpert et al. (18) the duration of obesity is significantly associated with the severity of possible heart conditions. In the light of this we introduce the term fat-years in comparison with the term pack years in smoking. End organ (cardiac) dysfunction is increased by severity in combination with duration of obesity. So anaesthesiologists should be aware of this and be careful with the older (>60 years of age) bariatric or obese patients. Admission to an advanced care unit might be necessary for this group. (54) In the current body of literature, there is extensive knowledge about the preoperative characteristics and aspects concerning patients with a history of heart disease(s) (55, 56), but less is known about ex-bariatric patients and the changes in cardiovascular hemodynamics and the possible implications for future surgery and anaesthesia. Also the literature is sparse about the long-term changes in cardiovascular parameters and therefore it is difficult to determine (based on the current literature) clinical implications. Long-term studies are needed to investigate cardiovascular changes as a result of surgical weight loss.

2.5 RECOMMENDATIONS

Based on current literature several recommendations can be made regarding the cardiac remodelling after bariatric surgery and its implications for clinical practice. As stated earlier in this review there is an extensive body of literature that shows that weight loss and in particular bariatric surgery has beneficial effects in terms of improvement of cardiac and hemodynamic function. In our opinion, every patient with a medical history that includes cardiac pathology and obesity, should be considered for bariatric surgery. The presence of hypertension or LVH seems to be a prerequisite for reverse remodelling after bariatric surgery. However, it is unclear which bariatric surgical procedure is the best choice to induce the aforementioned cardiac function and hemodynamic changes. Most of the current research is done in patients who had either a laparoscopic gastric bypass or laparoscopic gastric sleeve. (9) Studies investigating the effects of the newer bariatric surgical procedures on cardiac function are sparse and in some cases not even available yet (for instance the effects of the diverted sleeve gastrectomy with either an ileal interposition of transit bipartition (57, 58)) This also included the effects of enteric hormones on cardiac and hemodynamic function (25, 45) that might indicate a possible physiological inotropic (inter)action on the myocardium through an enterocardiac axis. (9, 43)

Second issue that arises is that we currently do not have insight in the exact long-term effects of bariatric surgery on cardiac function. Most of the studies have a short follow-up length, so to give a recommendation regarding the long-term effects is simply not possible. Therefore we desperately need large randomised controlled trials to investigate these effects.

2.6 CONCLUSION

Bariatric surgery offers beneficial cardiac effects. These effects might be the result of a combined hemodynamic and metabolic effect of surgical modulation of the enterocardiac axis. Essential for reverse cardiac remodelling seems to be age, the pre-existence of hypertension and left ventricular hypertrophy. The current IFSO guidelines regarding indications for bariatric surgery need to be changed with great urgency, because bariatric surgery is essential for cardiac remodelling in the obese, and to improve their (cardiac) disease.

Future studies must focus on identifying the most successful bariatric surgical procedure in preventing and treating obesity-related heart disease. Also the long-term changes in cardiovascular parameters after surgery and implications for future anaesthesia and surgery are directions for future research.

2.7 CARDIAC REMODELLING DEFINITIONS

To describe the cardiovascular physiology and cardiac remodelling in obese before and after bariatric surgery, specific measurements are used. Systolic function represents the contractility of the ventricle and can be described in terms of ejection fraction, fractional shortening, stroke volume and cardiac output. (5, 61) Diastolic function represents the filling ability of the ventricle and can be described in terms of E/A-ratio, left atrial dimensions, deceleration time and isovolumetric relaxation time. (5), (61)

General:

- BSA = body surface area
- CO = cardiac output; blood volume pumped out of the ventricle per time period, calculated by stroke volume x heart rate (SV x HR)
- DT = deceleration time of early diastolic filling (E); the time peak velocity of early diastolic filling (E) declines in early diastole
- E/A-ratio = ratio of peak velocity of early diastolic filling (E) to peak (atrial) velocity of late diastolic filling (A)
- EDD = end-diastolic dimension; diameter across the right or left ventricle at the end of diastole (5)
- EDV = end-diastolic volume; the volume of the right or left ventricle at the end of diastole (5)
- EF = ejection fraction; percentage of blood volume that is pumped out of the right or left ventricle with each cardiac contraction, calculated by ((EDV-ESV)/EDV) x 100% or (SV/EDV) x 100%.
- ESD = end-systolic dimension; diameter across the right or left ventricle at the end of systole (5)
- ESV = end-systolic volume; the volume of the right or left ventricle at the end of systole (5)
- FAC = fractional area change; percentage in change between the area from end diastole to end systole, calculated by ((end-diastolic area – end-systolic area)/end-diastolic area) x 100%
- FS = fractional shortening; percentage of change in right or left ventricle dimension between end-diastole and end-systole dimension, calculated by ((EDD-ESD)/EDD) x 100% (61)
- HR = heart rate; the number of cardiac contraction during a certain time period (often per minute)

- IVCT = isovolumetric contraction time; time between the end of diastole and the opening of the semilunar valves, when the pressure in the ventricles rapidly increases while blood volume remains constant (5)
- IVRT = isovolumetric relaxation time; time between the end of systolic ejection and the opening of the atrioventricular valves, when the pressure in the ventricles rapidly decreases while blood volume remains constant (5)
- IVSd = interventricular septum dimension; diameter of the ventricular septum at end-diastolic (61)

Left ventricle:

- LAD = left atrial dimension; diameter across the left atrium at the end-ventricular systole (61)
- LAV = left atrial volume; volume of the left atrium at the end-ventricular systole (61)
- LVEDD = left ventricular end-diastolic dimension; diameter across the left ventricle at the end of diastole (5)
- LVEDV = left ventricular end-diastolic volume; the volume of the left ventricle at the end of diastole (5)
- LVESD = left ventricular end-systolic dimension; diameter across the left ventricle at the end of systole (5)
- LVESV = left ventricular end-systolic volume; the volume of the left ventricle at the end of systole (5)
- LV geometry = left ventricular configuration patterns; the LV can be classified in four different types based on LVM and RWT: eccentric hypertrophy (increased LVM and normal RWT), concentric hypertrophy (increased LVM and RWT), concentric remodelling (normal LVM and increased RWT) and normal geometry (normal LVM and RWT) (61)
- LVH = left ventricular hypertrophy; defined as an increased LVM due to an increase in LV dimension or wall thickness or both at end-diastole. For classification of LVH in concentric or eccentric RWT is used (61)
- LVM = left ventricular mass; is estimated by LV dimension and LV wall thickness (IVSd and PWd) at end-diastole and is used to define LVH. (61)LVM can also be described as LVM/height2, LVM/height2.7, LVM/lean body mass, LVM/BSA or LVM/LVEDV to improve comparison between subjects (5)
- PWd = posterior wall dimension; diameter of the posterior wall of the LV at end-diastolic (5)

Right ventricle:

- RVEDD = right ventricular end-diastolic dimension; diameter across the right ventricle at the end of diastole (5)
- RVEDV = right ventricular end-diastolic volume; the volume of the right ventricle at the end of diastole (5)
- RVESD = right ventricular end-systolic dimension; diameter across the right ventricle at the end of systole (5)
- RVESV = right ventricular end-systolic volume; the volume of the right ventricle at the end of systole (5)
- RVET = right ventricular ejection time; duration for the blood to be pumped out of the right ventricle during contraction. This measurement is used for the calculation of the RVMP (61)
- RVMPI = right ventricular myocardial performance index (also called Tei index); index measurement for global systolic and diastolic ventricular function, calculated by (IVCT+IVRT)/RVET or (TCOT-RVET)/RVET (61)
- RWT = relative wall thickness; calculated by (2 x PWd)/LVEDD and is used to distinguish, concentric and eccentric LVH (61)
- SV = stroke volume; volume of blood pumped out of the right or left ventricle with each cardiac contraction, calculated by EDV-ESV or estimated by echocardiography.
- TCOT = tricuspid valve closure to opening time; time between closing and opening of the tricuspid valve. This measurement is used for the calculation of the RVMPI (61).

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3. VALIDATION OF THE NEXFIN® NON-INVASIVE CONTINUOUS BLOOD PRESSURE MONITORING VALIDATED AGAINST RIVA-ROCCI/KOROTKOFF IN A BARIATRIC PATIENT POPULATION

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ABSTRACT

Background

The present study aimed to validate the Nexfin® monitor and to assess the accuracy compared to classical sphyganomanometry (Riva-Rocci/Korotkoff (RRK)) blood pressure (BP) measurements in patients with obesity scheduled for bariatric surgery.

Methods

The validation process was done according to the protocols developed by the European Society of Hypertension from 2010. The Nexfin® monitor (Edwards Lifesciences / BMEYE B.V., Amsterdam, the Netherlands) calculates beat-to-beat blood pressure from finger pulse wave analysis. Measurements of systolic and diastolic BP were obtained using classical sphygmomanometry and the Nexfin® alternatingly. In total 33 patients were asked to participate in the validation process.

Results

In total 99 pairs of BP measurements were used. The device failed pass phase 1 as 65 systolic readings fell within 5 mmHg (73 required). And 61, 76 and 90 diastolic readings fell within 5, 10 and 15 mmHg respectively. Finally, it failed to pass phase 2 as 23 patients for systolic and 25 for diastolic had at least 2/3 of their comparisons falling within 5 mmHg (24 required) but 10 subjects for systolic and 8 for diastolic had all three comparisons more than 5 mmHg different from the RRK readings (zero allowed). Mean differences were 7.8 ± 6.9 mmHg for SBP and 8.0 ± 7.2 mmHg for DBP.

Conclusion

This study aimed to validate the Nexfin® monitor against Riva-Rocci/Korotkoff (RRK) blood pressure measurements in patients with obesity. Using the revised protocol of the European Society of Hypertension, the Nexfin® device was not able to pass validation. However using the original protocol, the Nexfin® device passed phase 1 and 2.1 of the validation process and failed to pass phase 2.2. Notwithstanding, these results, we think that the Nexfin® device is a reliable measurement tool to detect changes in cardiovascular hemodynamics.

3.1 INTRODUCTION

Finger arterial pressure measurements can be used for non-invasive continuous blood pressure measurements. These methods use volume clamp methodology to reconstruct intra-arterial pressures based on population- and individual patient characteristics. (1-3) Since the initial development of the volume-clamp methodology of Penaz (4) and the Physiocal criteria of Wesseling. (2), continuous blood pressure (BP) measurement became widely available and is used as substitute for intra-arterial BP measurements in both clinical and research settings. (5-7)Finger arterial pressure measurements, such as Nexfin®, proof to be reliable under various conditions. These devices have been extensively validated for clinical practice and are being used in a variety of settings. [5-8] In 2009 Eeftinck Schattenkerk et al. (8) validated the Nexfin® monitor against Riva-Rocci/Korotkoff (RRK) BP measurement in healthy subjects. In a recent study by de Wilde et al. (9) the Nexfin® monitor was compared with radial arterial blood pressure in patients following major upper abdominal surgery. In terms of arterial blood pressure no significant differences were found between the radial arterial blood pressure and blood pressure measured with the Nexfin® monitor.

However, at the extreme ranges of patient characteristics, such as extreme/morbid obesity, general population characteristics may not apply and potential errors in blood pressure measurement may be introduced. The increasing prevalence of obesity makes validation of finger blood pressure measurements for this group clinical valuable, (10) because blood pressure cuff readings as well as intra-arterial line placement in (morbid) obese individuals can be challenging or even impossible. Fingers remain relatively thin in obesity, which may imply that finger blood pressure measurements using the volume clamp methodology may be feasible. The difficulty to assess blood pressure in morbid obese individuals makes an alternative technique very valuable.

The present study aimed to validate the Nexfin® monitor and to assess it's accuracy compared to classical sphyganomanometry (Riva-Rocci/Korotkoff (RRK)) BP measurements in patients with obesity scheduled for bariatric surgery.

3.2 METHODS

PATIENTS/ SUBJECTS

Patients, who attended the Obesity Center in the Catharina Hospital in Eindhoven the Netherlands, were asked to take part in this validation study. Patients for revisional bariatric surgery, with hypertension, using antihypertensive drugs, with diabetes or renal disease were excluded. All measurements were performed within one session of 5 minutes per patient. This study was approved by the Medical Ethics Committee of the Catharina Hospital Eindhoven the Netherlands and all participants gave written informed consent.

NON-INVASIVE CONTINUOUS BLOOD PRESSURE MEASUREMENT USING NEXFIN® HEMODYNAMIC MONITORING DEVICE

The Nexfin® device uses the volume clamp method described by Penaz (3) and the Physiocal criteria of Wesseling (4), implemented in the TNO Finapres model 5 and Ohmeda Finapres 2300. Whereas the Nexfin uses the same principles to measure BP as TNO Finapres model 5 and Ohmeda Finapres 2300, the finger cuffs have been redesigned with a more efficient light emitting diode (LED) and photo-diode for a better signal-to-noise ratio. Secondly, the Nexfin® displays continuous pressures, which are based on reconstructed brachial wave shapes and levels. (11-14)

RIVA-ROCCI/KOROTKOFF BLOOD PRESSURE MEASUREMENTS

Riva-Rocci blood pressure measurements were used a reference method for validation. Since the mercury sphyganomanometry is no longer allowed in Dutch clinical practice, an automated cuff in- and deflation system with built in manometer was used (Boso Clinicus II, Henry Schein Medical, Almere, The Netherlands). This manometer shows an analogue representation of a mercury column and digital real time valves. Deflation rate was 2mmHg/s. The manometer was calibrated before the start of the study and checked after the conclusion of the study.

The validation team consisted of two persons (SP, BL). Both observers were trained in BP measurement according to the recommendation of the European Society of Hypertension. (15) Before the start of the study, the observers were instructed on how to use the Nexfin® device. Both the observers had no history of hearing problems and before the study started, five measurement sessions took place on volunteers, to accustom the observers to the procedure. A high-end stethoscope (Littmann, 3M Healthcare) with dual, clean and well fitting earpieces was used for RRK measurements.

MEASUREMENTS

All measurements were done in a comfortable and quiet temperature controlled room. The participants were asked to relax for 10 minutes and any form of disturbance was prevented. Only two observers (SP and BL) were present. Each study participant was asked to sit in a comfortable chair and was asked neither to speak nor to move during the measurement. Appropriate cuff size was determined for both the finger and the arm in each participant, based on the circumference of the upper arm and the circumference of the midphalanx of the third digitus. An inflatable cuff with a length of 80% and a width at least 40% of the circumference of the upper arm deemed suitable according to Pickering et al. (16) The Nexfin® finger cuff was attached to the mid-phalanx of the third digit of the patients left hand; the manometric arm cuff was attached to the left upper arm. The heart reference system was placed on the middle of the left side of the thorax. The measured hand and the manometric arm cuff were placed at the mid-thorax to account for hydrostatic pressure differences. (15, 16)

PROCEDURE

Two observers (SP and BL) were blinded from each other's and the measurements of the Nexfin® device and took five consecutive RRK BP measurements. The manometric arm cuff was inflated up to approximately 20 mmHg above the systolic pressure and was automatically deflated at a rate of 2 mmHg/s. All BP measurements were recorded to the nearest 2 mmHg and respectively Korotkoff sound I and V were used. To eliminate possible inter-observer discrepancies in RRK measurements, a maximum difference of 4 mmHg was accepted (both systolic and diastolic pressure).

After the complete deflation of the manometric arm cuff the Nexfin® signal was inaccurate for approximately 10 seconds due to post-occlusive hyperemic response which causes finger BP to swing. (15, 16) After a period of approximately 30 seconds the Nexfin® calculated the mean BP over a period of 30 seconds. After the Nexfin® measurement the next RRK measurement took place. In total nine sequential measurements took place between the Nexfin® device and the RRK measurements. An overview of these measurements is shown in table 3.1. Of these measurements the first two (the entry RRK measurement and Nexfin®) were not included in the statistical analysis.

STATISTICAL ANALYSIS

This validation study followed the revised protocol developed by the European Society of Hypertension published in 2010. (17) Statistical Package for Social Sciences for Mac (SPSS, Chicago, IL, USA Version 20.0) was used to prepare the database and for statistical analysis. Continuous variables were presented as mean ± standard deviation (SD). Categorical variables were presented as frequency with percentages. Data distribution was verified using the Shapiro-Wilk test. Values of $p<0.05$ were considered statistically significant. Of BP1, BP3, BP5 and BP7 the mean of each pair of the observer measurements was calculated. The means were used to flank each Nexfin® measurement (BP2, BP4 and BP6). So BP2 was flanked by BP1 and BP3, BP4 by BP3 and BP5, and BP6 was flanked by BP5 and BP7. Differences were calculated between the observer measurements and the Nexfin® measurements. The difference was categorized into one of four categories (15); 0 – 5 mmHg (measurements are very accurate, no error of clinical relevance), 6 – 10 mmHg (slightly inaccurate), 11 – 15 mmHg (moderately inaccurate) and > 15 mmHg (very inaccurate). The RRK measurements with the smallest differences were used for the comparison with the Nexfin® device.

In total the validation process (according to the original protocol(17)) consisted of two phases. The first phase determines how accurate the device will be for individual measurements and second phase 2.2 determines the accuracy for individual measurements. Determining the number of differences within 5, 10 and 15 mmHg, and then determining the accuracy will do this. (17)

To pass phase 1 there must be a minimum of respectively 65, 81 and 93 comparisons falling within 5, 10 and 15 mmHg. Furthermore, there must be a minimum of either 73 comparisons within 5 mmHg and 87 comparisons within 10 mmHg, or 73 comparisons within 5 mmHg and 96 comparisons within 15 mmHg, or 87 comparisons within 10 mmHg and 95 comparisons within 96 mmHg. (17)

For phase 2 the number of comparisons falling within 5 mmHg is calculated per subject. At least 24 of the 33 subjects must have at least two of their three comparisons lying within 5 mmHg. (17) Finally, visual inspection of Bland-Altman plots was performed to determine the agreement between the RRK BP measurements and the Nexfin® device. (18, 19)

POWER AND SAMPLE SIZE CALCULATION

Both the original and the revised protocol of the European Society Of Hypertension recommend 33 test subjects for the validation of blood pressure monitoring devices. [15, 17] Therefore no (additional) power and sample size calculations were performed.

TABLE 3.1. Overview of measurements by observers and Nexfin® device

Measurement		Systolic BP	Diastolic BP
BPA	Entry RRK BP measurement	A) 136 ± 13 B) 141 ± 18	89 ± 9 91 ± 11
BPB	Entry Nexfin® BP measurement	130 ± 21	86 ± 14
BP1	Two observers with RRK BP measurement	A) 136 ± 16 B) 140 ± 17	91 ± 10 90 ± 15
BP2	With Nexfin® device	131 ± 25	87 ± 16
BP3	Two observers with RRK BP measurement	A) 133 ± 14 B) 139 ± 18	90 ± 9 92 ± 10
BP4	With Nexfin® device	131 ± 21	86 ± 13
BP5	Two observers with RRK BP measurement	A) 133 ± 15 B) 138 ± 18	91 ± 10 92 ± 10
BP6	With Nexfin® device	134 ± 22	88 ± 12
BP7	Two observers with RRK BP measurement	A) 134 ± 14 B) 138 ± 17	90 ± 8 92 ± 10

Abbreviations: BP = blood pressure (mmHg), RRK = Riva-Rocci/Korotkoff, A) = Observer A, B) = Observer B

3.3 RESULTS

The present study was conducted between February and April 2016 according to the revised validation protocol of the European Society of Hypertension. [17] Figure 3.1 will elucidate the study process and table 3.1 gives an overview of the study measurements.

PATIENT CHARACTERISTICS

Table 3.2 gives an overview of the characteristics of the included patients. Of the 33 included patients, 3 had a history of cardiac disease (one myocardial infarction and two patients with stable angina), 4 had a history of thromboembolic disease (two patients with a pulmonary embolism and two with a deep venous thrombosis) 8 patients had a history of pulmonary disease (all of them had Chronic Obstructive Pulmonary Disease (COPD)) and 8 patients had a history of surgery (4 laparoscopic cholecystectomy, 2 laparoscopic appendectomy, 1 laparoscopic hysterectomy and 1 inguinal hernia repair). None of the included patients had hearth rhythm disorders, like atrial fibrillation.

PHASE 1

After completion of the measurements on all 33 patients all 99 comparisons between the RRK standard and the Nexfin® were analysed. Table 3.3 shows that the Nexfin® device did not pass the first phase of the revised validation protocol (17), with respectively 65, 82 and 77 measurements in ranges within 5 mmHg, within 10 mmHg and within 15 mmHg for SBP and 61, 76 and 90 measurements for DBP. Mean differences were 7.8 ± 6.9 mmHg for SBP and 8.0 ± 7.2 mmHg for DBP, as shown in Bland Altman plots (18, 19) (Figure 3.1 and 3.2).

PHASE 2

In phase 2.2 the data was analysed per patient to determine the accuracy of the Nexfin® device for individual measurements. Of the 33 patients, 23 of them fell within the 5 mmHg for SBP and 25 of them for DBP (≥ 22 required to pass) respectively. Ten patients had all three of their comparisons over 5 mmHg for SBP and 8 for DBP (≤ 3 required to pass). (15) As shown in table 3.4, the Nexfin® device failed to pass phase 2. Figures 3.2 and 3.3 show Bland Altman plots for the analysis of the differences between respectively SBP and DBP measurements between the observers and Nexfin® values. (18, 19)

TABLE 3.2. Patient characteristics

Patients (N=33)	
Age (years)	40 ± 12
Height (cm)	171 ± 8.8
Weight (kg)	125 ± 21.9
Waist circumference (cm)	125.8 ± 15.9
BMI (kg/m^2)	42 ± 6.4
Comorbidities:	
Diabetes Mellitus	0
Hypertension	0
Osteoarthritis	13 (39.4%)
Obstructive Sleep Apnoea	3 (9.1%)
Hypercholesterolemia	5 (15.2%)
Medical history:	
Cardiac disease	3 (9.1%)
Pulmonary disease	8 (24.2%)
Thromboembolic	4 (12.1%)
Previous surgery	8 (24.2%)
SBP (in mmHg)	139 ± 13
DBP (in mmHg)	90 ± 7

Abbreviations: BMI = Body Mass Index, SBP = systolic blood pressure, DBP = diastolic blood pressure

TABLE 3.3. Phase 1: - Performance requirements versus the actual performance of the Nexfin® according to the protocol of the European Society of Hypertension (17)

		Within 5 mmHg	Within 10 mmHg	Within 15 mmHg	Recommendation	Mean difference	Standard deviation
	Two of All of	73 65	87 81	96 93			
Achieved	SBP	65	82	77	Fail	7.8 mmHg	6.9 mmHg
	DBP	61	76	90	Fail	8.0 mmHg	7.2 mmHg

Abbreviations: SBP = systolic blood pressure, DBP = diastolic blood pressure

TABLE 3.4. Phase 2: - Performance requirements versus the actual performance of the Nexfin® according to the protocol of the European Society of Hypertension (17)

		2/3 within 5 mmHg	0/3 within 5 mmHg	Recommendation
		≥ 24		
Achieved	SBP	23	10	Fail
	DBP	25	8	Fail

Abbreviations: SBP = systolic blood pressure, DBP = diastolic blood pressure

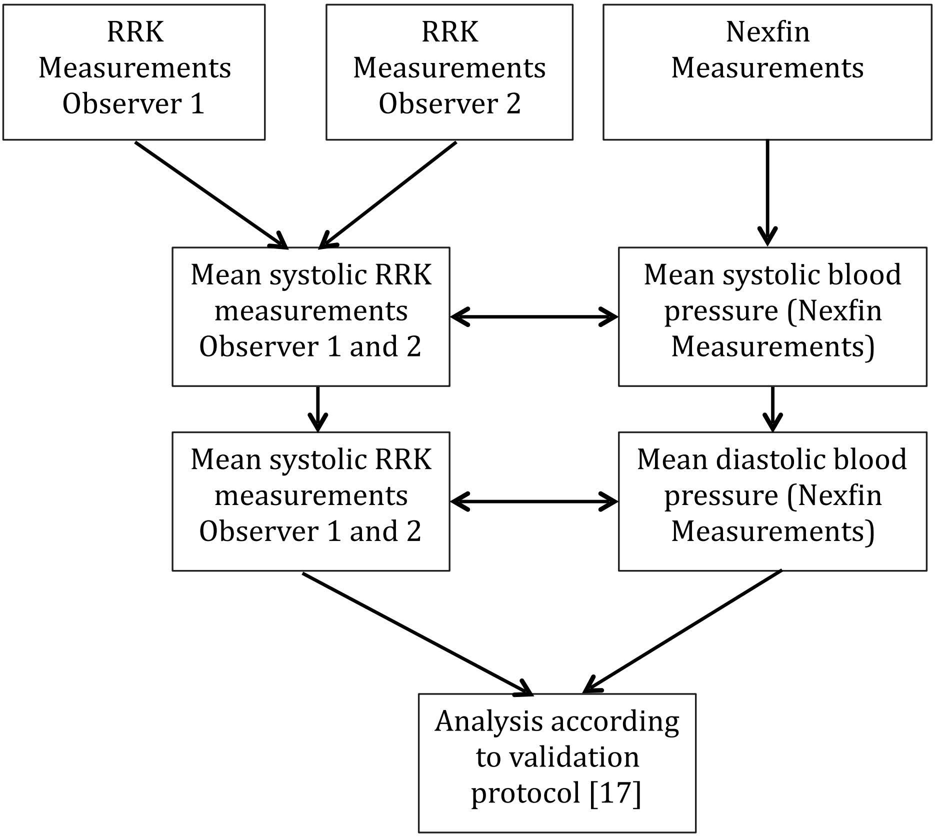

FIGURE 3.1. Graphic overview of the study process
⟷ Comparison between the observed values between the Nexfin and the mean RRK blood pressure measurements between observer 1 and 2

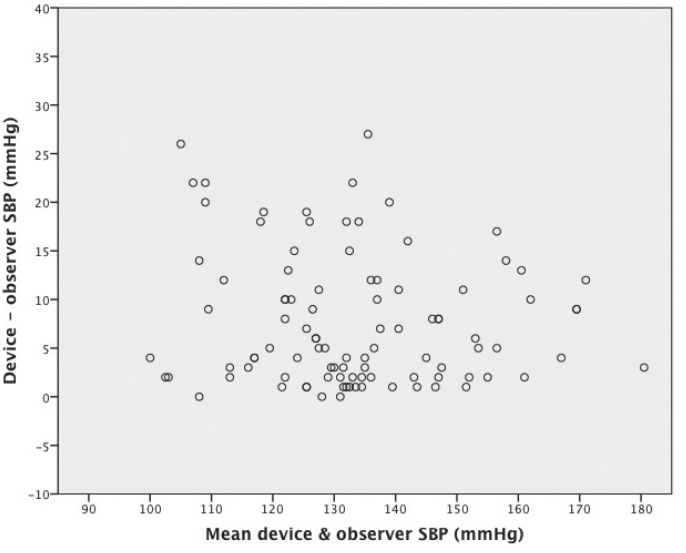

FIGURE 3.2: Bland-Altman plot showing the systolic blood pressure (SBP) differences between the Nexfin® device and the observer measurements (mean difference 7.8 ± 6.9 mmHg, agreement interval between -6 and 21.6, 99 comparisons were used in the analysis)

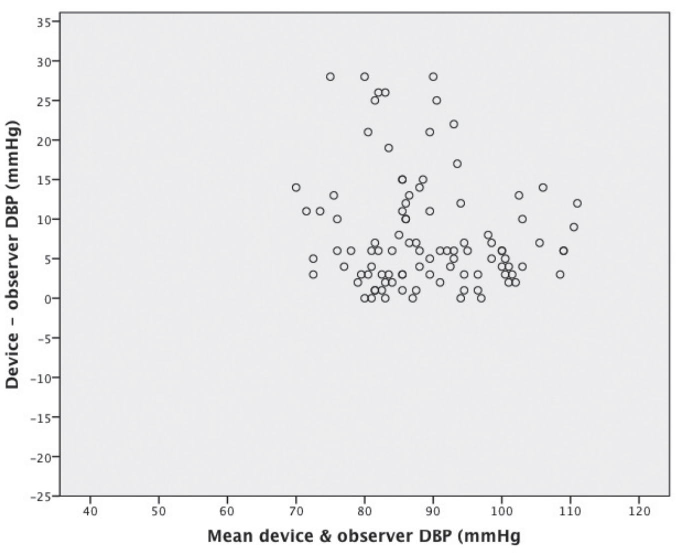

FIGURE 3.3: Bland-Altman plot showing the diastolic blood pressure (DBP) differences between the Nexfin® device and the observer measurements (mean difference 8.0 ± 7.2 mmHg, agreement interval between -6.4 and 22.4, 99 comparisons were used in the analysis)

3.4 DISCUSSION

In the present study we aimed to validate non-invasive continuous finger blood pressure measurements against classical sphyganomanometry blood pressure measurements in obese individuals. We have found that the Nexfin® device failed to pass the revised protocol for validation of the European Society Of Hypertension (17). When looking at the original validation protocol published in 2002 (15), several changes have been made. In the revised protocol published in 2010 phase 1 of the validation process was omitted and the criteria for phase 2.1 and 2.2 were sharpened.

Table 3.5 gives an overview of the criteria for validation according to the original protocol. (15) When comparing the obtained data with the revised protocol (17), the Nexfin® device was not able to pass part 1 and 2 of the validation (the former phase 2.1 and 2.2). These results are in line with a review by Stergiou and colleagues (20) assessing the effect of more stringent validation criteria on earlier validation studies. Not surprisingly, they found and increase in failure rate (from 17% using the protocol of 2002 to 42% using the protocol published in 2010). However they state that a consistent trend toward improved performance of oscillometric devices assessed on the basis of the criteria established by the European Society of Hypertension and therefore by acknowledging the revised protocol this trend will allow more accurate devices to enter the market. (20, 21) These changes in validation criteria are the main reason why the Nexfin® device failed to pass the revised protocol for validation.

TABLE 3.5. Validation criteria according to the original protocol of the European Society of Hypertension published in 2002 (15)

		Within 5 mmHg	Within 10 mmHg	Within 15 mmHg	Recommendation
Phase 1	One of	25	35	40	
Phase 2.1	Two of	65	80	95	
	All Of	60	75	90	
Phase 2.2 *		2/3 within 5 mmHg	0/3 with 5 mmHg		
		≥ 22	≤ 3		

Abbreviations: SBP = systolic blood pressure, DBP = diastolic blood pressure
* Individual measurements

However, we think that the use of Nexfin® device can be valuable in a population of obese patients scheduled for bariatric surgery. Both protocols (15, 17) do not make any recommendations for special groups like patients with obesity. However, by selection of obese patients with a BMI 42.8 ± 6.4 kg/m^2 (10) and by exclusion of hypertension and type

2 diabetes mellitus, our group should be sufficiently uniform to enable application of the protocol. (15, 17)

We focused on obese patients scheduled for bariatric surgery, because hypertension is one of the comorbidities associated with (morbid) obesity (22) and evaluating the effects of bariatric surgery on hypertension is clinically important for bariatric and metabolic surgery. (22, 23) It has been recognized that RRK BP measurements can give an overestimation of the BP of obese patients due to the cuff size and the circumference of the upper arm. (24, 25) This can lead to misdiagnosing and potential over-treating hypertension in this population. (24-26) Although it is recommended to use a larger cuffs in obese individuals to ensure a reliable ratio between the cuff width and the upper arm circumference for reliable blood pressure measurements. (26) However, these recommendations in clinical practice are not always applied and overestimation of the BP can occur. Secondly we hypothesize that the blood pressure at the finger level gives a better representation of the brachial blood pressures (RRK measurements) in obese patients. Therefore non-invasive beat-to-beat BP monitoring could be a valuable addition to standard care for obese patients.

The overestimation of RRK BP measurements in obese patients is supported by several studies. (24-26) Conceivably, the systolic BP recorded at the wrist may better reflect 'true' systolic BP prevailing in the artery than the systolic BP measured at the arm. (27) This possibility is supported in the study by de Senarclens et al. (27) by the observation that the ratio of width (the decimal log arm of circumference calculated in obese patients) was higher than the optimal value originally validated by Marks et al. (26) This basically means that in our study the arm systolic blood pressure is an overestimation of the 'true' blood pressure. Notwithstanding these results, small BP differences may exist between the brachial artery and the radial artery, ranges of 1-4 mmHg. (28) So basically in our study population the blood pressure measured with the Nexfin® device is he 'true blood pressure.' Secondly, the overestimation of the BP of our study population (because we used RRK BP measurements as reference) can also be a reason that the Nexfin® device did not pass the validation protocol. This also explains why there is less differences between the Nexfin® measurements and other reference methods (such as radial artery blood pressure, used in a recent study by De Wilde et al. (9)) Thirdly, we have to take into account that the shape of a blood pressure wave constantly distorts as it travels from the central elastic arteries toward the muscular conduit arteries. This physiological phenomenon is known as pulse wave amplification, that the blood pressure, as a periodically oscillating wave, travels and reflects in occasionally differently structured portions of the viscoelastic arterial system. In healthy individuals, the pulse wave amplitude (pulse pressure (PP)) increases from the aorta/carotid section to the brachial/radial section without added energy, such that the arterial central pressure and the diastolic pressure remains almost unchanged.

Nowadays several strategies for BP measurement exist, of which intra-arterial BP measurement (mostly in the radial artery) is considered to be the most accurate. (16) Because of its invasiveness and its technical difficulty in the obese population, risk for infection it is not suitable for routine BP measurement in obese patients scheduled for bariatric surgery. Secondly, we have the standard auscultatory sphygmomanometry, widely used in clinical practice, based on the principles of Riva-Rocci/Korotkoff. (16) Thirdly, there is a wide range of automated devices (the oscillometric type) that provide BP measurements of one systolic and diastolic beat. (15, 16) Finally, finger blood pressure measurements devices, such as Nexfin®, derive non-invasive continuous blood pressure waveforms from pressure waveforms in the finger using algorithms to calculates the beat-to-beat brachial BP. (2-4, 8)

LIMITATIONS:

Firstly, the simultaneous measurement of the Nexfin® device and the reference method on the ipsilateral arm is, for obvious reasons, not possible, and the spontaneous variability in BP will thus contribute to the error. Nonetheless, ipsilateral measurements are preferred to contralateral measurements since an unknown left to-right difference might also afflict the comparison. Another disadvantage is that the RRK reference measurement itself often disturbs the test measurement: with temporal occlusion of the brachial artery, the BP distal to the arm cuff becomes strongly reduced. Subsequent release of the arm cuff may affect finger arterial pressure measurements by inducing a post occlusion hyperemic response. (6-8, 12)

3.5 CONCLUSION

This study aimed to validate the Nexfin® monitor against classical sphyganomanometry (Riva-Rocci/Korotkoff (RRK)) blood pressure measurements in patients with obesity scheduled for bariatric surgery, using the validation protocol developed by the European Society of Hypertension. Using the revised protocol (17) the Nexfin® device was not able to pass validation. Using the original protocol (15), the Nexfin® device passed phase 1 and 2.1 of the validation process, but failed to pass phase 2.2. However the Nexfin® device could be of value in clinical settings and/or research settings as blood pressure measurement device.

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4. SHORT-TERM CHANGES IN CARDIOVASCULAR HEMODYNAMICS IN RESPONSE TO BARIATRIC SURGERY AND WEIGHT LOSS USING THE NEXFIN® NON-INVASIVE CONTINUOUS MONITORING DEVICE: A PILOT STUDY

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ABSTRACT

Background

Compared to healthy individuals, obese have significantly higher systolic and diastolic blood pressure; mean arterial pressure, heart rate and cardiac output. Aim of this study was to evaluate cardiovascular hemodynamic changes before and 3 months after bariatric surgery.

Methods

Patients scheduled for bariatric surgery between the 29th of September 2016 and 24th of March 2016 were included and compared with 24 healthy individuals. Hemodynamic measurements were performed preoperatively and 3 months after surgery, using the Nexfin® non-invasive continuous hemodynamic monitoring device (Edwards Lifesciences / BMEYE B.V., Amsterdam, the Netherlands).

Results

Eighty subjects were included in this study, respectively 56 obese patients scheduled for bariatric surgery and 24 healthy individuals. Baseline hemodynamic measurements showed significant differences in cardiac output (6.5 ± 1.6 versus 5.7 ± 1.6 l/min, p=0.046), mean arterial pressure (107 ± 19 versus 89 ± 11 mmHg, p=0.001), systolic (134 ± 24 versus 116 ± 18 mmHg, p=0.001) and diastolic blood pressure (89 ± 17 versus 74 ± 10 mmHg, p=0.001) and heart rate (87 ± 12 versus 76 ± 14 bpm, p=0.02) between obese and healthy subjects. Three months after surgery, significant changes occurred in mean arterial pressure (89 ± 17 mmHg, p=0.001), systolic (117 ± 24 mmHg, p=0.001) and diastolic blood pressure (71 ± 15 mmHg, p=0.001), stroke volume (82.2 ± 22.4 ml, p=0.03) and heart rate (79 ± 17 bpm, p=0.02).

Conclusion

Three months after bariatric surgery significant improvements occur in hemodynamic variables except cardiac output and cardiac index, in the patient group.

4.1 INTRODUCTION

Obesity is a recognized risk factor for cardiac dysfunction, atherosclerosis and cardiovascular disease. (1, 2) When combined with hypertension, dyslipidaemia and type 2 diabetes mellitus, it is known as 'metabolic syndrome', which in itself is an independent predictor of cardiac dysfunction and cardiovascular disease. (1, 3) Increasing evidence from large population based studies (such as the Framingham Heart Study) and cardiac imaging trials show that long-term obesity can lead to structural changes in cardiac structure, such as left ventricular (LV) dilatation, hypertrophy and even heart failure. (1, 4) Adipose tissue itself contributes to the circulating volume and must increase cardiac output. (5)

The literature suggests that weight loss is able to improve cardiac structure and function, decrease cardiovascular risk (due to reverse remodelling). (6, 7) Aggarwal et al. (6) summarised the beneficial effects of bariatric procedures on cardiac functional imaging endpoints, but short-term hemodynamic changes have not been studied that extensively. Namely the presence of left ventricular hypertrophy (LVH) and hypertension are a prerequisite for cardiac remodelling after bariatric surgery, and in this review by Aggarwal et al. (6) mostly cardiac structure changes were evaluated, without looking at the short-term hemodynamic changes after bariatric surgery.

The aim of the present study was to evaluate the cardiovascular hemodynamic changes before and 3 months after bariatric surgery. It was hypothesized that bariatric surgery (irrespective of the type of surgical procedure) gives a decrease in cardiac output and in systolic and diastolic blood pressure.

4.2 METHODS

This study was approved by the Medical Ethics Committee of the Catharina Hospital in Eindhoven, The Netherlands and adheres the principles of the declaration of Helsinki. Informed consent was obtained of all patients included. This study was conducted according to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement. (8)

PATIENT POPULATION

A multidisciplinary team screened all included patients preoperatively, consisting of a physician assistant, a psychologist, a nutritionist and a surgeon. Patients were eligible for surgery if they had a BMI of 40 kg/m^2 or higher, or a BMI between 35 and 40 kg/m^2 with significant co-morbidities, with serious attempts to lose weight in the past. Co-morbidities were considered significant when medication had to be used, or if continuous positive airway pressure (CPAP) had to be used in case of obstructive sleep apnoea (OSAS). Patients with pre-existing cardiac and/or pulmonary and/or kidney diseases were excluded from this study.

The subjects in this study were divided into two groups. Group A of morbidly obese patients scheduled for bariatric surgery that were measured preoperatively and three months after bariatric surgery. Group B was a control group of, healthy, health professionals recruited from the research team..

NEXFIN® HEMODYNAMIC MONITORING DEVICE

The Nexfin® device (Edwards Lifesciences/BMEYE B.V., Amsterdam, the Netherlands) is based on the volume clamp method first described by Penaz and the Physiocal criteria of Wesseling, and provides a reconstructed continuous brachial arterial BP that are used to derive stroke volume. (9-14)

PROCEDURE AND DATA COLLECTION

All hemodynamic measurements were obtained before and only the patient's measurements were repeated 3 months after bariatric surgery. Patients were asked to relax for 10 minutes in a comfortable chair and any form of disturbance was prevented. After that each study participant was asked neither to speak nor to move during the measurement. Appropriate cuff size was determined for both the finger and the arm in each participant. The Nexfin® finger cuff was attached to the mid-phalanx of the third digit of the patients left hand. Data of interest were anthropometric variables and comorbidities, hemodynamic variables (systolic and diastolic blood pressure, cardiac output, cardiac index, stroke volume and heart rate). Secondly, operative details and evolution of weight and comorbidities were recorded, in terms of remission of type 2 diabetes, hypertension, hypercholesterolemia, sleep apnoea and osteoarthritis.

Primary endpoint of the study was the change in cardiac output, cardiac index and systolic and diastolic pressure 3 months after bariatric surgery. Secondary endpoints were other hemodynamic parameters such as stroke volume and heart rate.

STATISTICAL ANALYSIS

Our hypothesis was that bariatric surgery gives a decrease in cardiac output and in systolic and diastolic blood pressure. In current literature, it is seen that bariatric surgery gives a mean reduction of 20% in systolic and diastolic blood pressure. (3, 15)

Using a two-sided 5% significance level and a power of 90%, a power analysis indicated a sample of 50 patients. Taking into account a dropout rate of 10% we have included 56 patients.

Continuous variables were shown as mean ± standard deviation (SD) and categorical variables as frequency with percentages. The Shapiro-Wilk test was used to test each variable for normality. Student's t-test for independent groups or the Mann-Whitney U test was used to compare the hemodynamic variables in the preoperative period, depending on the normality or non-normality of the data distribution. To determine whether the hemodynamic variables 3 months reach normal values, these follow-up values were compared with the baseline values of group B (the health professionals), assuming these measurements would not change in 3 months. In all tests, values of $p<0.05$ were considered statistically significant. Statistical Package for Social Sciences (SPSS, Chicago, IL, USA Version 20.0) was used to prepare the database and for statistical analysis.

4.3 RESULTS

A total of 80 subjects were included in this study, respectively 54 patients in group A, and 24 healthy individuals in group B. Three months after surgery, follow-up data was available of 51 patients in group A. Three patients were unable to attend the follow-up visits at our clinic; one was admitted in a hospital because of a cerebral infarction and two patients were lost to follow-up. Table 4.1 gives an overview of the characteristics of each study group. A significant difference was found between group A and group B in terms of weight, waist circumference and body mass index (BMI).

WEIGHT LOSS AND RESOLUTION OF COMORBIDITIES

Table 4.1 gives an overview of the weight loss profiles in group A after three months, the group of patients that underwent bariatric surgery. In total 29 patients (53.7%) had a Roux-en-Y gastric bypass (RYGB), 25 (46.3%) underwent a Sleeve Gastrectomy (SG). In terms of resolution of comorbidities after three months; 15 patients (12.7%) had partial remission and 3 patients (2.5%) had complete remission of hypertension. Hypercholesterolemia resolved partially in 5 patients (4.2%) and completely in 6 patients (5.1%). Obstructive sleep apnoea syndrome (OSAS) resolved partially in 7 patients (5.9%) and completely in 2 patients (1.7%). The remission of Type 2 diabetes (T2DM) was partial in 8 patients (6.8%) and complete in 3 patients (2.5%).

BASELINE CARDIOVASCULAR HEMODYNAMIC VARIABLES

Table 4.2 gives an overview of the baseline hemodynamic variables between groups A and B. Between groups A and B no significant differences were found in stroke volume (SV) and cardiac index (CI)

TABLE 4.1. Demographics of the study population

	Group A (N=54)	Group B (N=24)	P-Value
Age (years)	44 ± 11	37 ± 13	0.09
Gender (Male: Female)	12/42	10/14	0.107
Height (cm)	168.9 ± 9.3	175.5 ± 8.2	0.08
Weight (kg)	119.9 ± 21.6	77.2 ± 16.6	**0.01**
Waist circumference (cm)	128.4 ± 15.4	85.6 ± 15.1	**0.01**
BMI (kg/m^2)	41.9 ± 5.7	25.1 ± 5.2	**0.01**
Comorbidities:			
Diabetes Mellitus	11 (19.6%)	1 (4.2%)	0.643
Hypertension	22 (39.3%)	1 (4.2%)	0.386
Osteoarthritis	44 (78.6%)	1 (4.2%)	0.367
Obstructive Sleep Apnoea	10 (17.9%)	1 (4.2%)	0.565
Hypercholesterolemia	12 (21.4%)	1 (4.2%)	0.181
Medical history:			
Cardiac disease	2 (3.6%)		0.645
Pulmonary disease	5 (8.9%)		0.573
Thromboembolic	7 (12.5%)		0.486
Type of bariatric surgery			
RYGB	29 (51.8%)		
SG	25 (44.6%)		
Follow-up			
Weight (kg)	97.4 ± 18.9		
Waist circumference (cm)	102.8 ± 14.7		
BMI (kg/m^2)	34.0 ± 5.2		
Absolute weight loss (kg)	-22.5 ± 5.7		
%TWL	-18.8% ± 4.1		
%EWL	-41.5% ± 58		
%BMIL (kg/m^2)	-22.5% ± 5.7		

Abbreviations: BMI = Body Mass Index, RYGB = Roux-en-Y Gastric Bypass, SG = Sleeve Gastrectomy, %TWL = %Total Weight Loss, %EWL = % Excess Weight Loss, %BMIL = %BMI Loss

TABLE 4.2. Baseline hemodynamic variables of each study group

	Group A (N=54)	Group B (N=24)	P-Value
SBP (mmHg)	134 ± 24	116 ± 18	**0.001**
DBP (mmHg)	89 ± 17	74 ± 10	**0.001**
MAP (mmHg)	107 ± 19	89 ± 11	**0.001**
CO (L/min)	6.5 ± 1.6	5.7 ± 1.6	**0.046**
CI (L/min/m²)	2.9 ± 0.8	3.0 ± 0.9	0.937
SV (ml)	75.5 ± 16.7	75.6 ± 16.7	0.930
HR (bpm)	87 ± 12	76 ± 14	**0.002**

Abbreviations: SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure, MAP = Mean Arterial Pressure, CO = Cardiac Output, CI = Cardiac Index, SV = Stroke Volume, HR = Heart Rate

TABLE 4.3. Changes in cardiovascular hemodynamics measured with the Nexfin® device, 3 months after bariatric surgery

Group A	Preoperative (N=54)	Postoperative (N=51)	P-Value
SBP (mmHg)	134 ± 24	117 ± 24	**<0.001**
DBP (mmHg)	89 ± 17	71 ± 15	**<0.001**
MAP (mmHg)	107 ± 19	89 ± 17	**<0.001**
CO (L/min)	6.5 ± 1.6	5.9 ± 2.1	0.082
CI (L/min/m²)	2.9 ± 0.8	2.9 ± 1.1	0.970
SV (ml)	75.5 ± 16.7	82.2 ± 22.4	**0.03**
HR (bpm)	87 ± 12	79 ± 17	**<0.001**

Abbreviations: SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure, MAP = Mean Arterial Pressure, CO = Cardiac Output, CI = Cardiac Index, SV = Stroke Volume, HR = Heart Rate

EFFECT OF WEIGHT LOSS ON CARDIOVASCULAR HEMODYNAMIC VARIABLES

Follow-up data was available of 51 patients (in group A). Table 4.3 gives an overview the changes in cardiovascular hemodynamic variables. There were no differences between postoperative and preoperative cardiac output (CO) and cardiac index (CI) (p-values respectively 0.082 and 0.970). Compared to group B, the postoperative hemodynamics of group A did not differ significantly from that of the healthy individuals. (Respectively p= 0.586 (Systolic Blood Pressure); 0.678 (Diastolic Blood Pressure); 0.778 (Mean Arterial Pressure); 0.335 (Cardiac Output); 0.246 (Cardiac Index); 0.890 (Stroke Volume) and 0.145 (Heart Rate).

We did a subgroup analysis to determine if there is a relationship between the type of bariatric surgery and the postoperative changes in cardiovascular hemodynamics. No significant differences were found between patients who underwent an SG or a RYGB of revisional surgery.

4.4 DISCUSSION

The present study assessed the effects of bariatric surgery on cardiovascular hemodynamics 3 months after bariatric surgery We have found that compared to healthy individuals, obese patients prior to bariatric surgery have significantly higher systolic and diastolic blood pressure, mean arterial pressure, heart rate and cardiac output. Three months after bariatric surgery significant improvements occur in all hemodynamic variables except cardiac output and cardiac index. Secondly, assuming that hemodynamic measurements of healthy individuals do not change over the course of three months, we do not see a significant difference in postoperative hemodynamics compared to healthy individuals that might be a clue that there is a normalisation of hemodynamic profile after 3 months.

With respect to hemodynamic changes after bariatric surgery, conflicting results are reported in current literature. Several studies report a significant decrease in systolic and diastolic blood pressure in the first weeks after bariatric surgery, but also over longer postoperative period. (16-23) A few reports only show a significant decrease in either mean arterial blood pressure (24, 25), a long-term significant decrease in systolic blood pressure (26-29) or a significant decrease in diastolic blood pressure. (30-32) In contrast to these positive results, others show no significant changes in blood pressure after bariatric surgery. (25, 27, 32-41) This may be explained by presence of hypertension and/or a high left ventricular mass (LVM) as postulated by Mukerji et al. (42) and Alpert et al. (43). Furthermore, a few studies found a significant short- and long-term decrease in heart rate after bariatric surgery,(16, 21, 23, 25, 28-32, 35, 36, 44) while others found no differences.. (24, 33, 34, 37-39, 41, 42, 45) The most intriguing fact of these results is that there must be an intrinsic morphological factor than makes the difference and explains us why these conflicting results exist. In current literature cardiac remodelling after bariatric surgery is seen mostly in patients with hypertension, LVH or both. (43) In our opinion, pre-existing hypertension or left ventricular hypertrophy might be prerequisite for reverse remodelling after bariatric surgery and thus the explanation for the conflicting results in current literature.

Regarding cardiac output we hypothesized that, due to volume decrease as result of weight loss, the cardiac output would decrease three months after surgery. Our data suggest that a slight decrease in cardiac output occurs, although significance was not reached (p =0.082). Moreover, in our patient population the heart rate decreased and stroke volume increased 3 month after bariatric surgery significantly. However there was a decreasing trend in cardiac output seen in our study, although not significant. This observation is in line with current literature, because in most of the studies a significant decrease after 6-24 months and even after 10 years in terms of cardiac output was seen. (21, 25, 28, 32, 41, 44) These changes might indicate an improvement in relative volume overload, which can be the start of normalization of cardiac remodelling. However the degree of remodelling in relationship with the time postoperative is not known.

The findings of cardiovascular changes after bariatric surgery are noticeable (6) and may represent a supra-physiological effect of metabolic/bariatric surgical procedures. (1) There might be a combination of weight-dependent (e.g. weight loss) and also weight-independent mechanisms (inotropic hormones, like GLP-1) that induce cardiac remodelling. This includes that there is a possibility of direct gut hormonal inotropic action on the myocardium through an enterocardiac axis. (1, 6) The classical hemodynamic weight-dependent effect of bariatric surgery is no longer thought to be the only one responsible for reverse remodelling seen after bariatric surgery, as the beneficial effects can be independent from changes in blood pressure. (15, 30)

Manipulation of enteric gut hormones has been shown to have beneficial effects on cardiovascular function through the enterocardiac axis. (1, 46) Hormones such as secretin, glucagon and vasoactive intestinal peptide, act as inotropes by activating cardiac membrane adenylate cyclase, which is a key enzyme in cardiac cellular energy physiology. (47) Although these mechanisms are not fully understood, it is thought that the energy metabolism of the heart is enhanced through intermediaries of TCA cycle, cardiorenal protectivity and caloric restriction. (48)

LIMITATIONS

There are some limitations that need to be addressed. Firstly, our sample size was calculated using the difference in systolic and diastolic blood pressure and therefore we might have been slightly underpowered to detect a difference in cardiac output between the preoperative and the postoperative measurements. Secondly our sample size was not suited to determine the influence of remission of comorbidities on cardiovascular hemodynamics. Finally, this study is the first to assess hemodynamic changes in bariatric patients and since this is a pilot study we had a short follow-up. Also to further substantiate the findings and generalizability of the device there should be a comparison with echocardiography findings. And if so a control group should also be matched according to gender, age, BMI and body surface are to avoid bias and heterogeneity among the group of patients.

4.5 CONCLUSION

In summary, the aim of this study was to assess the cardiovascular and hemodynamic changes 3 months after bariatric surgery. We have found that compared obese patients prior to bariatric surgery have increased systolic, diastolic and, mean arterial pressure, heart rate and cardiac output that all normalized within three months after bariatric surgery except cardiac output. This suggests that bariatric surgery can have beneficial effects for cardiovascular hemodynamics in the early postoperative phase.

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5. PERIOPERATIVE RESPIRATORY CARE IN OBESE PATIENTS UNDERGOING BARIATRIC SURGERY: IMPLICATIONS FOR CLINICAL PRACTICE

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ABSTRACT

Obesity is an increasing problem worldwide. The number of people with obesity doubled since the 1980's to affect an estimated 671 million people worldwide. Obese patients in general have an altered respiratory physiology and can have an impaired lung function, which leads to an increased risk of developing pulmonary complications during anaesthesia and after bariatric surgery (approximately 8%). Therefore the respiratory management of the bariatric surgical patient provides a number of challenges. This review will focus on the perioperative respiratory care in bariatric surgical patients discussing respiratory physiology in the obese and perioperative respiratory care in bariatric surgery. Finally the value of preoperative pulmonary function testing and preoperative OSAS screening will be discussed.

5.1 INTRODUCTION

Obesity is an increasing problem worldwide. The number of people with obesity doubled since the 1980's to affect an estimated 671 million people worldwide. (1, 2) Among these, the number of people with the highest Body Mass Index (BMI > 40 kg/m^2) grew twice as fast as the group of people with a BMI of 30-40 kg/m^2. (2, 3) In the Netherlands, 48.3% of the people aged 19 years and older have overweight (defined as a BMI > 25 kg/m^2). (2)

The only treatment with a longstanding effect is bariatric surgery. (4) With the increasing prevalence of obesity, the worldwide numbers of bariatric surgical procedures are also increasing. (4) With obesity affecting many organ systems, under which the respiratory system, it is therefore not surprising that the respiratory management of obese subjects undergoing bariatric surgery represents a growing challenge.

This review will focus on the perioperative respiratory care in bariatric surgical patients discussing the following subjects:

- Respiratory physiology in the obese patients
- Perioperative respiratory care in bariatric surgery
- The value of preoperative pulmonary function testing and OSAS screening

5.2 RESPIRATORY PHYSIOLOGY IN THE OBESE

Obesity negatively affects many organ systems, including the respiratory system. It is associated with an altered lung function, characterised by a reduction of lung volumes, mostly a restrictive pattern. The pathogenesis behind this is multifactorial, but an increased truncal fat load is one of the possible mechanisms. (5) A restrictive pattern is seen when both the vital capacity (VC) and the total lung capacity (TLC) is below 80% of their predicted value and the Tiffeneau index (forced expiratory volume in 1 second (FEV1)/VC) is ≥ 0.7.

Because of affected respiratory physiological parameters such as compliance, neuromuscular strength, work of breathing (WOB), lung volumes and spirometric measurements (6, 7), obese subjects are prone to develop pulmonary complications after bariatric surgery.

RELATIONSHIP BETWEEN ANTHROPOMETRIC VARIABLES AND LUNG FUNCTION

Soriano et al (8) investigated over 3000 people in Spain and found a restrictive pattern in 12.7%. A higher BMI (> 30 kg/m^2) was independently associated with a restrictive spirometry.

(8) This was confirmed by Mannino et al. (9) who measured spirometry in different locations around the world. He found that a BMI below or above the reference categories (18.5-24 kg.m2) was a significant risk factor for a restrictive pattern. (9) Less is known about the prevalence of a restrictive lung function among obese people. Most research was done with obese people who were a candidate for bariatric surgery. Groups were small, varying between 20-150 patients and the prevalence varied between 6-50%. (10-13)

The impact of obesity on the respiratory system may vary from patient to patient and cannot be predicted from weight and/or BMI measurements alone. While assessment of BMI gives an impression about overall nutritional status, it does not differentiate lean mass, fat mass and the distribution of adipose tissue. This distinction might be important as lean- and fat mass have an opposite effect on lung function and the distribution of fat seems more relevant than total body fat per se. Body fat percentage was associated with decreased FVC, FEV1 ratio and FEV1/VC ratios in men and women respectively. (14-18) Moreover, others showed an adverse relation with waist to hip ratios and the respiratory system. High waist to hip ratios were associated with reduced lung function and poorer gas-exchange (15, 16, 18, 19)

Most studies use spirometry to assess lung function. Babb et al. (19) took a different approach. They state that the End-Expiratory Lung Volume (EELV or residual volume (RV)) is very sensitive to changes in static compliance of the lung and chest wall. Deposits of fat on the chest wall thus specifically alter the EELV. (19) They measured absolute and relative fat mass with MRI and compared it to the End-Expiratory Lung Volume (EELV). They found that fat distribution is relatively similar between lean and obese men and women, and that therefore the increase in chest wall fat distribution is proportional to the increase in obesity. (19) This means that measurements of overall obesity are significantly related to lung function as measured with EELV. So far, the books are not yet closed on which measurement should be used to assess the effect of obesity on lung function, but a combination of Waist/Hip (W/H) ratio and BMI seems recommended.

RESPIRATORY COMPLIANCE

Respiratory compliance is the ability of the respiratory system to stretch during a change in volume relative to an applied change in pressure. (6) Total respiratory compliance (e.g. the compliance of the pulmonary and extrapulmonary structures in the thoracic cage) can be reduced in obesity and in patients with the obesity-hypoventilation syndrome to as little as one-third of the normal values. (6, 20) This is mainly the result of reduced distensibility of extrapulmonary structures due to excess truncal fat. (6, 20) Secondly, the increase in pulmonary blood volume and increased closure of dependant airways may also contribute to the low lung compliance seen in obese people. (21) These physiological changes are even more pronounced during recumbency in obese subjects (as compared to normal weight subjects), due to increased gravitational effects of the abdomen. (22)

LUNG VOLUMES

The most consistent indicator of obesity is a reduction in expiratory reserve volume (ERV). This is due to a displacement of the diaphragm more cranially into the thoracic cage by the 'obese' abdomen and the increased chest wall mass. (6, 23, 24) This association is seen in modest obesity, but the ERV rapidly decreases with increasing BMI. (6, 25, 26) The ERV decreases because the 'obese' abdomen inhibits the diaphragm to extend in caudally.

On the other hand, obesity has modest effects on residual volume (RV) and total lung capacity (TLC), but a relatively larger effect in reducing functional residual capacity (FRC). (26-28) In some studies the reduction of the FRC is so marked that it approaches RV. (27) When the reduced FRC is equal to or lower than the closing volume, thoracic gas trapping may take place in obese subjects, as indicated by an elevated RV/TLC ratio. (28-30) The effects of obesity on lung volumes are shown in figure 5.1.

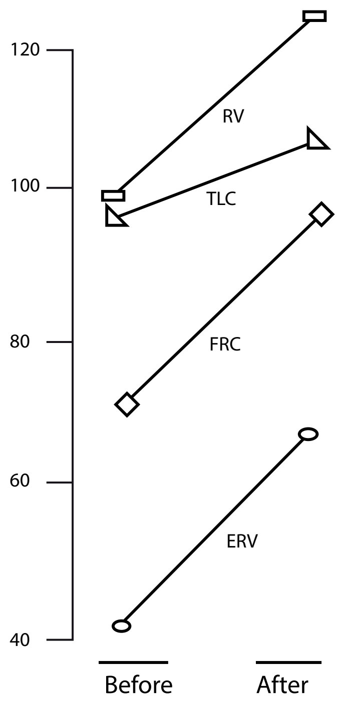

FIGURE 5.1: Lung function parameters before and after surgical weight loss *(Adapted from Thomas et al. (93))*

Abbreviations: ERV = Expiratory Reserve Volume, FRC = Functional Residual Capacity, TLC = Total Lung Capacity, RV = Residual Volume

WORK OF BREATHING

To compensate the reduced respiratory compliance, (severely) obese subjects may breathe rapidly and shallowly, to maintain eucapnia. (6, 23, 31-33) Therefore people with obesity have a higher Work of Breathing (WOB). Because of a restrictive pattern, breathing takes place at a less compliant part of the pressure-volume curve. Thus they can develop a rapid, shallow breathing pattern, which comes with a higher oxygen cost. (6, 23, 24) The oxygen cost of breathing is an index that represents the energy required to breathe. (21) This index shows the oxygen consumed by the respiratory muscles per litre of ventilation. (21) Kress et al. (34) investigated eighteen severely obese patients and found a 16% reduction in oxygen consumption after elective intubation, mechanical ventilation and anaesthesia from the baseline values, as compared to <1% reduction among controls. This (relative) respiratory inefficiency among the obese suggests a decreased ventilatory reserve and a (possible) predisposition to respiratory failure. (6, 23, 24, 34)

RESPIRATORY MUSCLE STRENGTH

Regarding respiratory muscle strength, different results are being reported in the current literature. Several studies indicate that obese people have greater risk of developing respiratory muscle inefficiency, in terms of less capability to generate normal maximal inspiratory pressure and expiratory pressures. (6) Other studies showed that there was no difference in inspiratory pressures between obese individuals and non-obese controls. (35-37) A possible explanation for impaired respiratory muscle function in obesity can be the increased elastic load that the respiratory muscles are required to overcome during inspiration. (6, 38)

A mechanical disadvantage exists because of an overstretched diaphragm, leading to decreased inspiratory muscle strength and efficiency. (6, 39) Also some studies indicate decreased levels of skeletal muscle glycogen synthase activity in obese subjects that can be a contributing factor in the decrease in isokinetic skeletal muscle endurance. (40, 41)

CLINICAL RELEVANCE OF PULMONARY FUNCTION CHANGES

The pulmonary function changes due to obesity can roughly be summarised in three parts I) a restrictive effect of mass on the chest wall, II) a tendency to breathe at low lung volumes and III) the effect of fat distribution on pleural pressure. (28, 42-47) The physiological changes are heightened during sleep in supine position, due to a negative impact pulmonary mechanics of diaphragm impedance by the abdomen with a change in lung volume. This leads to intolerability for apnoeic episodes and to early desaturation. These pulmonary mechanics changes in obesity lead to a lower FRC, FVC and FEV_1. (28, 42-47)

OBSTRUCTIVE SLEEP APNOEA SYNDROME (OSAS) AND OBESITY HYPOVENTILATION SYNDROME (OHS)

Research in patients with the Obesity Hypoventilation Syndrome (OHS: the existence of alveolar hypoventilation which cannot be explained by an other neuromuscular or pulmonary disorder) demonstrated that these patients exhibit a lowered neuromuscular respons to hypercapnia and hypoxemia, caused by a blunted central drive. (6, 23, 31-33) It is unclear, however, what causes this blunted central drive. A lowered chemosensitivity could be genetic, but other factors such as a distorted sleep-breathing pattern (Obstructive Sleep Apnoea Syndrome (OSAS)) and neuro-hormonal factors could also play a role. The fact that effective treatment of the obstructed breathing may partly correct nocturnal hypoxemia and awake hypercapnia, seems to prove that upper airway obstruction and flow limitation are important factors in the development of OHS. (6, 23, 24)

But few patients, even among those with severe OSAS, develop daytime hypercapnia. Possibly, the severity of the nocturnal hypoxemia is important. (6, 26, 31-33) Despite a similar BMI, severity of the apnoea/hypopnea index, arousal indices and sleep architecture, OHS patients exhibit a more severe desaturation compared to the eucapnic obese group (23).

TABLE 5.1. Correlation between anthropometric variables and pulmonary function parameters

	Gender	Anthropometric variable	Pulmonary function variable	Correlation
Jung et al. (14)	Men Women	Body fat percentage Body fat percentage	FVC and FEV_1 FEV_1/VC	Negative Negative
Zavorsky et al. (15, 16)	Men Women	Waist/hip ratio Waist/hip ratio	Gas exchange Gas exchange	? ?
Wehrmeister et al. (17)	Men	Waist circumference	FEV_1 and FVC	Inverse
Rossi et al. (18)	Men Woman	Body fat percentage Body fat percentage	FVC and FEV_1 FVC and FEV_1	Inverse Inverse
Babb et al. (19)	Men Women	Fat deposition thorax Fat deposition thorax	RV RV	Inverse Inverse

Abbreviations: FVC = Forced Vital Capacity, FEV_1 = Forced expiratory volume in 1 second, RV = Residual Volume

Animal research showed that nocturnal hypoxemia lowers the hypoxic ventilatory drive and raises the arousal threshold, possibly because of an effect on the synthesis and turnover of neurotransmitters. (23, 48-51) Because of this, patients fail to compensate adequately after an episode of hypoventilation. This causes decreased ventilation in between episodes for a given CO2-load, combined with a relatively shorter time-span between episodes considering the duration of apnoeic episodes. (48, 50, 51) Norman et al. (52) hypothesizes that repeated nocturnal CO2-accumulations cause bicarbonate retention by the kidneys. Most patients have enough time to compensate for this brief raise in CO2. But if patients compensate insufficiently after an event, chronic bicarbonate retention develops, raising the threshold for hypercapnia. (23, 52) What causes this diminished response is yet to be discovered. Possible actors might be leptin and IL-GF-1 because of their stimulating effect on central respiratory centres. (23)

5.3 PERIOPERATIVE RESPIRATORY CARE IN BARIATRIC SURGERY

Because the percentage of obese people in the population increases (2, 3), more people are at risk for an altered lung function due to obesity. As a consequence, the risk of respiratory complications under general anaesthesia might increase as well. This can result in hypoxemia, hypercapnia and increased formation of atelectasis.

INDUCTION AND AIRWAY MANAGEMENT

Obesity increases the risk of a difficult airway during induction, because of an altered upper airway anatomy. (6, 7, 23) Heinrich et al. (53) found that 6% of cases of a difficult laryngoscopy over a 6-year period occurred in patients with a BMI ≥ 35 kg/m^2. The incidence of a difficult intubation is increased from 5.8% in the general population and 15.8% in people with a BMI > 30 kg/m^2. (54) The restricted lung function leads to a greater risk of desaturation during induction. The lowered FRC can approach the closing capacity, which can lead to closing of airways during tidal breathing. (6, 54, 55) This leads to shunting and a ventilation/perfusion mismatch. This is exaggerated by a supine position, in which the abdominal pressure and the pulmonal blood volume are increased and decruitment of dependent alveoli exists, and by an increased oxygen demand. (55)

Techniques that can be used to reduce this risk are:

- **Prediction difficult intubation:** indirect mirror laryngoscopy. (56)

- **(Awake) videolaryngoscopy:**

Moore et al. (57) found that 96% of 50 morbid obese patients undergoing bariatric surgery and classified as having a difficult airway were successfully intubated using awake videolaryngoscopy.

- **Head-up induction:**

Several studies have investigated different positioning techniques to improve the laryngeal view in patients with morbid obesity. Lee et al. (58) found that the laryngeal view can be significantly improved when patients were put in a 25 degrees head-up position when compared with the conventional supine position. Collins et al. (59) found a statistical significant better laryngeal view when morbidly obese patients were placed in the 'ramped' position, in which the external auditory meatus was at the same level as the sternal notch. Gupta et al. (60) compared rapid sequence induction (RSI) in semi-erect position with the investigator in front of the patient compared to RSI in supine position with the GlideScope videolaryngoscope of morbidly obese patients, but found no significant differences between the two groups when it comes to intubation parameters or patient safety.

- **Pre-oxygenation:**

Dixon et al. (61) found obesity achieved higher oxygen tensions and therefore a clinically significant increase in the desaturation safety period in the 25 degrees head-up position. Ramkumar et al. (62) investigated the 20 degrees head up pre-oxygenation in non-obese individuals, and found that time to desaturation (< 93%) was significantly prolonged as well.

- **Apneic oxygenation:**

Ramachandran et al. (63) found that providing obese patients with additional nasal O2 during simulated difficult laryngoscopy was associated with a significant prolongation of SpO2 ≥ 95%, a significant increase in patients with SpO2 ≥ 95% apnoea at 6min, and a significantly higher minimum SpO2. Resaturation times were no different.

VENTILATION STRATEGIES IN OBESE PATIENTS

General anaesthesia and paralysis negatively affect pulmonary gas exchange and respiratory mechanics (figure 5.2). When PEEP is not applied, atelectasis formation is present in 90% of patients under general anaesthesia. (64, 65)

Patients with morbid obesity have a higher risk of atelectasis formation, exhibit more profound changes in respiratory function and are at a higher risk for hypoxemia. (6, 7, 66) Pelosi et al. (66) found that under general anaesthesia, PaO_2 is inversely related to BMI. The severity of atelectasis formation is related to body weight and extends longer in the postoperative phase when patients are severely overweight. (67, 68)

Reinius and colleagues (68) showed in obese patients under general anaesthesia that PEEP in combination with recruitment manoeuvres reduced atelectasis and improved PaO2/FiO2 ratio. This effect was still present 40 minutes later. The compliance was also improved. (68) Aldenkortt et al. (69) found similar results based on their performed meta-analysis on the effects of different ventilation strategies in obese patients. Also Aldenkortt et al. (69) compared pressure- and volume-controlled ventilation (PCV and VCV). In terms of intraoperative PaO_2, FiO_2 ratio and tidal volumes no significant differences were found between the both ventilation strategies. (69)

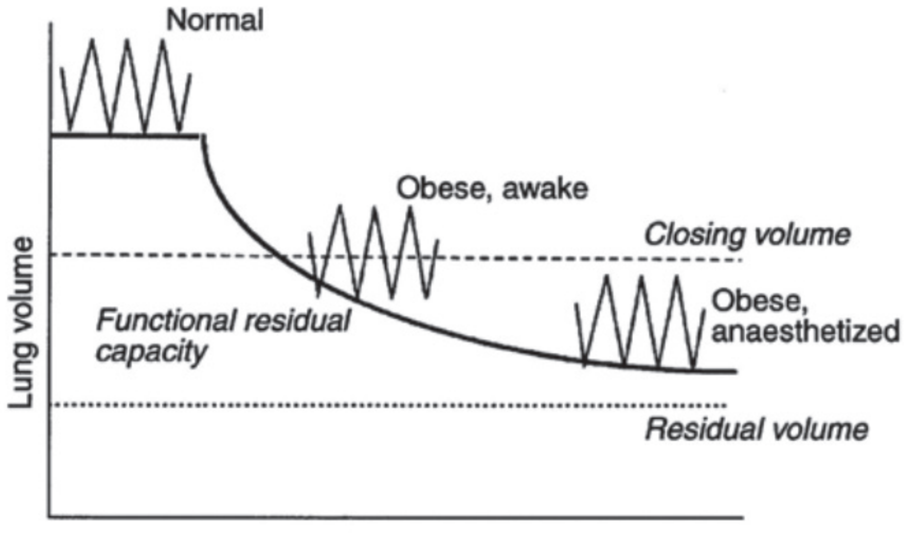

FIGURE 5.2: Effects of anaesthesia on the functional residual capacity of the obese (30)

POSITIVE AIRWAY PRESSURE (BIPAP)

Yu et al. (70) hypothesized that biPAP ventilation may diminish the development of pulmonary shunt and may improve ventilation-perfusion mismatch when compared to standard IPPV, with or without PEEP when neuromuscular paralysis has been used during surgery. They found that biPAP ventilation was beneficial in decreasing ventilation-perfusion mismatch and improving oxygenation when compared with conventional IPPV (with or without PEEP) (70)

Ebeo et al. (71) investigated the effect of BiPAP on pulmonary function in obese patients following open gastric bypass surgery. This resulted in significantly higher VC and FEV_1 12-24 hours postoperative, but did not result in fewer hospital days or lower complication rates. (71) Joris et al. (72) found similar results in terms of postoperative pulmonary function, but no significant differences were found between the BiPAP and control group in terms of peak expiratory flow rate. (72)

NON-INVASIVE VENTILATION STRATEGIES (CPAP AND NIV)

Continuous positive airway pressure (CPAP) and NIV have been used to prevent and treat acute respiratory failure after surgery or to treat acute respiratory failure. (73, 74) What the most ideal ventilation strategy is to reduce postoperative morbidity is unclear. A meta-analysis (75) showed that CPAP following abdominal surgery significantly reduced postoperative pulmonary complications, atelectasis and pneumonia, which is in contrast with a recent Cochrane review (76) that stated the evidence is of low quality.

The feasibility and safety of NIV use in the recovery room after various types of surgery has been demonstrated (77) and also a recent meta-analysis (78) showed that in perioperative bariatric care NIV is well tolerated and significantly reduces respiratory complications. However there is still lack of comparative studies to determine which ventilation strategy is superior in perioperative bariatric care.

INFLUENCE OF METABOLIC SYNDROME AND COMORBIDITIES ON THE PERIOPERATIVE PERIOD

Bariatric surgery is an acceptable and effective method to manage obesity-related comorbidities in morbidly obese patients. (79, 80) Nearly four in five patients scheduled for bariatric surgery has metabolic syndrome. (80) In particular the presence of cardiac, pulmonary, metabolic and hepatic comorbidities may vary in patients scheduled for bariatric surgery, thus posing particular challenges to the anaesthesiologist. (79) Hypertension (both systemic and pulmonary), dyslipidaemia and hyperglycaemia respond to bariatric surgery. (79-81) A large retrospective study by Purnell et al. (80) showed that there was no significant difference in perioperative complications in patients with our without metabolic syndrome.

5.4 IS PREOPERATIVE PULMONARY FUNCTION TESTING NECESSARY IN BARIATRIC SURGERY?

The current body of literature is sparse regarding the effects of an impaired pulmonary function and its relation with the occurrence postoperative complications in bariatric surgery. A study conducted by van Huisstede et al. (82) investigated the relationship between pulmonary function parameters and the risk of postoperative complications in a 485 patients. They found 53 complications of which 8 of them were from pulmonary origin. Patients with complications had a significantly lower FEV_1 (mean 86.9% of predicted) and FVC (mean 95.6% of predicted) compared to patients without complications ($P<0.05$). (82) A FEV_1/FVC <70% and a δFEV1 ≥ 12% were found to be predictors for pulmonary complications. (82) In the study by Sood et al. (83) morbidly obese patients (with a BMI >40 kg/m^2) have increased odds of developing pulmonary complications

Questions arise whether it might be useful to perform preoperative pulmonary function testing in patients scheduled for bariatric surgery. And which BMI group is at risk for postoperative (pulmonary) complications and does this increased risk has a relation with the lung function. A second problem that may arise is the possible need for screening for OSAS, in this population. Because this co morbidity occurs frequently and if untreated, it might result in postoperative complications. (84-87)

Lastly, we searched the literature for evidence for preoperative strategies that might be applied in obese patients with impaired pulmonary function to prevent postoperative complications.

PREOPERATIVE PULMONARY FUNCTION SCREENING

The current body of literature regarding the clinical utility of preoperative pulmonary assessment in bariatric surgery remains questionable. Reasons to preoperatively screen patients is to identify those who are at high risk of developing postoperative pulmonary complications. To assess the utility and predictive value we must separate the literature regarding open and laparoscopic bariatric procedures.

Farina et al. (12) investigated the value of spirometry as a preoperative screening tool to identify patients scheduled for open bileopancreatic diversion at risk for postoperative pulmonary complications (PPC). They found a very low rate of PPC's (7.5%) in patients with suspected restrictive pulmonary impairment. (12) Hamoui et al. (88) investigated the usefulness of pulmonary function tests in predicting the overall risk for complications (including PPC's). They found on multivariate analysis that age (p=0.01) and a decreased VC (p=0.0007) were significant predictors for postoperative pulmonary complications. (88)

Catheline et al (10) screened 77 patients prior to bariatric surgery on cardiac and pulmonary abnormalities and found no consequences for the management of the perioperative period. Notwithstanding their results they still found based on their clinical experience that cardiac and pulmonary screening essential prior to bariatric surgery. (10)

PREOPERATIVE OSAS SCREENING

Nepomnayshy et al. (89) investigated the additive value of screening for sleep apnoea prior to laparoscopic bariatric surgery for predicting postoperative pulmonary complications and compared them with obese patients undergoing orthopaedic surgical procedures. As a result of screening, of 882 patients, 119 bariatric patients (25%) were newly diagnosed with OSAS. The orthopaedic surgery group had 17.3% (72 of 415 patients) with pre-existing OSAS. The unscreened orthopaedic patients had complication rate of 6.7% compared to 2.6% for the screened bariatric patients. This difference was not statistically significant after adjusting for age and comorbidity (p=0.3383). (89)

Peromaa-Haavisto et al. (90) showed that in a population of 197 obese patients scheduled for bariatric surgery, there was a prevalence of OSAS was 71%, with a significantly higher prevalence in males (90%) compared with women (60%). According to their study results, they recommend OSAS screening preoperatively especially in obese men. (90)

PREOPERATIVE PULMONARY PREPARATION

The current evidence around preoperative pulmonary preparation (in case of an impaired lung function found during screening) is lacking. Also the effects on postoperative complications are not clear.

In a study by Barbalho-Moulim et al. (91) randomised 32 obese women undergoing elective open bariatric surgery to either an inspiratory muscle-training group or usual care group. Compared to the preoperative values, the MIP decreased significantly in both groups after surgery. However the reduction in MIP was 28% in the inspiratory muscle training group en 47% in the usual care group. (91) There was a significant reduction in postoperative complications in the inspiratory muscle-training group.

Van Huisstede et al. (82) concluded that the risk of pulmonary complications after laparoscopic bariatric surgery is low. However patients with abnormal spirometry test results have a threefold risk of complications after laparoscopic bariatric surgery. (82)

In obese patients with asthma, van Huisstede et al. (92) recently showed that bariatric surgery has beneficial effects on lung function, in terms of small airway function, decreased systemic inflammation and the number of mast cells in the airways compared to obese patients without asthma. In both groups FEV_1, FVC and TLC significantly improved, whereas FEV_1/VC only improved in the obese patients with asthma. (92) Unfortunately it is unclear whether obesity/morbid obesity and preoperative asthma control has influence on the postoperative outcomes.

It can be hypothesized that perioperative respiratory physiotherapy (in bariatric surgery) might have a role in preventing PPC's in patients with a (obesity induced) respiratory defect. Also for specific groups (asthma, OSA and OHS patients) pulmonary function tests may be useful and might bring clinical advantages.

5.5 CONCLUSION

The majority of the obese patients have an altered respiratory physiology and have an impaired lung function, which leads to an increased risk of developing pulmonary complications during anaesthesia and after bariatric surgery. Therefore the respiratory management of the bariatric surgical patient is challenging. There are a growing number of studies in particular around optimal ventilation strategies to minimize the risk of postoperative complications. Unfortunately, this is still a grey area because not one ventilation strategy has shown superiority in preventing postoperative atelectasis after bariatric surgery. Whether patients scheduled for bariatric surgery need to be screened for obesity related pulmonary function impairment (and OHS/OSAS) is still subject to discussion.

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6. EFFECTS OF BARIATRIC SURGERY ON INSPIRATORY MUSCLE STRENGTH

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ABSTRACT

Background

The respiratory function is affected by obesity due to an increased deposition of fat on the chest wall. The objective of this study was to investigate the strength of the inspiratory respiratory muscles of obese individuals and the possible influence of bariatric surgery on it by measuring the Maximum Inspiratory Pressure.

Methods

Patients referred to a bariatric centre between the 3rd of October 2011 and the 3rd of May 2012 were screened preoperatively by a multidisciplinary team. Their Maximum Inspiratory Pressure (MIP) was measured at screening and 3, 6 and 9 months postoperative. In case of a preoperative MIP lower than 70% of predicted pressure training was provided supervised by a physiotherapist.

Results

The mean age of 124 included patients was 42.9 ± 11.0 years and mean BMI was 43.1 ± 5.2 kg/m^2. The mean predicted MIP preoperatively was 127 ± 31 in cm H_2O and the mean measured MIP was 102 ± 24 in cm H_2O. Three patients (2.4%) received training. Three months after surgery the MIP was 76 ± 26 cm H_2O, after 6 months 82 ± 28 cm H_2O and after 9 months 86 ± 28 cm H_2O. All postoperative measurements were significant lower than preoperatively ($P<0.05$). The only influencing factor for the preoperative MIP was age ($p=0.014$).

Conclusion

The preoperative MIP values were significantly lower than the predicted MIP values, probably due to altered respiratory mechanics.

6.1 INTRODUCTION

Obesity is a chronic disease characterised by an excessive accumulation of body fat and causes damage to various body functions, such as cardiovascular, musculoskeletal, and metabolic functions amongst others. (1) Also the respiratory function is affected by obesity due to an increased deposition of fat on the chest wall. This causes a reduction in thoracic compliance, lung volumes and capacities. (2-4) Respiratory dysfunction in this patient population can occur due to changes in the relationship between lung, chest wall and diaphragm, causing an impairment of respiratory mechanics and also changes in gas exchange. (5)

Several studies have demonstrated that weight loss due to bariatric surgery has resulted in a huge improvement in some functions, such as a decrease in haemoglobin and haematocrit (6), decreased heart rate and oxygen consumption (6) and a reduction in insulin resistance. Bariatric surgery also showed an improved lung function with increased forced vital capacity (FVC) (7, 8), forced expiratory volume in one second (FEV1), and improved alveolar-capillary diffusion capacity (6) and an improvement in gas exchange (7, 8). However, studies on the respiratory muscle function of the obese population (before and after bariatric surgery) show conflicting results. (5, 9-12)

Thus, the objective of this study was to investigate the strength of the respiratory muscles of obese individuals (before and after bariatric surgery) by measuring the maximum inspiratory pressure (MIP). Also we have investigated the influence of patient related factors and type of operation (sleeve gastrectomy or gastric bypass) on the MIP before and after bariatric surgery. Furthermore, the association of the body mass index (BMI) and the presence of comorbidities with the respiratory muscle strength were reviewed.

6.2 METHODS

This study was approved by the Medical Ethics Committee of the Catharina Hospital Eindhoven and adheres the principles of the declaration of Helsinki. Informed consent was obtained of all patients included.

PATIENT POPULATION

Patients were referred to a bariatric centre by their general practitioner or other physicians. A multidisciplinary team screened all patients preoperatively, consisting of a physician assistant, a psychologist, a nutritionist and a surgeon. Patients were eligible for surgery if they had a BMI of 40 kg/m^2 or higher, or a BMI between 35 and 40 kg/m^2 with significant co-morbidities, with serious attempts to lose weight in the past. Co-morbidities were considered significant when medication had to be used, or if continuous positive airway pressure (CPAP) had to be used in case of obstructive sleep apnoea (OSAS). The indication for a bariatric procedure was made in a multidisciplinary consultation, taking into account the patients' preference, age, polypharmacy, reflux complaints, body composition in relation to BMI and bowel diseases. Patients with pre-existing pulmonary and/or neuromuscular diseases were excluded from this study.

RESPIRATORY MUSCLE FUNCTION AND MIP ASSESSMENT

Respiratory muscle strength was assessed by measuring the maximal inspiratory pressure (MIP) with a digital mouth pressure meter (± 300 cm H_2O). The manometer (Micro RPM®, Carefusion, USA) was calibrated in accordance with the manufacturer's recommendations. (13)

The maximal static respiratory pressure generated in the mouth, after complete inhalation and exhalation, carries out the measurement of respiratory muscle strength, divided in the Maximal Inspiratory Pressure (MIP) and Maximal Expiratory Pressure (MEP), which are indicative of the strength of the inspiratory and expiratory muscle groups. (14) MIP is a measure of inspiratory muscle strength (which is representative for the function of the diaphragm), whereas MEP measures the strength of the abdominal and intercostal muscles. (15-17)

The assessment of the respiratory muscle strength took place before bariatric surgery and 3, 6 and 9 months postoperatively by an independent and trained physiotherapist using the ATS/ERS guidelines. (13, 18) The MIP values were compared to each other and to the normal values adjusted for their sex and age. (19)

When the actual preoperative measured MIP was ≤ 70% of the predicted MIP, patients were asked to conduct respiratory function training prior to surgery. The protocol for training of the respiratory function was adapted from a study of Hulzebos and colleagues. (20)

DATA COLLECTION

Data were collected prospectively using an online registry (Patients Outcome Measurement Tool). The patients who got approval between the 3rd of October 2011 and the 3rd of May 2012 were included in this study as during this period the inspiratory muscle function was measured.

Data of interest were MIP values, patients' characteristics, operative details, hospital stay and evolution on weight and comorbidities. Furthermore were included the postoperative pulmonary complications defined as pulmonary infections as determined by the physician, thromboembolic events, and respiratory distress resulting into additional care.

STATISTICAL ANALYSIS

Continuous variables were presented as mean ± standard deviation (SD). Categorical variables were presented as frequency with percentages. The Shapiro-Wilk test was used to test each variable for normality. Student's t-test for independent groups or the Mann-Whitney U test was used to compare the MIP values in the preoperative period and changes in MIP values over time, depending on the normality or non-normality of the data distribution. To compare the MIP values at different times (preoperatively, and after 3, 6 and 9 months after surgery), repeated measures ANOVA was used. To assess postoperative MIP values (and the difference with preoperative MIP values) between patients who had a sleeve gastrectomy and gastric bypass, the two-repeated ANOVA was used.

The Pearson correlation coefficient was used to determine the correlation between de following parameters: preoperative BMI and preoperative MIP; Prevalence of OSAS and preoperative MIP; weight loss 3 months after surgery and MIP 3 months after surgery; weight loss 9 months after surgery and MIP 9 months after surgery; smoking and MIP values (preoperative and after 3, 6 and 9 months); gender and preoperative MIP and age and preoperative MIP.

In all tests, values of $p<0.05$ were considered statistically significant. Statistical Package for Social Sciences (SPSS, Chicago, IL, USA Version 20.0) was used to prepare the database and for statistical analysis.

6.3 RESULTS

PATIENTS AND PROCEDURES

All 124 patients completed the 9 months follow-up and were all available for the final analysis. The majority of the included 124 patients were female (n=106). The mean age was 42.9 ± 11.0 years and mean BMI was 43.1 ± 5.2 kg/m^2. Related comorbidities encountered were diabetes (20.2%), OSAS (13.7%), hypertension (33.9%) and dyslipidaemia (20.2%). Among the patients 17 (13.7%) were tobacco users and 11 (8.9%) used alcohol. Half the patients underwent a sleeve gastrectomy (n=60; 49.2%) and the other half received a gastric bypass (n=64; 50.8%). These interventions resulted into a weight loss of 18 ± 26 kg (13 ± 21 %TWL) and 51 ± 29 kg (41 ± 23 %TWL) respectively at three months and one year postoperative. No pulmonary complications as defined in the methods section were seen postoperatively.

MAXIMAL INSPIRATORY PRESSURES

In the preoperative period, the mean predicted MIP was 127 ± 31 in cm H_2O and the mean measured MIP was 102 ± 24 in cm H_2O (Table 6.1). Based on these results, only three patients were asked to train their respiratory function, because they had a preoperative measured MIP value <70% of predicted. Three months after surgery the MIP was 76 ± 26 cm H_2O, after 6 months the MIP was 82 ± 28 cm H_2O and after 9 months 86 ± 28 cm H_2O. At all three measure moments this decrease was significant compared to the preoperative value (P=0.01).

TABLE 6.1. Maximal inspiratory pressures of obese patients before and after a bariatric procedure

Predicted MIP* (n=124)	Actual MIP preoperative* (n=124)	After 3 months* (n=124)	After 6 months* (n=124)	After 9 months* (n=124)
127 ± 31	102 ± 24^{A}	76 ± 26^{B,C}	82 ± 28^{B,C}	86 ± 28^{B,C}

* In cm H_2O
^{A} significant difference compared with Predicted MIP (p=0.019)
^{B} significant difference compared with Actual MIP (p=0.01)
^{C} no significant difference between 3, 6 and 9 month values (p=0.273)

TABLE 6.2. Mean MIP changes (± SD) in cm H_2O between different time points

	MIP after 3 months	MIP after 6 months	MIP after 9 months
Compared with:			
Actual Preop MIP	-26.65 ± 22.30	-20.61 ± 20.58	-16.54 ± 21.08
MIP after 3 months		6.03 ± 19.99	10.11 ± 20.65
MIP after 6 months			4.07 ± 11.98
MIP after 9 months			

SLEEVE GASTRECTOMY VERSUS GASTRIC BYPASS

The preoperative MIP, the MIP 3 months after surgery, 6 months after surgery and 9 months after surgery did not significantly differ between patients who had a sleeve gastrectomy compared to a gastric bypass (P=0.590, P=0.592, P=0.165 and P=0.895 respectively).

CHANGES IN MIP VALUES OVER TIME

Table 6.2 gives an overview of the mean MIP changes between different time points. There was a significant difference between the mean changes in MIP after 3 months and 6 months (respectively -26.65 ± 22.30 and 6.03 ± 19.99 cm H_2O, p=0.001) and there was a significant difference in the mean changes in MIP after 3 and after 9 months (respectively -26.65 ± 22.30 and 4.07 ± 11.98 cm H_2O, p=0.001)

CORRELATIONS BETWEEN DIFFERENT VARIABLES

Table 6.3 gives an overview of the correlations investigated. There was no linear correlation between the preoperative BMI and preoperative MIP (r=-0.045, p=0.619), the prevalence of OSAS and the preoperative MIP (r= -0.025, p=0.779), weight loss 3 months after surgery and MIP 3 months after surgery (r=-0.187, p=0.008), weight loss 9 months after surgery and MIP 9 months after surgery (r=-0.075, p=0.072) and smoking and the MIP values preoperative (r=-0.003, p=0.976) and 3, 6 and 9 months postoperative (r=0.070, p=0.439; r=0.054, p=0.552; and r= 0.014, p=0.877 respectively). The correlation between gender and the preoperative MIP showed a trend towards significance (r=-0.155, p=0.085). The only (negative) linear correlation found was between age and the preoperative MIP (r=-0.220, p=0.014).

TABLE 6.3. Overview of the correlations between different variables (n=124 patients)

Variable 1	Variable 2	Correlation coefficient	P-value
Preoperative BMI	Preoperative MIP	r=-0.045	p=0.619
Prevalence of OSAS	Preoperative MIP	r=-0.025	p=0.779
Weight loss 3 months after surgery	MIP 3 months after surgery	r=-0.075	p=0.408
Weight loss 9 months after surgery	MIP 9 months after surgery	r=-0.187	p=0.072
Smoking	MIP preoperative MIP after 3 months MIP after 6 months MIP after 9 months	r=-0.003 r=0.070 r=0.054 r= 0.014	p=0.976 p=0.439 p=0.552 p=0.877
Gender	Preoperative MIP	r=-0.155	p=0.085
Age	**Preoperative MIP**	**r=-0.220**	p=0.014

6.4 DISCUSSION

The actual measured MIP was significantly lower than the predicted values in the present study. The Maximum Inspiratory Pressures at 3, 6 and 9 months after bariatric surgery were decreased significantly compared with the preoperative MIP. The only (negative) linear correlation found was between the age and the preoperative MIP, which is corresponding with earlier studies on this subject. (5, 19)

Obesity has a detrimental effect on the pulmonary physiology, including respiratory mechanics, airway resistance, respiratory muscle function, lung volume, work of breathing (WOB) and gas exchange. (21) Morbidly obese patients present with increased metabolic demands due to a deposition of fat in the chest wall, which results in an increased mass to move during breaths and therefore a higher WOB. This elevated WOB results in reduced chest wall compliance. Also there is an elevation of the diaphragm, which (upon contracting) acts under pressure of a distended abdomen. (22-24)

This ‘overload’ triggers a variety of mechanisms in the activity of the respiratory muscles and causes a long term training effect, which can increase muscle strength. (5, 22, 23) It is believed that this muscle strength decreases when patients develop a condition such as OSAS. (5) In the postoperative period, weight reduction may promote an improvement in respiratory mechanics and compliance, improving the efficiency of the respiratory muscles. (4) In the present study, the MIP after was decreased 3 months after surgery, but at 6 months and 9 months after surgery it increased. This is the effect of weight loss, which reduces the earlier mentioned ‘overload’ and therefore creates a new setpoint to which the respiratory muscle strength has to adjust. This could be an explanation for the fact that the MIP decreased 3 months after surgery in our study. However we found a trend towards a negative correlation between weight loss 9 months after surgery and the MIP 9 months after surgery ($p=0.072$), which indicates a decrease in respiratory muscle strength when the weight loss increases. The explanation for this matter lies in the earlier mentioned ‘overload’, which vanishes after successful bariatric surgery. Whether this earlier mentioned new ‘setpoint is due to an improvement in diaphragm muscle function or a change lung compliance is unknown.

Also animal studies in rabbits show that chronically increased intra-abdominal pressure induce several histological and cellular changes in composition of greater abdominal muscles, especially the rectus abdominis and diaphragm muscle. (25-28) Changes in muscle fiber composition of the muscles were observed, an increased ratio of type II muscle fibers that are mainly anaerobically active. (25-28)

Studies investigating indices of respiratory muscle strength in obese patients and comparing them with eutrophic individuals or comparing them with normal values showed no consistent results. (3, 5, 10) Kelly et al. (10) found no significant results in MIP values among obese individuals (with an average of 183% of the predicted weight) and individuals with an average of 99% of the weight. Sarikaya et al. (3) showed a significantly reduced MIP in obese individuals with no significant difference compared with eutrophic individuals. Magnani et al. (5) found that the MIP was within normal values for age and gender in 99 obese individuals (23 men and 76 women). There was no significant difference between different BMI groups (35-40, 40-45, 45-50 and ≥ 50 kg/m^2). (5)

In the literature investigating the effect of bariatric surgery on respiratory pressures, there are also conflicting results. Weiner et al. (4) showed that maximum respiratory pressures increased 6 months after bariatric surgery when compared with the preoperative values in 21 obese patients.

Parreira et al. (23) assessed the MIP of 30 morbidly obese patients (24 women and 6 men) preoperatively and 1 and 6 months after surgery. They found no significant difference in MIP 1 and 6 months after surgery compared to the preoperative values (preoperative MIP: 96 ± 35; after 1 month: 100 ± 38; after 6 months: 104 ± 33 cm H_2O). (23) When comparing the MIP values of 17 individuals 36 months after surgery, they found a significantly increased MIP (121 ± 35 cm H_2O) compared to the preoperative MIP (96 ± 35 cm H_2O). (23)

Cherniack and colleagues (29) found that obese individuals have inefficient respiratory muscles due to reduced chest wall compliance or lower lung volume. Also the MIP was lower than the predicted value. (29) Wadström and coworkers (30) found that, despite a weight loss of 18% and improvement of lung volumes, the included obese individuals showed no significant change in respiratory muscle strength.

Barbalho-Moulim et al. (15) randomised 32 obese women undergoing elective open bariatric surgery to either an inspiratory muscle-training group or usual care group. Compared to the preoperative values, the MIP decreased significantly in both groups. However the reduction in MIP was 28% in the inspiratory muscle training group en 47% in the usual care group. (15) In a different patient cohort (24 obese women scheduled for Roux en-Y gastric bypass), Barbalho-Moulim et al. (16) found that compared to preoperative MIP values, the MIP 1 year after bariatric surgery significantly decreased (preoperative: 78.75 ± 20.07 cm H_2O; 1 year after surgery: 69.17 ± 18.86 cm H_2O, p=0.0183). (16)

Various studies have examined the correlation between MIP and body composition but found different results. Vincken and colleagues (31) found that body composition did not contribute in explaining MIP variability. Enright et al. (32) reported that weight and waist circumference was negatively related to the MIP. Carpenter et al. (33) showed that individuals with a higher BMI had a lower MIP. We have not found a significant correlation between body composition and MIP. A possible explanation could be the difference in sample size, than the earlier mentioned studies. (31-33)

Different results were mentioned about the correlation between smoking status and MIP. Hautmann et al. (34) demonstrated that there was no significant relation between smoking status and MIP. Leech et al. (35) also did not found a significant relation between smoking status and MIP. Therefore Enright et al. (36) found that smokers had a 15% lower MIP than non-/former smokers. In our study we could not find a relationship between smoking and the MIP values. A possible explanation for this matter is the small number of smokers in our study population (17 (13.7%)).

Our study has several limitations. First, our male/female equilibrium was not equal. The majority of our patients were female. Second, there is a known difference between the MIP values between males and females (33, 34), which could be a confounding factor in the interpretation of the results.

The significant difference between the predictive MIP and the preoperative measured MIP was found using the equation by Wilson et al. (19) This could imply two remarks. First, is unknown whether or not the used predictive equation is suitable for the obese population and secondly other commonly used predictive equations could influence the results. (12, 14, 37, 38)

The clinical relevancy of measuring the MIP prior to and after bariatric surgery is questionable. Two questions need to be answered to determine the clinical relevancy 1) How many bariatric surgical teams measure MIP routinely and 2) if the MIP is measured, what is its influence on the decision-making progress in qualification and preparation of patients for bariatric surgery?

The earlier mentioned study of Barbalho-Moulim et al. (15) found that inspiratory muscle training prevented a reduction in MIP postoperatively. Another study by Barbalho-Moulim (39) compared the effect of laparoscopic bariatric surgery with open bariatric surgery on the lung function, without preoperative training of the patients. In both groups, there was a decrease in MIP postoperatively, 23% in the laparoscopic group compared to 37% in the open group. (39) Both studies did not investigate the effect on postoperative (pulmonary) complications.

In the current Dutch bariatric practice, almost all bariatric interventions are performed via laparoscopic procedures and pulmonary complications are rarely seen. Also in this study no pulmonary complications were seen. Therefore in other types of surgery, per example cardio-thoracic surgery, determining the MIP is useful for clinical purposes. This because after coronary artery bypass grafting surgery, pulmonary complications are more frequently seen and therefore inspiratory muscle training. (20) In our opinion, based on the current body of literature, the clinical relevance of measuring MIP prior to bariatric surgery remains questionable. Therefore further research is needed to investigate the clinical usefulness of this MIP measurement, especially in patients with obesity-induced respiratory dysfunction.

6.5 CONCLUSION

The preoperative Maximum Inspiratory Pressure values were significantly lower than the predicted MIP values. Only three patients were indicated to train their respiratory function preoperatively. Also a significant decrease in maximum pressures was found 3, 6 and 9 months after bariatric surgery each compared to the preoperative measurements. A negative significant correlation was observed between age and preoperative MIP. Due to conflicting results in the current literature, the low number of pulmonary complications seen after bariatric surgery the clinical relevancy of measuring the MIP prior to and after bariatric surgery remains questionable.

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7. COMPARATIVE ANALYSIS OF RESPIRATORY MUSCLE STRENGTH BEFORE AND AFTER BARIATRIC SURGERY USING FIVE DIFFERENT PREDICTIVE EQUATIONS

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ABSTRACT

Background

Obesity has detrimental effects on general health and respiratory function. This study aimed to evaluate respiratory muscle strength in the morbidly obese population, before and after bariatric surgery, and to compare these estimates with the predictive values using different mathematical equations available.

Methods

The Maximum Inspiratory Pressure (MIP) was measured at screening and 3, 6 and 9 months postoperative. Predictive values were calculated using five different mathematical equations. Visual inspection of Bland-Altman plots was performed to determine the agreement between the equations studied.

Results

In total 125 patients were found eligible and 122 patients were available for the final analysis, among them were 104 females and 18 men, with a mean age was 43.02 ± 11.11 years and mean BMI was 43.10 ± 5.25 kg/m^2. In the preoperative period, the predicted MIP according to the Harik-Khan, Neder, Costa and Wilson equation were significantly different compared to the Actual MIP ($p<0.05$). The predicted MIP according to the Enright equation was not significantly different ($p>0.05$). Postoperatively, there was a significant difference between the MIP values after 3 and 6 months and the predicted MIP values according to Harik Khan, Neder and Enright equation. After 9 months all predicted MIP values were significantly different from the predicted values. Bland Altman analysis showed that the Enright equation was best suitable for predicting the MIP.

Conclusion

Of the five mathematical equations studied that of Enright and collegues was found best suitable for predicting the MIP in the obese population studied.

7.1 INTRODUCTION

Obesity is the most common chronic metabolic disease worldwide and its prevalence has been strongly increasing. (1) Obesity is a risk factor for various conditions like, cardiovascular disease, type 2 diabetes, rheumatoid arthritis and neoplasms. It is also associated with respiratory dysfunction often leading to obstructive sleep apnoea and obesity hypoventilation syndrome. (1)

OBESITY AND RESPIRATORY FUNCTION

Over the last years, the effect of obesity on respiratory function has been studied; however there is no consensus as to the physiological mechanisms that lead to respiratory dysfunction and/or complications. Respiratory dysfunction is associated with restrictive lung function disorder. Restrictive pulmonary dysfunction could be explained by the alterations in ventilatory mechanics experienced in the obese. (2)

An increased deposition of fat on the chest wall causes a reduction in thoracic compliance and lung volumes. (3-5) The distorted balance in the interaction between lung, chest wall and diaphragm in this patient population causes impairment in respiratory mechanics and gas exchange. (6)

To evaluate pulmonary function, spirometry is the first step. A pattern of restriction includes: 1. Reduced forced vital capacity (FVC), 2. Reduced forced expiratory volume in one second (FEV_1), 3. A normal ratio between these two (Tiffeneau Index, which is FEV_1/FVC) and 4. Reduced total lung capacity. In case of unexplained respiratory dysfunction, the measurement of maximal inspiratory pressure (MIP) can be of value in the evaluation of the differential diagnosis.

Studies on the behaviour of respiratory muscle strength in morbidly obese patients have showed conflicting results. (4-12) Magnani et al. concluded that neither excess of body mass nor fat distribution on the thorax cage promote respiratory muscle dysfunction. (6) On the other hand respiratory dysfunction is reported in this patient population, which might be due to an increased tensile strength caused by excessive adipose tissue in the thorax region and the abdomen. This can lead to a potential disadvantage in respiratory muscle mechanics. (4, 13)

ASSESSMENT OF RESPIRATORY PRESSURES

Assessing the maximal static respiratory pressure generated in the mouth, after complete inhalation and exhalation, carries out the measurement of respiratory muscle strength, divided in the Maximal Inspiratory Pressure (MIP) and Maximal Expiratory Pressure (MEP), which are indicative of the strength of the inspiratory and expiratory muscle groups. (14) MIP is a measure of inspiratory muscle strength, whereas MEP measures the strength of the abdominal and intercostal muscles. (15-17) In cardiothoracic surgery, decreased respiratory muscle strength is associated with higher incidence of postoperative pulmonary complications. (18, 19) Preoperative inspiratory muscle training can significantly reduce these postoperative pulmonary complications. (18, 19) Obese patients have an altered pulmonary function and gas exchange and are therefore prone to postoperative pulmonary complications. (3, 20)

PREDICTIVE EQUATIONS

Measuring MIP values can give valuable information about the respiratory muscle strength in the obese and can be used as a reference value for training of respiratory muscle strength. To set adequate training goals, the use of predictive equations is mandatory to set training goals. (14, 16, 21-23) However, the current predictive equations and reference values (of MIP and MEP) are based on the normal populations and less is known about the recommended reference values for respiratory muscle strength in the morbidly obese population. Also there is no consensus on the best suitable mathematical equation for predicting respiratory muscle strength in this population.

Objectives

- Primary objective of this study is to identify which of the existing predictive equations is the most suitable for the morbidly obese patient.
- Secondary objective is to evaluate respiratory muscle strength in the morbidly obese population, before and after bariatric surgery, and to compare these estimates with the predictive values using different mathematical equations available.

Hypotheses

- Predictive equations that include anthropometric variables will either predict correctly or will overestimate the MIP.
- Predictive equations that without anthropometric variables will underestimate the MIP.

7.2 METHODS

This study was approved by the Medical Ethics Committee of the Catharina Hospital Eindhoven and adheres the principles of the declaration of Helsinki. Informed consent was obtained of all patients included prior to the study.

PATIENT POPULATION

A multidisciplinary team screened all patients preoperatively, consisting of a physician assistant, a psychologist, a nutritionist and a surgeon. Eligibility criteria for surgery were if patients had a BMI of 40 kg/m^2 or higher, or a BMI between 35 and 40 kg/m^2 with significant co-morbidities, with serious attempts to lose weight in the past. Co-morbidities were considered significant when medication had to be used, or if continuous positive airway pressure (CPAP) had to be used in case of OSAS. The indication for a bariatric procedure was made in a multidisciplinary consultation, taking into account the patients' preference, age, poly-pharmacy, reflux complaints, body composition in relation to BMI and bowel diseases. Patients with pre-existing pulmonary and/or neuromuscular diseases were excluded from this study.

ANAESTHESIA AND PERIOPERATIVE CARE

All anaesthesia given and perioperative care was according to fast track (FT) protocol, previously described. (24, 25) Patients received 5000 units of low-molecular weight heparin as thrombosis prophylaxis. Premedication consisted of only acetaminophen 1000mg. Anaesthesia was induced using a combination of piritramide (0.2-0.3 mg/kg), propofol (2mg/kg) and suxamethoniumchloride (1-1.5mg/kg). Anaesthesia maintainance was conducted with desflurane (6.0 vol%) in combination with remifentanil (5-15µg/kg/hr) (26). By standardizing discontinuation of desflurane and remifentanil upon notification of the surgeon during application of the last sutures, patients were directly extubated after the procedure and able to replace themselves to their bed. Fluid administration was restricted to 1 litre of lactated Ringers intraoperative and to a maximum of 1 litre of lactated Ringers postoperatively (27). Postoperatively analgesia consisted of parecoxib (40mg) once followed by acetaminophen (1000mg four times daily) and tramadol (100mg). In case of inadequate analgesia (NRS score >4) piritramide (0.2-0.3 mg/kg, on average about 20mg i.m.) was administered for pain relieve. After approximately one hour in the postanaesthesia care unit, all patients (including the extremely obese) were transferred to the surgical ward. On the ward, patients are directly mobilized as part of thrombosis prophylaxis. (24, 25)

PREDICTIVE EQUATIONS

Harik-Khan Equation (16):
Women: MIP = 171 - (0.694 x age) + (0.861 x body mass (kg)) – (0.743 x height (cm))
Men: MIP = 126 – (1.028 x age) + (0.343 x weight (kg))

Neder Equation (22):
Women: MIP = (-0.49 x age) + 110.4
Men: MIP = (-0.80 x age) + 155.3

Costa Equation (14):
Women: MIP = (-0.46 x age) + 74.25
Men: MIP = (-1.24 x age) + 232.37

Enright Equation (21):
Women: MIP = (0.133 x weight (kg)) - (0.805 x age) + 96
Men: MIP = (0.131 x weight (kg)) - (1.27 x age) + 153

Wilson Equation (23):
Women: MIP = -43 + (0.71 x height (cm))
Men: MIP = 142 – (1.03 x age)

DATA COLLECTION

Data were collected prospectively using an online registry (Patients Outcome Measurement Tool). The patients who got approval between the 3rd of October 2011 and the 3rd of May 2012 were included in this study as during this period the inspiratory muscle function was measured.

OUTCOME MEASURES

Respiratory muscle strength was assessed by measuring the maximal inspiratory pressure (MIP) with a digital mouth pressure meter (± 300 cm H_2O). This procedure was performed by a trained independent physiotherapist according to the ATS/ERS protocol (28, 29) and took place took place before bariatric surgery and 3, 6 and 9 months postoperatively. The manometer (Micro RPM®, Carefusion, USA) was calibrated in accordance with the manufacturer's recommendations. Predictive MIP values were calculated using the earlier mentioned five different predictive equations. The predicted MIP values were compared with each other, with the actual MIP and the postoperative MIP values. Patient characteristics and weight loss profiles were obtained from medical charts of each patient.

STATISTICAL ANALYSIS

Continuous variables were presented as mean ± standard deviation (SD). Categorical variables were presented as frequency with percentages. Data distribution was verified using the Shapiro-Wilk test. To compare the MIP values the paired t-test was used for parametric data or the Mann-Whitney U test was used, for non-parametric data. To compare the MIP values at different times (predicted, preoperatively, and after 3, 6 and 9 months after surgery), repeated measures ANOVA (parametric data) was used or the Kruskall Wallis test (non-parametric data).

Visual inspection of Bland-Altman plots was performed to determine the agreement between the equations studied. Values of $p<0.05$ were considered statistically significant. Statistical Package for Social Sciences (SPSS, Chicago, IL, USA Version 20.0) was used to prepare the database and for statistical analysis.

7.3 RESULTS

PATIENTS AND PROCEDURES

In total 125 were found eligible for this study and 122 patients were included in this study, among them were 104 females and 18 men. Three patients did not meet the inclusion criteria because of pre-existing neuromuscular and/or pulmonary diseases (see Figure 7.1 for the CONSORT diagram).

The mean age was 43.02 ± 11.11 years, mean height was 169.03 ± 8.42 cm, mean weight was 123.46 ± 19.45 kg and mean BMI was 43.10 ± 5.25 kg/m^2. Half the patients underwent a sleeve gastrectomy (n=60; 49.0%) and the other half received a gastric bypass (n=62; 51.0%). Postoperatively, the mean weight and BMI 3, 6 and 9 months after surgery were respectively 105.1 ± 18.1 kg (BMI: 37.0 ± 5.3 kg/m^2), 91.7 ± 15.2 kg (BMI: 32.0 ± 6.7 kg/m^2) and 82.8 ± 16.8 kg (BMI: 29.0 ± 7.2 kg/m^2). Table 7.1 gives an overview of the preoperative and postoperative characteristics.

PREDICTED MIP AND THE PREOPERATIVE MEASURED MIP

In the preoperative period, the predicted MIP according to the Harik-Khan (16), Neder (22), Costa (14) and Wilson (23) equation were significantly different compared to the Actual MIP ($p<0.05$) (Table 7.2). Only the predicted MIP according to the Enright (21) equation was not significantly different compared to the Actual MIP ($p>0.05$).

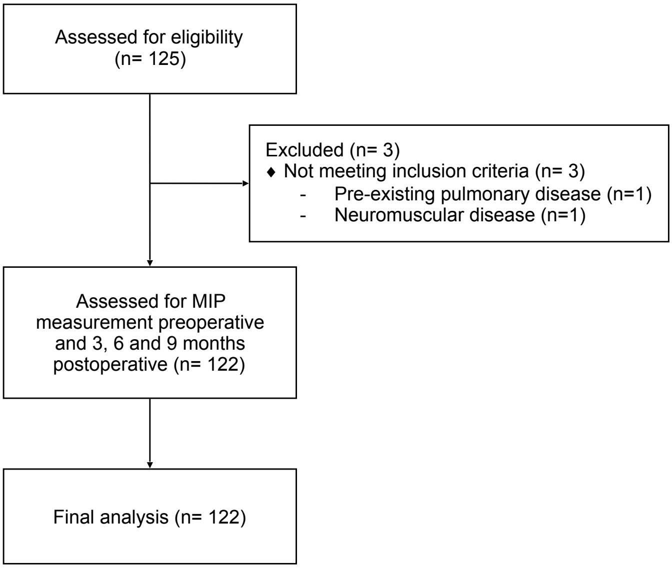

FIGURE 7.1: CONSORT diagram for the study

PREDICTED MIP AND MIP 3, 6, 9 MONTHS AFTER SURGERY

In the postoperative period, the MIP was 75.58 ± 26.10, 81.61 ± 28.12 and 85.69 ± 27.97 cm H_2O respectively 3, 6 and 9 months after surgery (Table 7.3). The was a significant difference between the MIP values after 3 and 6 months and the predicted MIP values according to Harik Khan (16), Neder (22) and Enright (21) equation. After 9 months all predicted MIP values were significantly different from the predicted values.

BLAND-ALTMAN ANALYSIS

For the actual MIP preoperative, the statistical graph analysis was performed between the preoperative measured values and those predicted by the used equations. (Figure 7.2 and 7.3) The Harik-Khan equation showed a mean difference of -19.72 cm H_2O and an agreement interval of -125.80 to 52.11 cm H_2O. The obtained preoperative values from the Wilson equation showed a mean difference of 23.18 cm H_2O and an agreement interval of -37.80 to 87.99 cm H_2O. The mean difference of the Enright equation was -0.69 cm H_2O with an agreement interval from -90.41 to 68.71 cm H_2O. The mean differences and agreement intervals of the Neder and Costa equation were 8.21 cm H_2O (agreement interval -60.30 to 73.12 cm H_2O) and 29.30 cm H_2O (agreement interval -119.77 to 107.83 cm H_2O).

TABLE 7.1. Overview of anthropometric variables and maximal inspiratory pressures of obese patients

Preoperative BMI	Preoperative Weight	Predicted MIP	Actual MIP preoperative	MIP 3 months	MIP 6 months	MIP 9 months	*Weight/BMI 3 months*	*Weight/BMI 6 months*	*Weight/BMI 9 months*
43.10 ± 5.25	123.46 ± 19.45	*Harik-Khan (16)* 121.95 ± 15.59	102.23 ± 23.99	75.58 ± 26.10	81.61 ± 28.12	85.69 ± 27.97	105.1 ± 18.1/ 37.0 ± 5.3	91.7 ± 15.2/ 32.0 ± 6.7	82.8 ± 16.8/ 29.0 ± 7.2
		Neder (18) 94.01 ± 12.96							
		Costa (14) 72.93 ± 45.25							
		Enright (19) 102.91 ± 19.84							
		Wilson (20) 79.05 ± 10.22							

MIP = Maximal Inspiratory Pressure (in cm H_2O); BMI = Body Mass Index (in kg/m^2); Weight in kilograms (kg)

TABLE 7.2. Maximal inspiratory pressures of obese patients 3, 6 and 9 months postoperatively and the preoperative predicted values using five different predictive equations

MIP 3 months*	MIP 6 months*	MIP 9 months*	Predicted MIP	P-value		
75.58 ± 26.10	81.61 ± 28.12	85.69 ± 27.97	*Harik-Khan (16)** 121.95 ± 15.59	0.001[A]	0.001[B]	0.001[C]
			*Neder (18)** 94.01 ± 12.96	0.001[A]	0.001[B]	0.001[C]
			*Costa (14)** 72.93 ± 45.25	0.529[A]	0.044[B]	0.004[C]
			*Enright (19)** 102.91 ± 19.84	0.001[A]	0.001[B]	0.001[C]
			*Wilson (20)** 79.05 ± 10.22	0.143[A]	0.311[B]	0.009[C]

* in cm H_2O
[A] compared with MIP 3 months
[B] compared with MIP 6 months
[C] compared with MIP 9 months

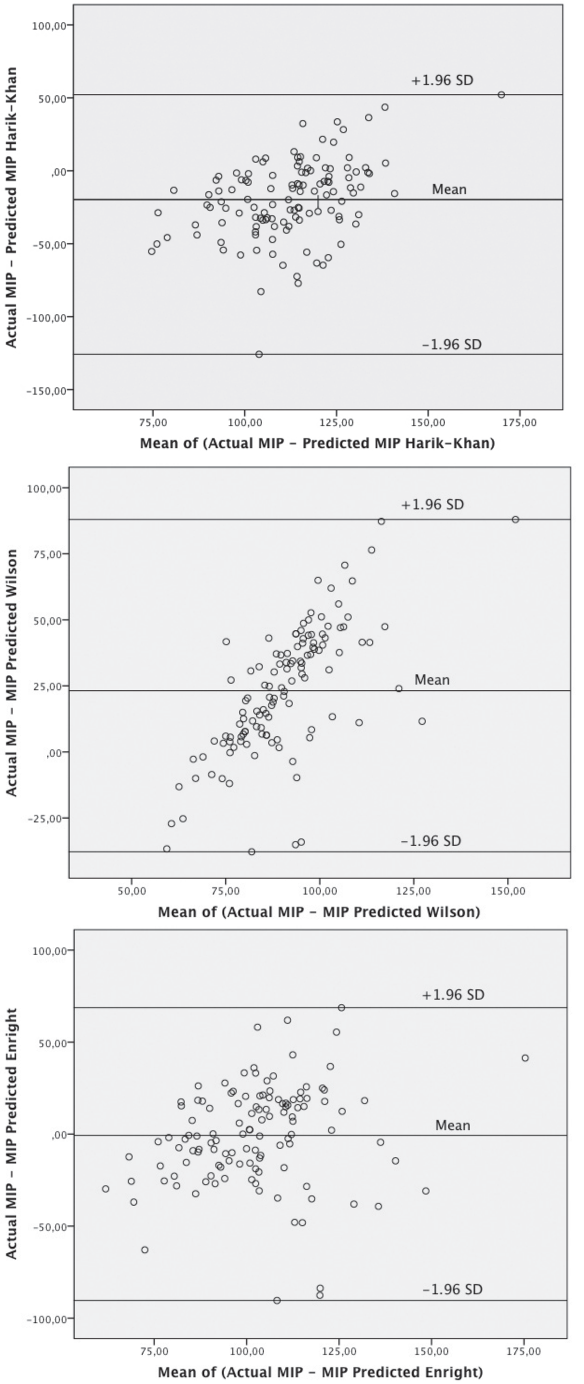

FIGURE 7.2: Concordance between mean values of MIP (actual preoperative and predicted) for Harik-Khan, Wilson and Enright.

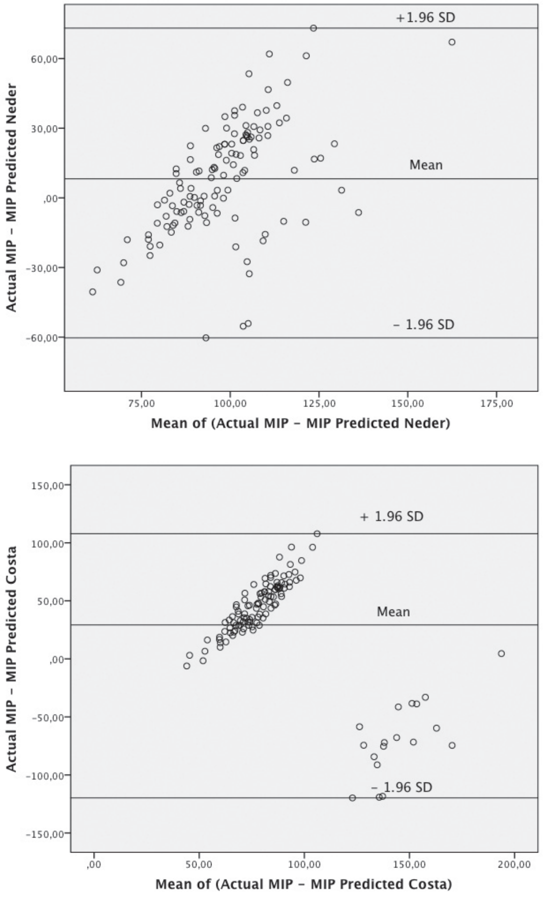

FIGURE 7.3. Concordance between mean values of MIP (actual preoperative and predicted) for Neder and Costa.

7.4 DISCUSSION

The measurement of the MIP is a simple and non-invasive clinical procedure for the determining the inspiratory muscle strength in healthy people and in patients with pulmonary, neuromuscular or cardiovascular disease. (30-33) In the latter group, MIP is indicative of ventilatory capacity and the development of respiratory insufficiency (31), and can be useful in assessing the degree of abnormality and in monitoring inspiratory muscle weakness in individual patients over time (30, 32) MIP can also be helpful in evaluating the success of weaning patients from mechanical ventilators (16, 31) and in predicting the outcome of cardiac transplantation surgery in patients with chronic heart failure. (33)

A recent study by Pazzianotto-Forti and colleagues compared three predictive equations (Harik-Khan (16), Neder (22) and Costa (14)) to investigate the behaviour of respiratory muscle strength in morbidly obese women. (17) They compared a cohort of 30 morbidly obese women with 30 normal weight subjects. They measured a mean MIP of 87.83 ± 21.40 cm H_2O in the obese group and 72 ± 15.23 cm H_2O in the normal weight group. In the obese group, the predicted MIPs (using the Harik-Khan, Neder and Costa equation) were respectively 130.71 ± 11.98, 94.55 ± 3.05 and 50.37 ± 2.86 cm H_2O. The Harik-Khan equation significantly overestimated the MIP, the Costa equation significantly underestimated the MIP and there was no difference in the MIP measured and predicted by the Neder equation. (17) Regarding the normal weight group, there was no difference in the measured MIP and and predicted by the Harik-Khan equation (respectively 72 ± 15.23 and 79.76 ± 5.31 cm H_2O). The MIP predicted by the Neder equation was significantly higher and the MIP predicted by the Costa equation was significantly lower (respectively 95.47 ± 2.57 and 60.23 ± 2.41 cm H_2O). Pazzianotto-Forti and colleagues concluded the Harik-Khan equation was the most suitable for predicting the MIP in the morbidly obese, because it's the only formula that inclus the body mass and height. (17)

In our cohort of 122 morbidly obese patients, the preoperative measured MIP was significantly different with the MIP values predicted by the Harik-Khan (16), Neder (22), Costa (14) and Wilson equation (23). The Wilson (23), Costa (14) and Neder (22) equation significantly underestimated the MIP and the Harik-Khan (16) overestimated the MIP. The MIP value predicted by the equation of Enright and colleagues was not significantly different from the preoperative measured MIP. These findings support our hypotheses. Our results regarding the Harik-Khan and Costa equation are supported by the study by Pazzianotto-Forti (17) Regarding the Neder equation Pazzianotto-Forti et al. (17) found no significant difference between the measured and predicted MIP, where we found a significant underestimation.

When we compared the postoperative measured MIP values (after 3, 6, 9 months) with the predicted values, several important facts become visible. When comparing the MIP values 3 months and 6 months after surgery, the following is seen: the Harik-Khan (16), Neder (22) and Enright (21) equation significantly overestimate the MIP; the predicted value of the Costa (14) equation was not significantly different (after 3 months), but after 6 months there was a significant underestimation; the predicted MIP by Wilson (23) equation did not significantly differ (after 3 and 6 months). After 9 months, the Harik-Khan (16), Neder (22) and Enright (21) equation showed a significant overestimation of the MIP and the Costa (14) and Wilson (23) equation showed a significant underestimation.

Explanations for the differences in results between our study and the study by Pazzianotto-Forti are the following: Pazzianotto-Forti investigated Brazilian patients and we focussed on

Caucasian patients, secondly the sample size of both studies differed (60 patients versus 122 patients) and thirdly we focussed on the postoperative measures and Pazzianotto-Forti did not. (17)

Four conclusions can be drawn for the clinical use of the predictive equations from our study. First of all, there were significant differences between the measured MIP values and the values predicted. Only there was no significant difference between the measured MIP values and the values predicted by the equation of Enright and colleagues. (21) Secondly, none of the mathematical equations used were able to precisely predict the MIP, which confirms the study's hypothesis that in the morbidly obese population it is difficult to predict respiratory muscle strength. Thirdly, the greatest agreement was found between de measured preoperative MIP and the predicted values using the Enright (21) equation (mean difference -0.69; agreement interval -90.41 to 68.71). Therefore, this equation was selected in this study as the most reliable for predicting the MIP in the morbidly obese. However when looking more closely to the distribution patterns on the Bland-Altman plots, two important aspects need attention. Bland-Altman plots are a comparison method which pairs the differences between measures taken using two devices to the mean of the two values, and therefore avoiding mathematical traps and statistical misconceptions. (34) But they need to be analysed with caution and precision. (34) First there are no values above and below the 95% confidence intervals. This can be a result of our misbalance of included males and females included study (there are more females than males included in this study, and there are known differences between the MIP values between males and females (6, 16, 17, 21)), however this does not clarify this phenomenon totally. Also race can be an important factor to clarify the differences in MIP values and also can clarify the distribution in the Bland-Altman plots. Secondly, an interesting fact is that there is no equal spreading of values around the mean difference, which is uncommon. In most cases, there is an equal spreading around the mean difference line in Bland-Altman. (34)

In studies investigating the respiratory muscle strength in the morbidly obese, several difficulties arise, as mentioned by Bruschi and colleagues. (32) Great variety in results were mentioned, due to variability to different methodology; such as the type of mouthpiece, the number of manoeuvres performed, body position and the differences in the populations studied. (17, 32, 35)

Interesting finding in our current study is that the MIP after 3 months decreased and after 6 and 9 months gradually increases. Three main factors have to be taken into account, muscle function of the respiratory muscles, abdominal muscles and the lung compliance. (36) The main reason is probably the decrease of fat mass (3 months after surgery) and adaptation of the respiratory muscle function (6 and 9 months after surgery)· (36)

In current Dutch bariatric practice, the clinical relevancy of the MIP measurement is questionable. This is because all bariatric surgical procedures are performed laparoscopically and therefore pulmonary complications are rarely seen. (1) But in other diseases (especially neuromuscular diseases, cardiac surgery or severe COPD) the MIP measurement might helpful for determining the clinical stadium of disease or to determine whether a patient is prone to postoperative pulmonary complications. A randomised clinical trial by Hulzebos et al. (18) investigated whether inspiratory muscle training is effective in reducing postoperative complications in patients scheduled for elective coronary artery bypass grafting (CABG) surgery. Inspiratory muscle training is effective in reducing postoperative pulmonary complications according to this trial. (18) In general, obesity is an increasing problem. (37) To determine the adequate training goal, there is increasing need for a mathematical equation which can adequately predict the respiratory muscle strength and therefore to set achievable training goals.

STUDY LIMITATIONS AND FUTURE RESEARCH

Our study has several limitations that have to be taken into account. First, our male/female equilibrium was not equal. Secondly, our study lacks of body composition analysis, which can give a clearer view of the influence of fat depositions on the measured MIP values. Also ethnic differences in MIP have to be studied, but our sample was too small to perform such an analysis.

To get more insight in the respiratory function of the morbidly obese and the influence of bariatric surgery on respiratory muscle function several function parameters have to be studied. As mentioned earlier, spirometry is the first step for testing pulmonary function. A comparative analysis between spirometric variables and maximal inspiratory/expiratory pressures can give more insight in the pulmonary physiology of the morbidly obese.

7.5 CONCLUSION

Of the five mathematical equations studied, that of Enright et al. (21) seems to be the most suitable for calculating the MIP reference values of the morbidly obese. Further research is necessary to gain more insight in the pulmonary function of the morbidly obese, the influence of bariatric surgery on the pulmonary function and to assess the MIP values in larger samples to develop a predictive equation for the obese.

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8. ASPECTS OF EXERCISE BEFORE AND AFTER BARIATRIC SURGERY: A SYSTEMATIC REVIEW

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ABSTRACT

Background

Bariatric surgery has a considerable effect on weight loss. A positive relation of exercise and weight loss has been described before. However, the mode of exercise and its timing pre- or postoperative or a combination remains unclear.

Methods

A multi database search was conducted. Identified articles were reviewed on description of exercise, timing around a bariatric intervention and outcome. Methodological quality of the included studies was rated using the Physiotherapy Evidence Database scale. A Cohen's kappa score assessed the level of agreement. Outcome measurements were improvement of anthropometric and physical fitness variables, operation related complications, weight regain and quality of life.

Results

A total of eight prospective studies were included. Four focussed on training before and four on training after a bariatric procedure. Details of exercises varied from 45 minutes treadmill up to full descriptive programs. Supervision was frequently included. Significant improvement was encountered for biometric results physical fitness variables.

Conclusion

In the majority of reports on exercising in a (future) bariatric population, a positive effect on anthropometrics, cardiovascular risk factors and physical fitness was described. However, the results were not unanimous, with a wide range of exercise programs and peri-operative timing and therefore hampering adequate practical guidance.

8.1 INTRODUCTION

Obesity is a major contributor to a wide variety of diseases, including diabetes, hypertension, dyslipidaemia and obstructive sleep apnoea syndrome. (1, 2) Over the last decade's dietary and exercise interventions had increasing public health and governmental attention. Nevertheless, the proportion of the population with morbid obesity gained every year. (3) The only treatment with a longstanding effect is bariatric surgery. (4, 5) However, these interventions are no universal remedy and a considerable proportion of patients has insufficient weight loss or regain in weight over time after the operation. (6)

The key elements for durable weight-loss are pre-operative screening, an appropriate algorithm of bariatric techniques and most important, a strict regime of follow-up. Follow-up should include medical and psychological guidance, including continuing dietary advice and maintenance of a physical exercise regimen.

There is extensive knowledge to substantiate that exercise helps to gain a better physical fitness and Quality of Life (QoL). A Cochrane review showed a reduction of 1.5 kg that was contributed to exercise (7). Another systematic review, focussing on physical training and obesity, found a 4% Excess Weight Loss (%EWL) (8). In their review, Egberts et al. found a reduction of 3.6 kg, related to physical exercise (9). In all three reviews, only prospective cohort studies were included as no randomized controlled could be identified. Weight measurement was merely self-reported and in the majority of studies the mode of physical activity was not defined. However, the positive relationship between exercise and weight loss seems evident. The problem is; what kind/type/mode of exercise should an obese patient be advised and what about it's timing, pre- or postoperative or a combination? These questions were the objective of the present review.

8.2 METHODS

A systematic search on the qualitative aspects and timing of physical exercise in bariatrics was conducted. The population of interest were all obese patients with a body mass index (BMI) ≥ 30 kg/m^2. The intervention of interest was exercise training compared to regular care (no specific physical exercise training program). Also included were the different modes of exercise training, those were compared to each other. Outcome measurements were; improvement of anthropometric and physical fitness variables; effect on weight and quality of life.

Pubmed, Embase and CINAHL were searched from the earliest date of each database up to July 2014. The search for publications was performed using the following search string: ((“Bariatrics”[Mesh] OR bariatrics OR bariatric surgery OR “Obesity, Morbid”[Mesh] OR morbid obesity)) AND (“Physical Therapy Modalities”[Mesh] OR physical therapy OR physiotherapy OR “Exercise”[Mesh] OR exercise)

Authors MW and SP, blinded for authors and journals, separately screened and selected the studies on the basis of title and abstract. After primary selection, both authors reviewed the full text of the selected studies to determine suitability for inclusion, based on the established selection criteria.

- Randomised controlled trial or prospective trial.
- Patients awaiting bariatric surgical intervention or with bariatric surgery in the past.
- A description of an exercise program, defined as a regimen of physical activities included.
- Modes of exercise training were defined as follows: strength training and/or endurance training or a combination of both. Also multimodal programs with exercise components were included.
- Registration of anthropometric and physical fitness variables, complications, effects on weight and quality of life.
- Physical fitness variables are defined as a percentage of VO_2 max and/or Heart rate reserve (HRR)/ Heart rate kinetics;

In addition cross-references were screened for further eligible studies. Disagreements between the two authors were resolved by discussion with each other and the senior authors (JT, SN) until consensus was reached. It was conceived in advance as having significant clinical heterogeneity for which a systematic review could be performed, not a meta-analysis

The methodological quality of the included studies was rated using the Physiotherapy Evidence Database (PEDro) scale (10), which has acceptable reliability (11). The PEDro scale consists of 11 criteria, with a maximum score of 10 (range 0-10) since the first item (the specification of the eligibility criteria) is not included in the total score. Two authors (MW and SP) separately assigned Pedro scores to each included study. For rating the methodological quality the following classification was used: a PEDro score of 4 indicated a poor methodological quality, a score between 4-5 fair quality, score 6-8 good quality and 9-10 excellent quality (12). A Cohen’s kappa score assessed the level of agreement between the authors. The score was determined as follows: <0.20 poor agreement; 0.21-0.40 fair agreement; 0.41-0.60 moderate agreement; 0.61-0.80 good agreement; 0.81-1.00 very good agreement (13).

8.3 RESULTS

The primary search produced 1023 results, including 81 duplicates. Sixteen studies were identified as possibly relevant and underwent a full text critical appraisal, resulting in eight exclusions. One study investigated exercise programs for Prader-Willi patients (14), three studies investigated pulmonary physiotherapy in the bariatric population (15-17), one publication appeared to be a case-report (18), one a research protocol (19), one article was only available in Swedish (20) and one article was only available in Spanish (21).

Figure 8.1 summarises the search results. The methodological quality of the included studies ranged from moderate to good quality, as indicated by The PEDro scale (table 8.1). The level of agreement between reviewers (MW and SP) was reflected by a Cohen's kappa 0.78, which represents a good agreement. The key findings of the included studies are shown in tables 8.2 and 8.3 divided in pre-bariatric surgery exercise and post-bariatric surgery exercise.

STUDY DESIGNS AND PATIENT POPULATION

In total four pre-bariatric studies (22-25) and four post-bariatric studies (26-29) were included. Of the four pre-bariatric studies, the follow-up was only preoperatively, respectively 7 days (24), 12 weeks (22, 23), 24 weeks (25). Of the four post-bariatric studies, one of them had a postoperative follow-up of 12 weeks (26), three of them had a preoperative and postoperative follow-up (respectively 1 week preoperative and 4 weeks postoperative (27), preoperative (unknown how long) and 4 months postoperative (28) and 1 week preoperative and 10 days postoperative (29)). A total of three randomised controlled trials (23, 26, 27) and five prospective trials (22, 24, 25, 28, 29) studying a patient population with age ranging from 28 to 54 years old and a mean body mass index ranging from 40.4 to 48.7 kg/m^2.

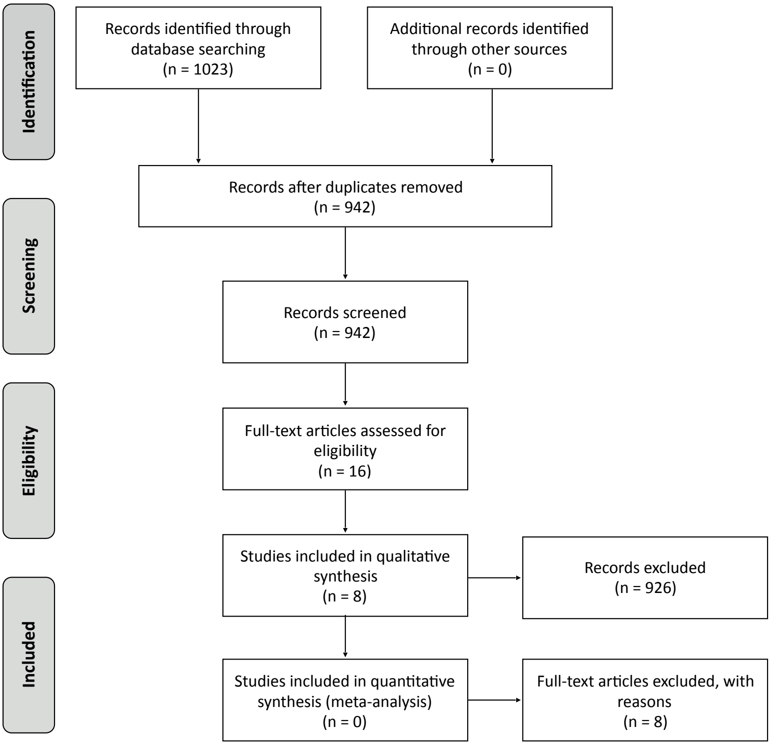

FIGURE 8.1. PRISMA Flowchart

TABLE 8.1. Methodological quality of included studies using the 'Physiotherapy Evidence Database (PEDro)' score (10)

	Criteria[a]											
	1	2	3	4	5	6	7	8	9	10	11	*Total*
Castello-Simoes *et al.* 2013 (27)	x	x	x	x	-	-	-	x	x	x	x	7
Funderburk *et al.* 2010 (23)	x	x	x	-	-	-	-	x	x	x	x	6
Hickey *et al.* 1999 (24)	x	-	-	x	-	-	-	x	x	x	x	5
Stegen *et al.* 2011 (28)	x	-	-	x	-	-	-	x	x	x	x	5
Baillot *et al.* 2013 (22)	x	-	-	x	-	-	-	x	x	x	x	5
Shah *et al.* 2011 (26)	x	x	x	x	-	-	-	x	x	x	x	7
Marcon *et al.* 2011 (25)	x	-	-	x	-	-	-	-	x	x	x	4
Berggren *et al.* 2008 (29)	x	-	-	x	-	-	-	-	x	x	x	4

[a]PEDro criteria: (1) Specification of eligibility criteria (this criterion was not counted for the final score), (2) Random allocation, (3) Concealed allocation, (4) Prognostic similarity at baseline, (5) Participant blinding, (6) Therapist blinding, (7) Outcome assessor blinding, (8) More than 85% follow-up of at least one key outcome, (9) Intention to treat analysis, (10) Between or within-group statistical comparison, (11) Point estimates of variability provided (10).

8.3.1 PRE-BARIATRIC SURGERY EXERCISE

Anthropometric variables

Four studies reported on the effects of exercise training on the anthropometric variables. Baillot et al. (22) reported a significant reduction in weight (before; 144.3 kg, after; 140.2, p=0.07), BMI (before; 51.4 kg/m^2, after; 47.2 kg/m^2, p=0.004), neck circumference (before; 42.2 cm, after; 41.0 cm, p=0.016) and fat mass (before; 72.1 kg, after; 69.1 kg, p=0.026) after supervised exercise training in 12 patients awaiting bariatric surgery.

Funderburk et al. (23) showed a reduction in body weight after 12 weeks supervised aquatic exercises of 5.0 kg in the intervention group and 2.3 kg in the control group. It was not reported whether this is a significant decrease. There was no significant change in body weight and free fat mass after a seven day exercise regimen investigated by Hickey et al. (24) Marcon et al. (25) found a significant decrease in body weight (- 5.3kg (p<0.001)) and BMI (-1.9 kg/m2 (p<0.001)) after 24 weeks supervised low intensity endurance training.

Compliance

Baillot et al. (22) had a high compliance to the preoperative exercise training program. They proposed 35 supervised exercise sessions in 12 weeks. Seven patients completed the full program and five had their bariatric surgery before the end of the program. The attendance of the supervised exercise sessions had a median of 57.3% (32.5 – 77.6%) and the attendance of the total exercise sessions had a median of 64.5% (47.5% - 79.9%).

Blood pressure

After 12 weeks of aquatic exercises, Funderburk et al. (23) found an increase in systolic blood pressure and decrease in diastolic blood pressure in the intervention group (+34 mmHg and -4 mmHg respectively). In the control group, there was a decrease in systolic blood pressure and the diastolic blood pressure remained unchanged (-57 mmHg and 0 mmHg). (23) After 24 weeks of supervised endurance training Marcon et al (25) reported a significant decrease in systolic and diastolic blood pressure (-23.8 mmHg (p=0.007) and -14.4 mmHg (p=0.001) respectively).

Cardiovascular risk factors and inflammation

Hickey et al (24) reported a significant decrease of fasting plasma insulin (-41.7 pM) after seven days of supervised exercise training, 60 minutes per day. There were no significant changes in glucose and blood lipid concentration after the exercise intervention. (24)

After 24 weeks of supervised endurance training a significant improvement was seen in blood lipid and glucose concentration in the study by Marcon et al. (25) (Total cholesterol: - 23.0 mg/dL; HDL-C: +1.7 mg/dL, LDL-C: -2.3 mg/dL, Triglycerides: -26.7 mg/dL, Glucose: -17.2 mg/dL (for all $p<0.007$)).

Physical fitness and functional capacity

Baillot et al. (22) found that all twelve patients completed the baseline symptom limited treadmill test with a median duration of 11.5 minutes (11.1 – 12.4). No major cardiac complication was noted during or after the test. The six-minute walk test distance, the time of the half-squat test and the number of flexion during the arm curl test were all significantly ($p<0.05$) increased after the preoperative exercise program (22).

Funderburk et al. (23) showed an increase in the six-minute walking test distance of 10.4 m, after 12 weeks of aquatic exercises, but strangely the control group showed an increase of 40.2 m. After 24 weeks Marcon et al. (25) also saw an improvement of six minute walking test distance (+69.8m ($p<0.0001$)).

Aerobic capacity

Hickey and coworkers (24) reported that after seven days of supervised exercise there was no significant difference in maximal oxygen uptake (which was measured by VO_2 peak) and indicates that there is no increase in physical fitness.

Quality of Life and satisfaction

Baillot et al. (22) showed that each of twelve patients who were in the exercise program, improved at least one level for endurance training and two levels for strength training. This increase appeared to be greater in the patients who trained longer. All patients were satisfied by the coaching and the advices given by the exercise professionals (22).

Also the total Health Related Quality Of Life (HRQOL) significantly improved after the exercise intervention ($p=0.012$). On the domains of emotions, social interaction and sexual life was also a significant improvement noted ($p=0.002$, $p=0.025$ and $p=0.003$ respectively) (22). Unfortunately, no significant change was seen in symptoms ($p=0.25$) activity/mobility ($p=0.07$) and personal hygiene/clothing ($p=0.078$) scores. (22)

Measured by the Short Form 36 (SF-36) questionnaire and the Beck Depression inventory, Funderburk et al. (23) found no significant post intervention difference between groups. In the aquatic exercise group there was a significant decrease in bodily pain and a significant decrease of the depression score after 12 weeks ($p<0.05$). In the control group was a significant increase in mental health ($p<0.05$). (23)

TABLE 8.2. Pre-bariatric surgery exercise regimes

Study	Exercise regime	Outcome
Baillot et al. 2013 (22)	The physical exercise sessions consisted of: 10 min of warm up, 30 min of endurance activity (treadmill, walking circuit), 20 to 30 min of strength exercises, 10 min of cooling-down. Supervision by a physical activity specialist and/or completed independently at home. The intensity of the endurance training was determined using the HRR method and using data from the previously performed symptom limited cardiac treadmill test. The progression of endurance intensity and duration according to physical fitness and physical activity. Electronic pulse monitors (Polar F4®) were used to control endurance exercise intensity during supervised sessions and at home. *Strength exercises:* Performed with small equipment easily available at home: dumbbells, elastic bands, and sticks. Three mini-circuits (upper body, lower body, and trunk) repeated by subjects according to their prescription.	*6MWT distance (m):* Before: 464 (412-501) After: 492 (450-531) ($p=0.05$) *Arm Curl Test (n):* Before: 22 (16.7-26) After: 26 (21-31) ($p=0.01$)
Funderburk et al. 2010 (23)	The intervention group did two sessions of 60 minutes of aquatic exercises including endurance and strength exercises for 12 weeks	*Weight loss:* I: -5.0kg C: -2.3kg *SBP and DBP:* I: +34 mmHg and -4 mmHg C: -57 mmHg and 0 mmHg *6MWT:* I: +10.4 m C: +40.2 m *QoL and depression score:* No significant post intervention difference between groups I: decrease in bodily pain and depression score ($p<0.05$) C: Increase in mental health ($p<0.05$)
Hickey et al. 1999 (24)	Seven days of supervised endurance training at 60% of VO_2 peak. Each session was 60 minutes.	Decrease of fasting plasma insulin (-41.7 pM) ($p<0.05$) No significant change in body weight, % fat mass, glucose and blood lipid concentration after intervention No significant change in VO_2 peak after exercise intervention

Marcon et al. 2011 (25)	24 weeks of supervised low intensity endurance training. One session per week, consisting of 209 minutes of exercise and 10 minutes stretching.	*Body weight and BMI* Decreased body weight - 5.3kg ($p<0.001$) Decreased BMI - 1.9 kg/m^2 ($p<0.001$) *SBP and DBP:* Decrease in SBP and DBP (-23.8 mmHg ($p=0.007$); -14.4 mmHg ($p=0.001$) Lipids and glucose: Improvement of TC, HDL-C, LDL-C, TG and glucose TC: - 23.0 mg/dL HDL-C: +1.7 mg/dL LDL-C: -2.3 mg/dL TG: -26.7 mg/dL Glucose: -17.2 mg/dL For all $p<0.007$ *6MWT:* - Improved walking distance; +69.8m ($p<0.0001$)

Abbreviations: HRR = Heart rate reserve, I = Intervention group, C = Control group, 6MWT = 6 minute walking test, n = number, SBP = Systolic blood pressure, DBP = Diastolic blood pressure, VO_2 peak = maximum oxygen consumption, BMI = Body mass index, TC = Total cholesterol, TG = Triglycerides

8.3.2 POST-BARIATRIC SURGERY EXERCISE

Anthropometric variables

Four studies reported on the effects of exercise training on the anthropometric variables. Stegen et al. (28) investigated the effect of an exercise program after gastric bypass surgery and found that both groups (gastric bypass + exercise training (GB+E) compared with gastric bypass only (GB)) had the same decrease 4 months postoperative in weight (GB = -26.6 ± 14.6 kg; GB+E = -22.7 ± 5.7 kg), BMI (GB = -8.3 ± 4.1 kg/m^2; GB+E = -8.1 ± 2.5 kg/m^2) and waist circumference (GB = -20.3 ± 11.6 cm; GB+E = -17.2 ± 8.1 cm) (28).

Castello-Simoes (27) investigated a post-bariatric training program and used three groups: a trained group (TG), a eutrophic group (EG) and a control group (CG). They found that there was a significant reduction in weight (TG: before 115.0 ± 6.9 kg; after: 92.0 ± 5.1 kg, CG: before 113.0 ± 4.7 kg, after: 89.0 ± 3.4 kg) and BMI (TG: before 45.5 ± 1.7 kg/m^2; after: 36.5 ± 1.3 kg/m^2, CG: before 43.6 ± 1 kg/m^2, after: 34.2 ± 1.1 kg/m^2) in TG and CG four months after bariatric surgery compared to the preoperative values (27).

Berggren and colleagues (29) investigated the skeletal muscle lipid oxidation before and after 10 days of endurance orientated exercise training. They found a significant weight loss after 10 days of exercise ($p<0.05$) (29). Shah et al. (26) investigated a high volume exercise program in 20 patients and found that in both the exercise group and the control group there was a significant reduction in body weight and hip circumference after 12 weeks (compared to baseline values).

Cardiovascular risk factors and inflammation

In contrast to the above mentioned, Shah et al. (26) found no difference in cardiovascular risk factors after a high volume exercise training program compared to the control group.

Physical fitness and functional capacity

Castello-Simoes (27) reported a significant increase in the 6 minute walking test distance (6MWT) after exercise training and bariatric surgery (before: 470 ± 23.9m; after: 515.0 ± 14.0m). Shah et al. (26) found a significantly increased energy expenditure and time spent on exercise in high-volume exercise group per day.

Aerobic capacity

In a maximal bicycle ergometer test before bariatric surgery, Stegen et al. (28) found that both groups (GB (gastric bypass only) and GB+E (gastric bypass and postoperative exercise program) reached their ventilator anaerobic threshold (VAT) at the power (GB = 93 ± 24 W; GB+E = 90 ± 24 W) with an equal time of occurrence (GB = 270 ± 107 s; GB+E = 266 ± 133 s) (28). Gastric bypass surgery did not improve time of occurrence of VAT and power at VAT. When patients followed an exercise program (GB+E group) postoperatively, the time of occurrence of VAT was delayed (349 ± 19 s) (28). Also Stegen and colleagues registered the peak exercise parameters. In the preoperative phase, morbidly obese patients reached a peak oxygen uptake of 17.4 ± 4.9 ml/kg/min (GB) and 17.6 ± 3.2 ml/kg/min (GB+E). Unfortunately, absolute peak oxygen uptake and power did not improve 4 months after an intensive exercise program, nor by bariatric surgery (28).

Castello-Simoes (27) reported a significant increase of the predicted forced vital capacity (before: 94.0 ± 3.1; after: 101.0 ± 2.5) in the trained group 4 months after bariatric surgery (27). In the same group there was a significant reduction of the dyspnoea score (before: 5.8 ± 0.6; after 2.7 ± 0.8) 4 months after bariatric surgery.

Muscle strength

Stegen et al. (28) found that the untrained patients (who only had a gastric bypass (GB)) had a decrease in dynamic muscle strength 4 months postoperative. They have lost 16% of their quadriceps strength, 36% of their biceps strength and 39% of triceps strength. Patients who had a gastric bypass and followed an exercise program postoperative prevented this decrease. Biceps (Pre = 21.8 ± 8.0 kg; Post = 25.9 ± 13.0 kg) and triceps (Pre = 24.3 ± 10.1 kg; Post = 30.7

± 23.0 kg) strength were preserved and both hamstrings and quadriceps strength increased (72% and 27% respectively) due to the exercise program (28). Static muscle strength, which is measured as handgrip strength, decreased in both groups 4 months after gastric bypass surgery with 18% and 7% respectively. Muscle fatigue was not influenced by gastric bypass surgery, nor by an additional exercise training program (28).

Fatty acid oxidation

Berggren et al. (29) studied the effect of weight loss through exercise training on the muscle fatty acid oxidation. Muscle fatty acid oxidation in extremely obese women who had lost weight (approximately 50 kg) was compared with extremely obese and lean individuals (29). There was no difference in muscle fatty acid oxidation between extremely obese and the weight loss groups. The fatty acid oxidation was depressed compared with the lean individuals (-45%; $P<0.05$). In contrast, ten days of exercise training increased fatty acid oxidation in the skeletal muscle of lean, obese and previously extreme obese subjects after weight loss (respectively + 1.7-fold, +1.8-fold and +2.6-fold) (29).

Quality of Life and satisfaction

Shah et al (26) reported in the high volume exercise group (HVEP) a significant improvement in health related quality of life on several domains including physical function ($p= 0.049$), self-esteem ($p=0.0002$), sexual life ($p=0.02$), public distress ($p=0.003$), and the total score ($p=0.0004$) over 12 weeks. The control group showed a significant improvement in self-esteem ($p=0.004$), sexual life ($p=0.04$), and work (or daily activities) ($p=0.04$) and the total score ($p=0.012$). (26) There was no group-by-week interaction for any of the scales except the interaction for self-esteem, which was approximately $p= 0.05$. The data from the SF-36 questionnaire showed that there was no group-by-week interaction for any of the scales, but the HVEP group reported a significant improvement in emotional well being ($p= 0.001$), energy levels ($p=0.0002$), and mental QOL total score ($p=0.006$) over 12 weeks whereas QOL in the control group did not change. (26)

TABLE 8.3. Post- bariatric surgery exercise regimes

Study	Exercise regime	Outcome
Shah *et al.* 2011 (26)	Energy expenditure ≥2,000 kcal/week in moderate-intensity aerobic exercise at 60–70% of maximal oxygen consumption (VO2max). The subjects were instructed to achieve these goals gradually and were asked to expend 500 kcal during the first week and increase by 500 kcal every week until they achieved their goal of ≥2,000 kcal/week. Each subject was asked to exercise on the treadmill at a certain speed and grade and on the cycle ergometer or rowing machine at a particular wattage that would correspond to 60–70% of her/his measured VO2max. Subjects who preferred to walk outside or on the walking track were asked to measure the distance that they walked and asked to complete this distance in a time period to achieve a pace associated with an intensity of 60–70% of the measured VO2max. The subjects were asked to exercise at least 5 days a week and to increase the intensity of exercise to remain the same level of exertion after each training. The exercise was partially supervised and the subjects were asked to come to the fitness center at least once or twice a week. Energy expenditure per week was calculated approximately from the work data shown on the exercise equipment and from the duration and distance of walking relative to body weight. Exercise away from the fitness center was monitored by asking the subjects to keep an exercise diary and/or using heart rate monitors.	*Energy expenditure (moderate physical activity) (kcal/kg/day):* I: Baseline 1.1 (0-5.8), 6 weeks 3.5 (0.4-8.2) ($p<0.02$), 12 weeks 4.1 (0-15.0) (p=<0.0001) *Time spent (moderate physical activity) (h/day):* I: Baseline 0.3 (0-1.5), 6 weeks 0.9 (0.1-2.1) ($p<0.02$) 12 weeks 1.0 (0-3.8) ($p<0.0001$)

Castello-Simoes *et al.* 2013 (27)	Start of aerobic training 48 hours after maximal exercise test. Session duration 1 hour on alternate days, 3 times a week, for 12 weeks, totaling 36 sessions. A session consisted of the following: initial 5 min stretching of upper and lower limbs and diaphragmatic breathing. 5 min warm up on a treadmill at 3 km/h. 40 min of exercise on a treadmill with speed and inclination varying according to the behaviour of HR, separated in 4 steps; Step 1 – intensity of exercise in which the HR remained at 50% of HR peak, reached in maximal exercise testing. Step 2 – 60% of HR peak. Step 3 – 70% of HR peak. Step 4 – Maintaining 70% of the HR peak. 1 min recovery at 3 km/h. 10 min of the same initial stretching and diaphragmatic breathing. HR and blood pressure were obtained at the beginning of the session, at the end of each step, recovery and at the end of the session.	*Lung Function* TG: BGBS FVC: 94.0 ± 3.1 4GBS FVC: 101.0 ± 2.5 CG: BGBS FVC: 99.0 ± 2.4 4GBS FVC: 100.0 ± 3.7 EG: FVC: 100 ± 4.0 *Mean Heart Rate (beats/min)* TG: BGBS 132.3 ± 6.0 4GBS 124 ± 5.9 CG: BGBS 138.2 ± 3.7 4GBS 125 ± 3.9 EG: 135.5 ± 3.5 6MWT Walking Distance (m) TG: BGBS 470.0 ± 23.9 4GBS 515.0 ± 14.0 CG: BGBS 453.0 ± 29.0 4GBS 505.0 ± 10.9 EG: 641.0 ± 10.4 Dyspnoea (0-10) TG: BGBS 5.8 ± 0.6 4GBS 2.7 ± 0.8 CG: BGBS 5.9 ± 0.5 4GBS 4.5 ± 0.9 EG: 2.8 ± 0.9

Stegen *et al.* 2011 (28)	*Strength exercises* were performed using stack-weight equipment (elbow flexion and extension and knee flexion and extension). Intensity of strength training was calculated from one repetition maximum (1RM) values. The starting level was 60% of 1RM, which increased up to 75% of 1RM. Patients were habituated to the exercises and equipment during the first three training sessions. In the next 15 sessions, two sets of 15 repetitions at 60% of 1RM were done. In the final 18 sessions, three sets of 10 repetitions at 75% were done. Resting periods between repetition sets were approximately 60 s. *Endurance training* consisted of cycling (10 min), walking (10 min), and stepping (10 min). Exercise intensity was initially set at 60% of heart rate reserve (HRR, defined as the difference between resting heart rate and peak heart rate) and was gradually increased up to 75% of HRR at the end of the training period. Stationary bicycles, treadmills, and steppers were used in a rehabilitation training room.	*Dynamic muscle strength in kg (4 months postoperative):* Quadriceps: I: 58.0 (±25.6) C: 45.9 (25.1) (p=0.002) Biceps I: 25.9 (±13.0) C: 20.8 (±8.8) (p=0.001) Triceps I: 30.7 (±23.0) C: 22.0 (±6.6) (p=0.038)
Berggren *et al.* 2008 (29)	10 consecutive days of endurance-oriented exercise training. An incremental, maximal stress test was initially performed to screen for underlying cardiovascular disease and determine the workload [%peak oxygen consumption and heart rate peak] for the exercise training. VO_2 peak was determined on an electronically braked cycle ergometer in the upright position, with oxygen consumption measured via open-circuit spirometry. The training program was based upon previous exercise prescriptions that improved whole body fat oxidation or increased mitochondrial content. Participants exercised 60 min/day at 70% VO_2 peak for 10 consecutive days on a cycle ergometer. All training was performed under direct supervision. Subjects were initially permitted to take a rest break (5 min) during exercise; by **day 5** all subjects exercised continuously.	Muscle fatty acid oxidation: Lean subjects: increase +1.7-fold Obese subjects: increase +1.8-fold Previously extreme obese subjects after weight loss: increase +2.6-fold

Abbreviations: GBS = Gastric Bypass, TG = Trained Group, CG = Control Group, EG = Eutrophic Group, BGBS = before gastric bypass surgery, 4GBS = 4 months after gastric bypass surgery, W = Weight, BMI = Body Mass Index (kg/m^2), 6MWT = 6 minute walking test, FVC = Forced Vital Capacity, HR = heart rate, 1RM = One repetition maximum. HRR = heart rate reserve, I = Intervention group, C = Control group

8.4 DISCUSSION

Considering the great value assigned to exercise, a search for evidence provided a relatively little number of prospective studies addressing this subject in relation to bariatric surgery. In the majority of reports a positive effect on anthropometrics, cardiovascular risk factors and physical fitness was described. However, the results were not unanimous, with a wide range of exercise programs and peri-operative timing and therefore hampering adequate practical guidance. Simplifying the common findings an exercise program lasts for a median of 12 weeks with an intensity of a median 65% peak heart rate/VO_2 max and at least partially supervised (table 8.4).

Two systematic reviews (by Baillot et al. (30) and Fonseca-Junior et al. (31)) assessed the impact of physical exercise and fitness in obese individuals, but without an in depth look on the timing peri-operatively and type of exercise needed to improve health in the bariatric population. The results of exercise in terms of weight loss and changes in the other anthropometric variables have been described before (1-3). However the type of exercise, used to achieve this weight loss, was not specified / given in detail. These details could be relevant as exercise regimes can include endurance training, strength training or combinations of intensity of both components. Unfortunately, it is difficult to assess the appropriate type and amount of physical activity for the bariatric surgical patient. It is unclear if preoperative exercise has the same effect as postoperative exercise. Also there is no uniformity on the outcome variables and little is known about the effect of exercise programs on the weight regain after bariatric surgical interventions. Nevertheless, it is known that exercise results in significant changes in anthropometric parameters (22-29) and results in more weight loss than bariatric surgery alone (7-9).

Exercise training demonstrates favourable effects on body composition, blood pressure control, insulin sensitivity, inflammation biomarkers and subclinical carotid atherosclerosis (CIMT). These effects have been associated with evidence of removal of oxidized phospholipids from the vessel wall, stabilisation of atherosclerosis and positive changes in LDL cholesterol (32). These changes have a strong correlation with increase in vascular function and regression in the burden of atherosclerosis (33). Ahmadi et al. (34) showed that the CIMT decrease was significantly greater in response to a 7-month exercise program than statin or niacin therapies in the ARBITER 6 trial (35). In other words, exercise training reduces cardiovascular risk in obese individuals.

TABLE 8.4. Common findings

	Shah *et al.* (26)	**Castello-Simoes** *et al.* (27)	**Stegen** *et al.* (28)	**Baillot** *et al.* (22)	**Funderburk et al. 2010 (23)**	**Berggren** *et al.* (29)	**Hickey** *et al.* **1999** (24)	**Marcon** *et al.* **2011** (25)
Duration (weeks)	12	12	16	12	12	2	1	24
Intensity	60-70% VO_2max	60-70% HR	60-75% HR/RM	55-85% of HRR	x	70% VO_2max	65% VO_2 peak	x
Supervision	Partial	Whole	Whole	Partial	Whole	x	Whole	Whole
Timing bariatric surgery	Post	Post	Post	Pre	Pre	Post	Pre	Pre

Abbreviations: HR = Heart rate, HRR = Heart rate reserve, RM = Repeated Measurements, 2KmWT = 2 kilometre walking test, x = unknown

Bariatric surgery is the only longstanding intervention when conservative therapy fails to succeed. However bariatric surgery also has consequences. One of them is a decrease of dynamic muscle strength after the operation (28). A possible explanation could be the found in a decrease of muscle mass after the operation. In the study of Stegen et al. (28) the untrained patients lost a total of 7.6 kg of muscle mass. That is 29.7% of the total body weight lost (-26.6 kg) through bariatric surgery.

Reviews by Stiegler et al. (36) and Chaston et al. (37) confirmed the positive correlation between weight loss and fat-free mass loss (FFML). Very low caloric diets result in a greater FFML compared to moderate caloric diets. Bariatric surgery results in greater FFML than very low caloric diets. Webster et al. (38) found that the FFML should not exceed the 22% of the total weight loss because of the function in resting metabolic rate, thermoregulation, oxidative capacity of the body and weight management. Exercise training can attenuate muscle atrophy and can maintain FFM during weight loss (36, 37), but the value of a perioperative exercise program for bariatric surgery has not been investigated.

It can be debated whether or not decrease of muscle strength is a problem for morbidly obese patients after weight loss. It is well known that obese individuals have higher absolute muscle strength compared to lean subjects, but there is lower relative muscle strength in terms of total body weight (39-42). This gives patients an impaired functional capacity, which results in the fact that more strength is needed to handle a heavier body. Therefore it might be important to prevent a decrease in muscle strength after bariatric surgery. However when investigating muscle changes before and after bariatric surgery, several factors have to be taken into account. One of them is the type of bariatric surgery. In the study by Stegen and coworkers (28) only patients who have undergone gastric bypass surgery were included. To our knowledge it is unknown whether there are differences in muscle loss between different types of bariatric surgery (per example gastric bypass surgery compared to a sleeve gastrectomy). Secondly, the patient compliance must also be studied, e.i. if patients followed-up the required dietary instructions ((re)substitution of proteins, vitamins and minerals). (36-38) None of these data were measured in the included studies.

It is known that obese patients have a reduced functional capacity and walking distance compared to lean subjects (43). A study of Tompkins and colleagues (44) showed that bariatric surgery leads to an improvement of approximately 75% in functional capacity and walking capacity 6 months after the operation. Weight loss (especially loss of body fat) makes walking less exhausting which was noticed by a decreased rate of exertion and heart frequency at the end of the 6 minute walking test in the studies of Stegen et al. (28) and Castello-Simoes et al. (27). Important predictors are not only the percentage of body fat, but also the maximum of oxygen uptake (VO_2 max) and the quadriceps muscle strength (43, 45, 46).

Exercise capacity can be measured by the anaerobic threshold (AT), which reflects the true aerobic capacity and by the maximal oxygen uptake (VO_2 peak). To interpret these parameters we must realise there are differences between obese and lean subjects. Healthy obese subjects undergoing weight loss will experience a decrease in the maximal oxygen uptake and peak work output, because of a decrease of muscle mass (47), and a elevated cardiac stress (which is training for the heart). This cardiac stress will fade away as matter of time (48).

In contrast, many obese patients suffer from obesity-related disorders, such as impaired cardiac function (49, 50), inefficient ventilatory work (51) and a decreased fatty acid oxidation (29, 52). These disorders are associated with a reduced exercise capacity. During weight loss, both the cardiac and pulmonary systems will restore and may overwhelm the decrease in muscle mass. This delicate balance might result in a stabilisation or even an improvement in maximal oxygen uptake.

Our study has several limitations that have to be taken into account. First, weight loss measured in the included studies was merely self-reported. In ideal circumstances, exercise programs and the effects of them must be monitored frequently (and objectively) by visiting a bariatric clinic. Second, because of the small sample sizes of the included studies and the heterogeneity in reported exercise programs and outcomes, it is difficult to interpret and generalise the findings for the whole bariatric population.

It is well known that exercise programs (with or without bariatric surgery) give a decrease in anthropometric parameters, but there are more beneficial effects of exercise. For future research there must be a focus to compare different exercise regimes (endurance and strength per example) in obese subjects. There is also an increasing need for randomised controlled trials that focus on the effect of peri-bariatric exercise on weight regain after bariatric surgery, because this is still an ongoing problem. Studies by Bond and colleagues (53) and Li and colleagues (54) investigate whether a preoperative exercise program has effects on the postoperative outcome. The definitive results of those studies are not published yet. Also the long-term effects of exercise programs on quality of life, depressive and anxiety symptoms and eating behaviour are not well understood.

8.5 CONCLUSION

In the majority of reports on exercising in a (future) bariatric population, a positive effect on anthropometrics, cardiovascular risk factors and physical fitness was described. However, the results were not unanimous, with a wide range of exercise programs and peri-operative timing and therefore hampering adequate practical guidance. Summarising our findings, a beneficial exercise program lasts for a median of 12 weeks with an intensity of a median 65% peak heart rate/VO_2 max and at least partially supervised.

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PART II: METABOLIC PHYSIOLOGY


FINAL

9. DIFFERENT SUPPLEMENTATION REGIMES TO TREAT PERIOPERATIVE VITAMIN B12 DEFICIENCIES IN BARIATRIC SURGERY: A SYSTEMATIC REVIEW

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ABSTRACT

Vitamin B12 dosage in multivitamin supplementation in the current literature is quite variable. There is no consensus about the optimal treatment of vitamin B12 deficiency.

A systematic literature search on different supplementation regimes to treat peri-operative vitamin B12 deficiencies in bariatric surgery was performed. The methodological quality of 10 included studies was rated using the Newcastle Ottawa scale and ranged from moderate to good. The agreement between the reviewers was assessed with a Cohen's kappa (0.69). The current literature suggests that 350 µg oral vitamin B12 is the appropriate dose to correct low vitamin B12 levels in many patients. Further research must focus on a better diagnosis of a vitamin B12 deficiency, the optimal dose vitamin B12 supplementation and clinical relevance next to biochemical data.

9.1 INTRODUCTION

Vitamin B12 deficiencies are common after bariatric surgery. Schilling et al. estimated the prevalence of vitamin B12 deficiency to be 12-33% (1). Other researchers have suggested a much greater prevalence of vitamin B12 deficiency in up to 75% of postoperative Roux-en-Y gastric bypass (RYGB) patients. However, most reports have shown approximately 35% of postoperative RYGB patients as vitamin B12 deficient (1-6). Experts have noted the significance of a functional/subclinical deficiency in the low-normal vitamin B12 range (defined as vitamin B12 levels between 140 and 200 pmol/l) that does not exhibit clinical evidence of deficiency. The methylmalonic acid (MMA) assay is the preferred marker of vitamin B12 status because metabolic changes often precede low vitamin B12 levels in the progression to deficiency. The evidence for the optimal vitamin B12 supplementation regimen after bariatric surgery is lacking (9). The dose of vitamin B12 in multivitamin (MV) supplementation in the current literature shows a wide range of variety. There is also no consensus about the optimal treatment of a vitamin B12 deficiency.

This systematic review specifically focuses on vitamin B12 supplementation regimes after bariatric surgery.

To disclose the current scientific knowledge regarding:

- The effect of additional vitamin B12 supplementation in this patient population
- The effect of different vitamin B12 supplementation regimens on blood levels of vitamin B12

9.2 METHODS

A systematic multi-database literature search was conducted. The patient population of interest were all patients before or after bariatric surgery. The intervention studied was vitamin B12 supplementation compared to no supplementation (or different supplementation vitamin B12 regimen). Outcome measures were blood levels of vitamin B12.

Pubmed, Embase, Medline, and The Cochrane Library were searched from the earliest date of each database up to December 2015. The search string used for the literature search used the following keywords and was modified for each database: ([bariatric surgery OR metabolic surgery OR sleeve gastrectomy OR roux-en-y gastric bypass OR mini gastric bypass OR omega loop gastric bypass OR biliopancreatic diversion OR duodenal switch OR single anastomosis duodeno-ileal bypass AND vitamin B12 supplementation AND blood levels vitamin B12]).

Authors HS and SP screened and selected studies on the basis of title and abstract, separately. After primary selection, authors (HS and SP) reviewed the full text of the selected studies and determined suitability for inclusion, based on the established selection criteria. For further eligible studies, cross-references were screened. Disagreements were solved by discussion with each other and the senior author (JS) until consensus was reached.

INCLUSION CRITERIA

- Randomized controlled trial, prospective or retrospective cohort study
- Patients who were scheduled for bariatric surgery or patients post-bariatric
- All surgical procedures were included (Laparoscopic Gastric banding, Vertical Banded Gastroplasty, Roux-en Y Gastric Bypass, Omega Loop Bypass, Duodenal Switch, biliopancreatic diversion, single anastomosis duodeno-ileal bypass)
- Outcome measure of interest was vitamin B12 levels

EXCLUSION CRITERIA

- Cross-sectional studies
- Studies looking at pre- and/or postbariatric patients with renal insufficiency
- Postbariatric body contouring surgery and vitamin B12 supplementation

For rating the methodological quality, The Newcastle-Ottawa Scale for non-randomized trials (NOS) was used (10). Stars awarded for each quality item serve as a quick visual assessment. Stars are awarded such that the highest quality studies are awarded up to nine stars. The NOS assigns up to a maximum of nine points for the least risk of bias in three domains: 1) selection of study groups (four points); 2) comparability of groups (two points); and 3) ascertainment of exposure and outcomes (three points) for case–control and cohort studies, respectively.

Two authors (HS and SP) separately assessed the NOS scale of the included studies. A Cohen's kappa score was calculated to determine the level of agreement between authors HS and SP. A Cohen's kappa score < 0.20 indicates a poor agreement; 0.21 – 0.40 a fair agreement; 0.41 – 0.60 a moderate agreement; 0.61 – 0.80 a good agreement; 0.81 – 1.00 a very good agreement (16).

All the included vitamin B12 levels were calculated in one general unit (pmol/L), if possible.

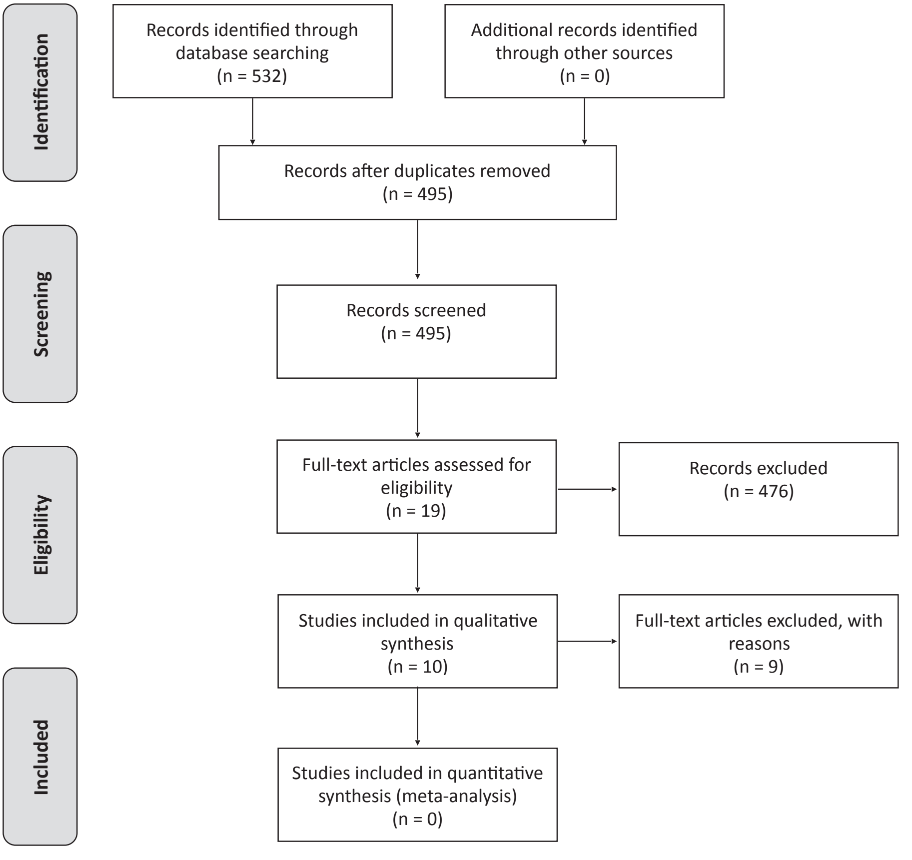

FIGURE 9.1: PRISMA Flowchart

9.3 RESULTS

The primary literature search produced 532 results, including 37 duplicates. After selection on title and abstract, 19 studies were found possibly relevant. Nine studies were excluded, 5 of them were conference abstracts, 2 of them were not online available, 1 study did not use MV supplementation and 1 study consisted of a survey among bariatric surgeons. Due to heterogeneity in patient populations, small sample size of the included studies and lack of standardized reporting of outcome measures (type of supplementation regime and dose of vitamin B12 in the prescribed supplementation), a meta-analysis was not conducted. In total 10 studies were included in this systematic review.

Figure 9.1. outlines our search strategy. The methodological quality of the included studies ranged from moderate to good, indicated by the NOS scale (Table 9.1). A Cohen's kappa of 0.69 reflected a good agreement between authors HS and SP. Table 9.2 gives an overview of the results of the included studies.

STUDY CHARACTERISTICS

Of all included studies, 1 study was a triple-blind randomized controlled trial (23), 4 studies were prospective cohort studies (9, 11, 12, 15) and 5 studies were retrospective cohort studies (6, 13, 14, 17, 18). In total, 10 studies consisted of 1277 participants.

INTERVENTION AND FOLLOW-UP LENGTH

The length of the intervention ranged from 3 months to 10 years postoperative. Intervention and follow-up length of all studies were described in table 9.3.

VITAMIN B12 SUPPLEMENTATION

In 8 studies, the dose of vitamin B12 in the MV supplementation was different (Table 9.4). The studies of Ramos et al., (18) and Brolin et al., (6) lacked of the dose of vitamin B12 of MV supplements.

OUTCOMES LABORATORY TESTS OF VITAMIN B12

Outcomes laboratory tests were described in table 9.5. All vitamin B12 levels were calculated in pmol/L, except the studies of Brolin et al., (6) and Ramos et al., (18) which suspectedly used wrong measurement units for indicating a vitamin B12 deficiency. Therefore, the original measurement units of the studies were used in this paragraph. Reference ranges of vitamin B12 levels of all studies were described in table 9.3.

COMPLAINTS AND CLINICAL EFFECTS

All included studies did not control the vitamin B12 deficient related complaints. Clinical relevance of the deployed supplementation regime has not been studied in all manuscripts.

TABLE 9.1. Assessment of methodological quality using The Newcastle-Ottawa Scale for non-randomized trials (10).

Criteria	S1	S2	S3	S4	C1	O1	O2	O3	T
Aasheim et al. [11]	*	–	*	*	**	*	*	*	*8*
Brolin et al. [6]	*	–	*	*	**	*	*	–	*7*
Capoccia et al. [13]	*	–	*	*	**	*	*	*	*8*
Dogan et al. [23]	*	*	*	*	**	*	*	*	*9*
Donadelli et al. [9]	*	–	*	*	**	*	*	–	*7*
Gasteyger et al. [17]	*	–	*	*	**	*	*	–	*7*
Homan et al. (2016)	*	*	*	*	**	*	*	*	*9*
Moore et al. (2014)	*	–	*	*	**	*	–	*	*7*
Ramos et al. (2015)	*	–	*	*	**	*	*	–	*7*
Rhode et al. [12]	*	–	*	*	**	*	–	*	*7*

Abbreviations: S1 = Representiveness, S2 = Selection, S3 = Ascertainment, S4 = Demonstration, C1 = Comparability, O1 = Outcome Selection, O2 = Outcome Follow-up, O3 = Adequacy

TABLE 9.2. Overview of the study results of the included studies

Study (+Design)	Participants --------------- N(male/female)	Characteristics	I: N (age ± SD) C: N (age ± SD)	Standard suppletion regime	Additional supplementation	Type of bariatric operation	Intervention/ treatment	Outcome measures	Study results
Aasheim et al., 2012 (11) PCT	50 (18/32)	Patients who have had RYGB and a control group who only have had a life style intervention	I: 27 (44 ± ?) C: 23 (45 ± ?)	I: Standardized supplements 1 pill/day; 1 µg B12. C: No supplements.	I: IM injections every 3 months (1 mg cyanocobalamin). C: no additional vitamin B12.	I: RYGB N: no operation	Biologic specimen collection and vitamin measurements were performed at baseline and 1 year after the intervention. Dietary intake was assessed by a structured interview performed in person by registered dieticians, at baseline and 1 year after intervention.	Blood tests	Vitamin B12 levels were increased (p <0.02) in group I compared to group C during follow-up.
Brolin et al., 1998 (6) RT	348 (? / ?)	Patients with (morbid) obesity who have had RYGB as a primary or revisional surgery	I: 348 (? ± ?)	Oral MVI supplement daily; dose of MV was not mentioned.	Low serum levels of vitamin B12 were treated either with MV or an additional supplement. Dose of vitamin B12 used in this study 500 µg	RYGB: 321 Revisional surgery: 27 -24: some form of gastroplasty as their initial operation. -3 patients had revision of jejunoileal bypass.	During a 10-year period, a complete blood count and serum levels of iron, total iron-binding capacity, vitamin B12 and folate were obtained preoperatively and postoperatively at 6-month intervals for the first 2 years, then annually thereafter.	Blood tests	Vitamin B12 deficiency was recognized in 122 patients (37%). The incidence of vitamin B12 deficiency was significant greater in the revision group. Taking standard MV did not prevent vitamin B12 deficiencies.

Capoccia et al., 2012 (13) RT	138 (28/110)	Patients with (morbid) obesity who have had LSG	I-a: 7 (36.7 ± 13.2) I-b: 29 (43.6 ± 10) I-c: 40 (44.4 ± 9.6) I-d: 33 (45.1 ± 12.8) I-e: 29 (43.7 ± 10.8)	Oral MV (1 tablet/day and provides 2,5 µg vitamin B12) for the first 6 months. Then, oral MV were stopped and 1000 µg/month of IM vitamin B12 were administered during all the follow-up period.	-	LGS	LGS patients with a standard MV were followed up with routine laboratory tests and anthropometric measurements and assessed for nutritional status every three months throughout 12 months.	Blood tests	Vitamin B12 was adequately supplemented for all the follow-up period. Greater weight loss does not require higher dosage of MV.
Dogan et al., 2014 (23) RCT	148 (46/104)	Patients who have had roux-en-y gastric bypass.	I-1: 74 (43.4 ± 10.0) I-2: 74 (45.3 ± 10.2)	I-1: Standard MV with a vitamin B12 dose of 12.5 µg/day. I-2: a vitamin B12 dose of 350 µg/day.	Vitamin B12 deficiency (levels < 150 pmol/L) was corrected with IM injection of 1000 µg hydroxocobalamin once every 2 months for 12 months.	RYGB	Patient were randomized in 2 groups, receiving 2 different MV supplements (standard MV and WLS Forte). Standard laboratory blood tests were performed at baseline, 6 and 12 months postoperative.	Blood tests	Using WLS Forte supplements after RYGB results in fewer deficiencies in vitamin B12 levels compared with standard MV supplements.
Donadelli et al., 2012 (9) PCT	58 (12/46)	Patients with (morbid) obesity after RYGB	I: 58 (41 ± 10)	MV on daily basis with a vitamin B12 dose of 12 µg/day.	-	RYGB	Patients' blood vitamin concentrations were evaluated preoperatively and at 3, 6, and 12 months after surgery.	Blood tests	Vitamin B12 levels were significantly decreased and 7% of all patients had a vitamin B12 deficiency by 12 month postoperatively.

Gasteyger et al., 2008 (17) RT	137 (27/110)	Patients with (morbid) obesity after RYGB	I: 137 (39.9 ± 10)	A standardized MV between the 1st and 6th month postoperative. Dose of vitamin B12/day: 3 µg/day.	Specific substitutive treatments were prescribed as soon as the value was below the lower value of the reference range. Dose oral vitamin B12: 1 mg/month.	RYGB	Between 1st and 6th months postoperative, a standardized MV was prescribed for all patients. Specific requirements for additional substitutive treatments were systematically assessed by a blood sample at 3, 6, 9, 12, 18 and 24 months.	Blood tests	3 months after RYGB, 34% of all patients required at least one specific supplement in addition to MV. At 6 and 24 months, this proportion increased to 59% and 95%, respectively. Of all patients, 80% is using additional vitamin B12 after 24 months.

Homan et al., 2016 (14) RT	137 (42/95)	Patients with (morbid) obesity after RYGB	I-1: 45 (46 ± 12) I-2: 64 (44 ± 9) I-3: 28 (43 ± 10)	I-1: Standard MV with a vitamin B12 dose of 12.5 µg/day. I-2: MV with a vitamin B12 dose of 350 µg/day. I-3: patients stopped using a supplement.	Vitamin B12 deficiency (levels < 150 pmol/L) was corrected with IM injection of 1000 µg hydroxocobalamin once every 2 months for 12 months.	RYGB	12-36 months follow-up of the study of Dogan et al. [23].	Blood tests	In the first 3 years, 22 patients developed a vitamin B12 deficiency and were prescribed IM injections. At time of diagnosis 5 of this subset of patients were using WLS Forte, 15 were using an standard MV and 2 were nonusers. After exclusion of the IM injection users, a significant difference in estimated mean serum vitamin B12 concentrations was found between WLS Forte and standard MV ($p < 0.001$).
Moore et al., 2014 (15) PCT	22 (0/22)	Woman with (morbid) obesity after RYGB	I: 22 (41 ± 12)	MV with 350 µg vitamin B12 daily for 3 months	-	LGS: 11 RYGB: 11	Blood vitamin concentrations were measured preoperatively and 3 months postoperative.	Blood tests	Vitamin B12 levels were increased after 3 months.

Ramos et al., 2015 (18) RT	137 (24/113)	Patients with (morbid) obesity after RYGB	I: 137 (? ± ?)	MV Dose of vitamin B12 was not mentioned	-	RYGB	Personal information, anthropometric and laboratory data in the preoperative, 12, 24, 36 and 48 months postoperatively were done.	Blood tests	Vitamin B12 was decreased at 48 months postoperatively in females. The values are within the reference standards.
Rhode et al., (12) PCT	102	Patients after bariatric surgery	I-a: ? (? ± ?) I-b: ? (? ± ?) I-c: ? (? ± ?) I-d: ? (? ± ?)	Dose of crystalline vitamin B12 between 4 groups: I-a:100 µg I-b:250 µg I-c:350 µg I-d:600 µg	-	RYGB: 94 VBG: 8	Blood profiles were determined at the initial evaluation and then at 3 monthly intervals, producing a hematological profile for the 3-, 6-, and 9- month time point. All patients were given 350 µg of vitamin B12 per day for the first 3 months, patients were assigned on a sequential basis for the next 3 months to receive one of four dosage levels of crystalline vitamin B12 – 100, 250, 350 or 600 µg per day. For the last 3 months they were instructed not to take any vitamin B12.	Blood tests	Serum vitamin B12 levels were greater than 150 pmol/L after 6 months in 83.3% of patients who received 100 µg; 92.3% of patients who received 250 µg; 94.7% after 350 µg and 95.2% after 600 µg ($p = 0.525$).

Abbreviations: *I = intervention group, C = control group, PCT = prospective cohort trial, IM = intramuscular, MV = multivitamin, RYGB: Roux-en-Y gastric bypass, LGS = laparoscopic gastric sleeve, DRI = dietary reference intake, BPD = biliopancreatic diversion, RT: retrospective cohort trial, BMI: body mass index, VBG = vertical banded gastroplast*

TABLE 9.3. Vitamin B12 supplementation regimen among the included studies

	Vitamin B12 per day in prescribed supplementation regime
Aasheim et al. (11)	Oral MV: 1 µg vitamin B12 per day and 1 mg IM cyanocobalamin injection every 3 months
Capoccia et al. (13)	First six months: oral MV with 2,5 µg vitamin B12 per day After six months: oral MV were stopped and 1000 µg/month of IM vitamin B12 were administered
Donadelli et al. (9)	Oral MV with 12 µg vitamin B12 per day
Gasteyger et al. (17)	First six months: oral MV with 3 µg vitamin B12 per day After six months: no MV, substitutive 1 mg/month oral vitamin B12 were prescribed below the lower reference range . When no satisfactory response was obtained, the doses were increased to IM injections. Dose of IM injections was not mentioned in the study.
Moore et al. (15)	Oral MV with 350 µg vitamin B12 per day for 3 months

MV: multivitamin, IM: intramuscular, µg: microgram

TABLE 9.4. Dosage of vitamin B12 among the included studies

	Vitamin B12 per day in prescribed supplementation regime
Aasheim et al. (11)	1 µg oral vitamin B12 per day and 1 mg IM injection every 3 months.
Brolin et al. (6)	The dose of vitamin B12 in de MV supplements was not mentioned in the study.
Capoccia et al. (13)	First six months: oral MV with 2,5 µg vitamin B12 per day. After six months: oral MV were stopped and IM injections with 1 mg/month were administered.
Dogan et al. (23)	I-1:supplement with 350 µg vitamin B12. I-2: standard MV supplementation with 12,5 µg vitamin B12. Treatment of a deficiency: IM injections with 1 mg per 2 months for 12 months.
Donadelli et al. (9)	12 µg oral vitamin B12 per day.
Gasteyger et al. (17)	First six months: 3 µg oral vitamin B12 per day. After six months: no MV, substitutive 1 mg/month oral vitamin B12 were prescribed below the lower reference range. When no satisfactory response was obtained, the doses were increased to IM injections. Dose of IM injections was not mentioned in the study.
Homan et al. (14)	I-1: supplement with 350 µg vitamin B12. I-2: standard MV supplementation with 12,5 µg vitamin B12. Treatment of a deficiency: IM injections with 1 mg per 2 months for 12 months.
Moore et al. (15)	350 µg oral vitamin B12 per day for 3 months.
Ramos et al. (18)	The dose of vitamin B12 in de MV supplements was not mentioned in the study.
Rhode et al. (12)	First 3 months: 350 µg oral vitamin B12 per day. Thereafter, in the following oral dosage for the next 3 months: I-1: 100 µg. I-2: 250 µg. I-3: 350 µg. I-4: 600 µg.

MV: multivitamin, I-1-4: intervention group 1-4, IM: intramuscular, µg: microgram, RDA: recommended daily allowance.

TABLE 9.5. Outcomes laboratory tests of vitamin B12

Aasheim et al. (11)	Vitamin B12 levels increases after intervention, compared with the control group (P < 0.02). Of 2 patients who developed vitamin B12 deficiency (compared with non in the control group), 1 reported not having had IM injections. Actual vitamin B12 levels were not mentioned in the study.
Brolin et al. (6)	Vitamin B12 levels were significantly lower than mean preoperative values only at 12 and 24 months after surgery. 37 % of the patients had a vitamin B12 deficiency and the incidence of vitamin B12 deficiency after surgery was significantly greater in the revision group (p ≤ 0.004). There was no correlation between regular ingestion of MV supplementation and the potential for developing a vitamin B12 deficiency. In this study more than 80% of the vitamin B12 deficiencies responded to oral supplementation (containing 500 µg vitamin B12). Actual vitamin B12 levels were measured but not mentioned in the study.
Capoccia et al. (13)	Vitamin B12 was adequately supplemented for all the follow-up period (before surgery and 12 months after surgery, 365.8 ± 193.7 pmol/L and 360.8 ± 169.0 pmol/L, respectively). Baseline vitamin B12 levels: 317.3 ± 132.8 pmol/L, 286.0 ± 188.7 pmol/L, 376.8 ± 197.8 pmol/L, 517.3 ± 191.0 pmol/L, 258.8 ± 303.5 pmol/L, for group A, B, C, D and E respectively. Follow up results 12 months after surgery: 338.7 ± 284.4 pmol/L, 349.8 ± 193.3 pmol/L, 268.6 ± 119.0 pmol/L, 284.4 ± 154.3 pmol/L, 303.5 ± 187.0 pmol/L, for group A, B, C, D and E respectively. Percentage deficiencies were not mentioned in the study.
Dogan et al. (23)	At baseline, vitamin B12 deficiency was diagnosed in 9 (6.1%) patients, that is, 5 (6.8%) patients in the standard MV group and 4 (5.44%) patients in the high dose group. These patients received IM injections by protocol. In total, 27 (18.2%) additional patients were treated with IM injections at any time during the 12 month follow-up: 17 (23%) in the standard MV group and 10 (13.5%) in the high dose group (p = 0.14). The results obtained after exclusion of these patients receiving IM injections: mean vitamin B12 serum levels decreased by 38.9 ± 141.3 pmol/L in the standard MV group and increased by 44.1 ± 138.8 pmol/L in the high dose group (p < 0.001) after 12 months, and as a result mean vitamin B12 blood serum levels at 6 months and 12 months were significantly higher with high dose compared with standard MV (p < 0.05). After 12 months, vitamin B12 deficiency had developed in 5 (7.9%) patients receiving standard MV versus 1 (1.6%) patient in the high dose group (p = 0.207).
Donadelli et al. (9)	Vitamin B12 levels remained constant up to 3 months (331.7 ± 183.9 pmol/L) until 6 months (295.8 ± 183.0 pmol/L) after surgery but were significantly decreased after 12 months (274.9 ± 196.9 pmol/L, p = < 0.05 versus basal). 7% of patients had vitamin B12 deficiency 1 year after surgery.
Gasteyger et al. (17)	10% of all patients used additional vitamin B12 at 3 months, 28% at 6 months, 62% at 12 months, 72% at 18 months and 80% at 24 months.
Homan et al. (14)	In the first 3 years, 22 patients developed a vitamin B12 deficiency and were prescribed IM injections. At time of diagnosis 5 of this subset of patients were using high dose vitamin supplements, 15 were using a standard MV and 2 were nonusers. The difference in IM injections use between high dose vitamin supplements (409 ± 25) and standard MV (330 ± 27) was significant (p = 0.001). After exclusion of the IM injection users, a significant difference in estimated mean serum vitamin B12 was found between high dose vitamin supplements (335 ± 12) and standard MV (264 ± 12) (p < 0.001). In total 7 patients were diagnosed with a vitamin B12 deficiency at 36 months (3 in the standard MV group and 4 in the nonusing group). Combining the IM injection users and the deficient patients resulted in a total of 29 patients with a vitamin B12 deficiency throughout the study (5 while using high dose vitamin supplements, 18 while using standard MV and 6 while using no supplement). The difference between high dose vitamin supplements and standard MV was significant (p < 0.001).

Moore et al. (15)	High dose MV supplementation daily for 3 months resulted in a 48% increase of serum vitamin B12. A significant increase was seen in all patients after LSG (from 356.5 ± 93.0 pmol/L to 466.4 ± 220.7 pmol/L, p = 0.0336) and in all patients after RYGB (from 377.1 ± 129.2 pmol/L to 605.9 ± 295.2 pmol/L, p = 0.033).
Ramos et al. (18)	Male: Preoperative: 464.0 ± 140.6 mg/dL. Postoperative: 12 months: 373.8 ± 148.3 mg/dL, 24 months: 317.8 ± 163.7 mg/dL, 36 months 401.4 ± 352.0 mg/dL, 48 months: 354.4 ± 186.6 mg/dL. Female: Preoperative: 512.5 ± 561.5 mg/dL. Postoperative: 12 months: 395.6 ± 247.0 mg/dL, 24 months: 391.5 ± 212.9 mg/dL, 36 months 351.3 ± 177.1 mg/dL, 48 months: 395.8 ± 220.3 mg/dL. Percentage vitamin B12 deficiencies was not mentioned in the study.
Rhode et al. (12)	Serum vitamin B12 levels were <100 pmol/L at baseline and greater than 150 pmol/L after 6 months in 83.3% of patients who received 100 µg; 92.3% of patients who received 250 µg; 94.7% after 350 µg and 95.2% after 600 µg (p = 0.525).

9.4 DISCUSSION

This systematic review highlights the current evidence on the effects of MV or additional vitamin B12 supplementation in patients after bariatric surgery. Vitamin B12 supplementation has an effect on the intracellular vitamin B12 content and in the optimal dosage it can prevent a vitamin B12 deficiency. However, vitamin B12 deficiencies preoperatively are not uncommon in morbidly obese people. In the study of Dogan et al., (23) a vitamin B12 deficiency was diagnosed in 9 patients (6.1%) and 3 patients (5.2%) in the study of Donadelli et al., (9) had a vitamin B12 deficiency in the preoperative period. This is not clearly reported in the other 8 studies.

There is no consensus about the optimal dosage of vitamin B12 supplementation after bariatric surgery worldwide. ASMBS guidelines advise oral vitamin B12 supplements of 350 to 500 µg, and if necessary, intramuscular (IM) injections of 1000 µg per month (24). The ACCE/TOS/ASMBS guidelines advise oral supplementation with crystalline vitamin B12 at a dosage of 1000 µg daily or more may be used to maintain normal vitamin B12 levels. Intranasally administered vitamin B12, 500 µg weekly, may also be considered. Parenteral (IM or subcutaneous) vitamin B12 supplementation, 1000 µg/month to 1000-3000 µg every 6 to 12 months, is indicated if vitamin B12 sufficiency cannot be maintained using oral or intranasal routes (25).

However, definitive conclusions cannot be made after this systematic review, because of the heterogeneity of MV supplementation or additional vitamin B12 IM injection regimes and timing of this additional vitamin B12 IM injections. Besides that, all the included studies did not control the vitamin B12 deficient related complaints. Clinical relevance has not been studied in all manuscripts. These data are needed to examine whether biochemical benefits of vitamin B12 supplementation are correlated with clinical improvement.

Two interesting findings were found in the included studies. First, in 4 included studies a dose of 350µg vitamin B12 per day was using (12, 14, 15, 23). In the study of Moore et al., (15) vitamin B12 levels of all patients were increased 3 months postoperatively. In the study of Dogan et al., (23) high dose vitamin B12 supplements results in fewer vitamin B12 deficiencies compared with standard MV supplements. The study of Homan et al., (14) showed that high dose vitamin B12 supplements is effective as MV supplement that is able to reduce the number of patients with vitamin B12 deficiencies, compared with a standard MV supplement. In the study of Rhode et al., (12) serum levels of vitamin B12 were > 150 pmol/L after 6 months in 95% of the patients.

Secondly, all the other studies used MV supplementation with a dose of vitamin B12 ranging from 3 to 12 µg per day (9, 17) or unknown dose of vitamin B12 (6, 18). The studies of Brolin et al., Donadelli et al. and Gasteyger et al., showed many vitamin B12 deficiencies in the follow up (6, 9, 17). Contrary results were found in the study of Ramos et al., (18), the vitamin B12 levels are within the reference standards. However, the dose of vitamin B12 in his study was unknown.

VITAMIN B12 SUPPLEMENTATION

Dose of vitamin B12 in the MV supplementation in all included studies, is varied from 1 µg/day to high dose supplementation with 350-600 µg/day. MV supplements with 350 µg vitamin B12 per day can maintain normal-high vitamin B12 levels in many patients (12, 14, 15, 23). The body's storage will be depleted much faster in patients who using standard MV supplementation with a low dose of vitamin B12. Of the included studies, the supplementation regimes with an oral vitamin B12 dosage < 350 µg/day, eight of the included studies showed persistence of deficiencies even after a period supplementation of vitamin B12. (6, 9, 11-14, 17, 23) In one study (6) no dosage of vitamin B12 was measured, in the other studies the dosage of vitamin B12 was lower than < 350 µg/day. (9, 11-14, 17, 23) In 2 included studies, IM injections are belong to the standard MV supplementation regime with a low dose of vitamin B12 (11, 13). Dose of the IM injections is equal but the frequency of given IM injections is also different (table 4). In the study of Aasheim et al., (11) 2 patients developed a vitamin B12 deficiency and in the study of Capoccia et al., (13) vitamin B12 levels decreased in many patients, which suggests that this both regimen were not optimal.

If MV supplementation with a high dose of vitamin B12 may improve the vitamin B12 levels in many patients, IM injections as a standard regime is not necessary and because of this, many patients were unnecessary loaded with IM injections. This seems like contradictory advice, but to determine whether IM injections of vitamin B12 are necessary, we need focus on the combination vitamin B12 and MMA. This is essential to assess whether there is an absolute of a functional deficiency of vitamin B12, because of the failure rate of the current vitamin B12 assays between 22-35% (7, 8, 19, 20). Therefore whether it is necessary to add IM injections to the standard supplementation regime. Besides that, these data are subjectively and it is unclear if patients take their supplements daily. Life-long compliance of daily supplement intake is hard to achieve. To measure adequate intake of MV supplementation, one can monitor the serum concentration of highly absorbable vitamins. Some investigators have reported that low folate levels reflect non-adherence to MV supplementation because the amount of supplemented folic acid properly corrects low serum folate levels (9, 23). Only two studies have looked at compliance of MV supplementation intake and distinction in processing these data (14, 23).

OUTCOMES LABORATORY TESTS OF VITAMIN B12 AND MMA

Vitamin B12 assays that are currently used to diagnose clinical vitamin B12 deficiency have a failure rate of 22-35% (7, 8, 19, 20). This failure rate may be due to the fact that 80% of the vitamin B12 in plasma is bound to the transport protein haptocorrin. This percentage is biologically unavailable and cannot be absorbed by the cells, which means that plasma vitamin B12 concentrations poorly correlate with the bioavailable intracellular vitamin B12 content (8, 21, 22). Measuring vitamin B12 is a poor predictor for a functional vitamin B12 status. In the study of Smelt et al., (8) more vitamin B12 deficiencies were found if MMA is included in the diagnosis. When a vitamin B12 level is between 140 and 200 pmol/l, additional MMA levels should be measured to determine whether there is a functional vitamin B12 deficiency. In this review, no included study used the additional parameter MMA. Given the high failure rate of vitamin B12 assays, many vitamin B12 deficiencies will be untreated.

STUDY LIMITATIONS

First, the following limitations are present when evaluating the literature: 1) heterogeneous patient populations being studied, 2) non-comparable vitamin B12 from supplements being evaluated, 3) lack of many data (some studies lacked of gender, age, reference range of vitamin B12 levels, actual vitamin B12 levels after intervention, lack of dose of vitamin B12 in MV supplementation) and 4) lack of well-designed prospective cohort and randomized controlled studies for the right use of vitamin B12 in post bariatric patients. Secondly, only biochemical data was measured and clinical relevance was not demonstrated.

9.5 CONCLUSION

In bariatric surgery, vitamin B12 deficiencies have a high prevalence. Unfortunately there is no consensus about multivitamin supplementation and any additional vitamin B12 supplementation. The current literature suggests that 350µg of oral vitamin B12 is the appropriate oral dose to correct low serum vitamin B12 levels in many patients. A lifelong follow-up regimen seems necessary, because MV supplementation with a high dose of vitamin B12 cannot prevent all deficiencies. Further research must focus on a better diagnosis of a vitamin B12 deficiency with possible additional parameters like MMA, the right dose of vitamin B12 supplementation and the clinical relevance beside biochemical data.

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10. COMPARISON BETWEEN DIFFERENT INTRAMUSCULAR VITAMIN B12 SUPPLEMENTATION REGIMES: A RETROSPECTIVE MATCHED COHORT STUDY

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ABSTRACT

Background

The incidence of vitamin B12 deficiency after bariatric surgery can range from 26-70%. There is no consensus on optimal vitamin B12 supplementation in postbariatric patients. The objective of this study was to compare three different regimes.

Methods

In this retrospective matched cohort study, we included 63 patients with MMA levels ≥ 300 nmol/L. Twenty-one received 5 intramuscular (IM) vitamin B12 injections including a loading dose, twenty one patients received 3 IM vitamin B12 injections without loading dose and twenty one patients received no IM vitamin B12 injections.

Results

The total patient population consisted of 14 males (22.2%) and 49 women (77.8%) with a mean current body mass index of 30.6 ± 8.0 kg/m². There is no significant difference in vitamin B12 and MMA levels between 3 groups at baseline. There was a significant difference in follow-up vitamin B12 levels of the 5 IM injection regime compared to the 3 IM injection regime ($p = 0.02$), 5 IM injection regime compared to no regime ($p=0.03$). In the follow-up results there is also a significant decrease in MMA levels of the 5 IM injection regime compared to 3 IM injections ($p = 0.02$), 5 IM injection regime compared to no regime ($p < 0.001$) and 3 IM injection regime compared to no regime ($p < 0.01$).

Conclusion

In this study, the 3 IM injection schedule without a loading dose is not sufficient to treat a vitamin B12 deficiency. A 5 IM injection regime with loading dose recovered all vitamin B12 deficiencies biochemically.

10.1 INTRODUCTION

The incidence of vitamin B12 deficiency after bariatric surgery can range from 26-70%. A vitamin B12 deficiency occurs in the relatively early stage postoperative but most commonly years after the surgery when the large liver stores are slowly depleted (1). Vitamin B12 deficiency can cause pernicious/megaloblastic anemia, fatigue, light-headedness, numbness and paraesthesia (tingling or prickly feeling) in extremities, demyelination and axonal degeneration (especially of peripheral nerves, spinal cord and cerebrum), changes in mental status ranging from mild irritability and forgetfulness to severe dementia or frank psychosis, ataxia and change in reflexes (8-10).

To prevent a vitamin B12 deficiency after bariatric surgery, all patients have started to use an oral vitamin supplement with vitamin B12 daily from 2 weeks postoperative. In order to detect a vitamin B12 deficiency, patients are screened preoperatively and postoperatively. We have added the additional analysis of methylmalonic acid (MMA) with vitamin B12 levels below 300 pmol/L who quantifies functional intracellular shortage since June 2013 in our bariatric centre. In the first months we did not yet start intramuscular injections based on MMA, because there was no clear cut-off value established for MMA in bariatric patients. Nowadays, we started intramuscular vitamin B12 injections in bariatric patients with MMA levels ≥ 300 nmol/L since August 2013. The first period we used an injection schedule, which consisted of 5 injections including a loading dose. According to current literature there is no consensus about the right regime of intramuscular vitamin B12 injections and the necessity of a loading dose (1-6, 8). An internal investigation at our bariatric centre showed that MMA improved yet after a few injections. Since then, our injection regime has been modified to 3 injections without a loading dose (dosage of both regimes is included in the vitamin B12 treatment section).

However, it is not clear whether the shorter injection schedule without a loading dose is just as effective as a longer injection schedule with a loading dose after six months. In this study we wanted to compare a longer injection regime with loading dose with a shorter injection regime without loading dose. These 2 regimes will be compared with a control group who had no injection regime. We hypothesized that patients receiving 5 injections of vitamin B12 will have higher plasma vitamin B12 levels and lower MMA levels after six months compared to 3 injections and no injections. Secondly, a faster elevation in MMA levels after 3 injections is expected compared to treatment with 5 injections.

10.2 METHODS

In this matched retrospective cohort study an analysis of vitamin B12 and MMA levels in bariatric patients was done. All patients underwent a sleeve gastrectomy or Roux-en-Y gastric bypass either as primary or a revisional procedure, from 2009 to 2015 in the Obesity Centre Catharina Hospital. Data of interest were patient characteristics, baseline levels vitamin B12 and MMA and follow-up vitamin B12 and MMA levels after 6 months.

We included 21 patients arbitrarily with complete data sets and MMA levels ≥ 300 nmol/L who received 5 intramuscular (IM) vitamin B12 injections including a loading dose, regardless of vitamin B12 levels. We also included 21 patients arbitrarily with complete data sets and MMA levels ≥ 300 who received 3 IM vitamin B12 injections without loading dose, regardless of vitamin B12 levels. In order to determine whether MMA levels recover spontaneously over time, we have included a control group of 21 patients with MMA levels ≥ 300 nmol/L. These patients did not receive IM vitamin B12 injections. Patients from the control group were selected arbitrarily from the database between June 2013 and August 2013.

All patients are advised to use a vitamin supplement daily. Initially, we recommended patients to use a high-dose weight loss surgery (WLS) supplement. However, these supplements are more expensive than over-the-counter supplements and some patients cannot afford these supplements. In case of side effects or intolerability for the supplements, an over-the-counter supplement was recommended (1, 7, 8). Table 10.1 gives an overview of the dosage and percentage vitamin B12 of these supplements. In total, 16 patients (25,4%) were using high-dose weight loss surgery (WLS) supplements, 43 patients (68,3%) were using over-the-counter multivitamin supplements and 4 patients (6,3%) did not use supplements.

TABLE 10.1. dosage of vitamin B12 in WLS supplements and over-the-counter supplements that are recommended in our centre

	Dosage tablets per day	Dosage vitamin B12 in mcg per tablet	Dosage vitamin B12 as a percentage per tablet
WLS sleeve	1	10	400%
WLS gastric bypass	1	350	14000%
Over-the-counter supplements sleeve	1	2.5	100%
Over-the-counter supplements gastric bypass	2	2.5	100%

VITAMIN B12 SUPPLEMENTATION

Vitamin B12 treatment consists of IM hydroxocobalamin injections, regardless type of regular vitamin supplements. Each injection contains 1000 micrograms of hydroxocobalamin.

Dosage of the old treatment regime: in total 5 injections with a loading dose of 1 injection every 2 weeks, during the first 8 weeks. Afterwards, one injection every three months.

Current treatment regime: in total 3 injections without loading dose. One injection in the first, second and the third month.

MMA MEASUREMENT IN BLOOD SAMPLING

MMA was measured in EDTA plasma using UPLC-MS/MS (Waters Xevo TQS). Methyl (D3)-malonic acid was used as internal standard. Mass transitions 116.9 - 73 and 119,9 - 76 were used to quantify these compounds, respectively. Ultrafiltration (Amicon Ultra 0.5 mL – 30K, Millipore) was used as sample preparation and reverse phase chromatography (ACQUITY HSS T3, 100 x 2,1 mm, Waters) was used for separation on UPLC. Evaluation of MMA values in our hospital laboratory: MMA levels < 300 nmol/L are considered normal, MMA levels between 300-430 nmol/L are considered moderate deficient and MMA levels > 430 nmol/L are considered severe deficient by our institutional laboratory (7).

STATISTICAL ANALYSIS

Data were retrospectively collected, managed, and analysed. Continuous variables were presented as mean ± standard deviation (SD). Categorical variables were presented as frequency with percentages. One-way ANOVA (with post-hoc Tukey-b test) was used to compare the baseline values and follow-up values of vitamin B12 and MMA.

A subanalysis of baseline vitamin B12 and MMA per type of surgery (sleeve gastrectomy, Roux-en-Y gastric bypass or revisional bariatric surgery) was performed also using the one-way ANOVA test. To analyse the differences in vitamin B12 and MMA levels, the delta was calculated (vitamin B12/MMA follow-up minus vitamin B12/MMA baseline). These data values were also analysed with the one-way ANOVA test.

In all tests, values of $p<0.05$ were considered statistically significant. Statistical Package for Social Sciences (SPSS, Chicago, IL, USA Version 22.0) for Windows was used to prepare the database and for statistical analysis.

10.3 RESULTS

The total patient population consisted of 14 males (22.2%) and 49 women (77.8%) with a mean current body mass index of 30.6 ± 8.0 kg/m². Table 10.2 gives an overview of the other baseline characteristics.

TABLE 10.2. Baseline characteristics (n= 63) (mean ± SD)

Different groups:	3 IM injection regime	5 IM injection regime	No injection regime	P-value
Age (years)	39 ± 11,9	43,5 ± 8,6	44,7 ± 9,0	P = 0,990
Gender (n):				
Male	3	5	6	P = 0,616
Female	18	16	15	
Preoperative body mass index (kg/m²)	43,8 ± 7,6	40,8 ± 6,6	43 ± 6,9	P = 0,368
Current body mass index (kg/m²)*	32,7 ± 12,4	28,8 ± 6,2	30,5 ± 5,5	P = 0,347
Procedures (n):				
Sleeve gastrectomy	10	9	8	P = 0,905
Gastric bypass	8	9	8	
Revision surgery	3	3	5	
Time postoperative (n):				
≤ 1 year	3	2	3	
2 years	9	6	9	
3 years	7	7	5	P = 0,951
4 years	1	3	2	
5 years	1	2	1	
> 5 years	0	1	1	

*Current body mass index measured at different time points postoperative.

Baseline levels and follow-up results showed a significant difference in vitamin B12 ($p < 0.05$) and MMA ($p < 0.05$) after 3 IM injections. However, not all patients improved sufficiently. In 6 patients, MMA levels are not normalized below 300 nmol/L after 3 IM injections. A significant difference was also seen in vitamin B12 ($p < 0.05$) and MMA ($P < 0.05$) after 5 IM injections. MMA levels have been normalized below 300 nmol/L in all patients after 5 IM injections. No significant difference was seen in vitamin B12 ($p = 0.083$) and a significant increase in MMA ($p < 0.05$) was seen without an IM injection regime (table 10.3). Eleven patients had MMA levels between 300 and 430 nmol/L (moderately deficient) and 5 patients had MMA levels above 430 nmol/L (severely deficient) at baseline without IM injection regime. In the follow up, all patients had MMA levels above 300 nmol/L, of which 12 patients had MMA levels > 430 nmol/L without IM injection regime. MMA levels cannot recover spontaneously over time. There is no significant difference in vitamin B12 and MMA levels between 3 groups at baseline. In the follow-up results there is a significant difference in vitamin B12 levels of the 5 IM injection regime compared to the 3 IM injection regime (p= 0.02), 5 IM injection regime compared to no regime (p=0.03) and 3 IM injection regime compared to no regime showed no significant difference (p = 0.64). In the follow-up results there is also a significant decrease in MMA levels of the 5 IM injection regime compared to 3 IM injections (p = 0.02), 5 IM injection regime compared to no regime (p = < 0.001) and 3 IM injection regime compared to no regime (p < 0.01) (Table 10.4).

TABLE 10.3. biochemical effects of the different IM injection regimes and no regime (mean ± SD).

		Baseline	Follow-up	P-value
3 IM injection regime	Vitamin B12	200,0 ± 45,6	332,9 ± 296,5	P = 0,046
	MMA	455,8 ± 168,1	281,7 ± 134,7	P = 0,001
5 IM injection regime	Vitamin B12	200,5 ± 36,0	550,3 ± 451,8	P = 0,002
	MMA	504,0 ± 261,3	181,1 ± 64,5	P = 0,000
No regime	Vitamin B12	226,2 ± 34,6	211,4 ± 37,6	P = 0,083
	MMA	407,1 ± 156,0	514,3 ± 235,9	P = 0,004

IM: intramuscular, MMA: methylmalonic acid

TABLE 10.4. Biochemical effects of vitamin B12 and MMA levels between 3 groups at baseline and follow-up

	3 IM regime	5 IM regime	No regime	P-value
Baseline:				
Vitamin B12	200,0 ± 45,6	200,5 ± 36,0	226,2 ± 34,6	NS
MMA	455,8 ± 168,1	504,0 ± 261,3	407,1 ± 156,0	NS
Follow-up:				
Vitamin B12	332,9 ± 296,5	550,3 ± 451,8	211,4 ± 37,6	*
MMA	281,7 ± 134,7	181,1 ± 64,5	514,3 ± 235,9	**

IM: intramuscular, NS: not significant

*Values of the 5 IM injection regime compared to 3 IM injection regime (p = 0.02), 5 IM injection regime compared no regime (p = 0.003), 3 IM injection regime compared to no regime (p = 0.64)

** Values of the 5 IM injection regime compared to 3 IM injection regime (p= 0.02), 5 IM injection regime compared no regime (p < 0.001), 3 IM injection regime compared to no regime (p < 0.01)

DELTA VITAMIN B12 AND DELTA MMA

Delta vitamin B12 and MMA was determined by the following calculation: "Follow up levels minus baseline values. Table 10.5 shows delta values of vitamin B12 and MMA levels. Vitamin B12 levels are rising faster and MMA levels give a faster decline after the 5 IM injection regime ($p<0.01$).

SUBANALYSIS SLEEVE GASTRECTOMY VERSUS ROUX-EN-Y GASTRIC BYPASS VERSUS REVISIONAL SURGERY

The surgical procedures consisted of 27 patients (42.9%) with a sleeve gastrectomy, 25 patients (39.7%) with a Roux-en-Y gastric bypass and 11 patients (17.5%) with revisional surgery. In the sleeve gastrectomy group, a significant difference in follow-up results of MMA levels was seen in 5 IM injection regime compared to no regime ($p = 0.001$). In the Roux-en-Y gastric bypass group, a significant difference in follow-up results of MMA levels was seen in 3 IM injection regime compared to no regime ($p = 0.005$) and 5 IM injection regime compared to no regime ($p < 0.001$). In the revisional surgery group, a significant difference in baseline vitamin B12 levels was seen in 3 IM injection regime compared to no regime ($p = 0.016$). A significant difference in follow-up MMA levels was seen in 3 and 5 IM injection regime compared to no regime ($p < 0.05$). An overview of differences in baseline and follow-up results of vitamin and MMA levels per surgical procedure are showed in table 10.6.

TABLE 10.5. Delta values of vitamin B12 and MMA levels in the follow-up

	3 IM injection regime	5 IM injection regime	No regime	P-value
Delta vitamin B12	132,9 ± 286,3	349,8 ± 454,6	-14,8 ± 37,1	*
Delta MMA	-174, 1± 193,0	-323,0 ± 276,4	107,2 ± 150,8	**

*Values of 5 IM injection regime significant increase compared to no regimes ($p < 0.01$), values of 5 IM injection regime compared to 3 IM injection regime showed no significant difference ($p=0.082$), values of 3 IM injection regime compared to no regime showed no significant difference ($p = 0.388$).
** Values of 5 IM injection regime showed a significant decrease compared to no regime ($p < 0.01$), values of 5 IM injection regime compared to 3 IM injection regime showed no significant difference ($p = 0.082$), values of 3 IM injection regime compared to no regime showed a significant difference ($P <0.01$).

TABLE 10.6. An overview of differences in baseline and follow-up results of vitamin B12 and MMA levels per surgical procedure.

		3 IM	5IM	No	P-value
Sleeve gastrectomy (n= 27)	**Baseline B12**	198.0 ± 31.6	214.4 ± 27.4	232.5 ± 37.3	NS
	Baseline MMA	463.7 ± 152.7	498.2 ± 123.1	354.5 ± 54.8	NS
	Follow-up B12	357.0 ± 405.9	665.6 ± 507.6	206.3 ± 38.9	NS
	Follow-up MMA	329.3 ± 165.7	188.7 ± 61.3	496.9 ± 177.6	*
Gastric bypass (n= 25)	**Baseline B12**	220.0 ± 57.1	191.1 ± 44.6	230.0 ± 37.8	NS
	Baseline MMA	403.4 ± 80.5	546.6 ± 382.9	351.6 ± 100.2	NS
	Follow-up B12	337.5 ± 184.8	528.4 ± 453.6	220.0 ± 46.6	NS
	Follow-up MMA	238.9 ± 79.6	183.2 ± 77.1	377.0 ± 75.3	**
Revision surgery (n= 11)	**Baseline B12**	153.1 ± 5.8	186.7 ± 20.8	210.0 ± 24.5	***
	Baseline MMA	569.3 ± 352.5	393.7 ± 94.3	579.8 ± 223.5	NS
	Follow-up B12	240.0 ± 45.8	270.0 ± 90.0	206.0 ± 19.5	NS
	Follow-up MMA	237.0 ± 118.5	151.7 ± 35.1	761.8 ± 313.5	****

* No regime compared to 5 IM injection regime ($p = 0.001$), 3 IM injection regime compared to no regime ($p = 0.065$), 3 IM injection regime compared to 5 IM injection regime ($P = 0.132$).
** No regime compared to 3 IM injection regime ($p = 0.005$), no regime compared to 5 IM injection regime ($p < 0.001$), 3 IM injection regime compared to 5 IM injection regime ($p = 0.459$).
*** No regime compared to 3 IM injection regime ($p = 0.016$), No regime compared to 5 IM injection regime ($p = 0.468$), 3 IM injection regime compared to 5 IM injection regime ($p = 1.00$).
**** 3 IM injection regime compared to 5 IM injection regime ($p = 1.00$), no regime compared to 5 IM injection regime ($p = 0.02$), no regime compared to 3 IM injection regime ($p = 0.04$).

10.4 DISCUSSION

This study showed that all patients with a vitamin B12 deficiency recovered well biochemically after 6 months follow up with the 5 IM injection regimen. After the 3 IM injection regimen some patients were still deficient after 6 months follow up. MMA levels cannot recover spontaneously over time without IM injection regime. In revision surgery procedures there was a significant difference in levels vitamin B12 and MMA at baseline in compared to sleeve gastrectomy and Roux-en-Y gastric bypass procedures. This is caused by the slowly depleted body storage of vitamin B12. After revisional surgery, the vitamin B12 storage may already be exhausted which possibly results in faster shortage after revision surgery. This may explain the differences at baseline levels in patients with revision surgery. MMA levels may be increased in renal insufficiency, dehydration and bacterial overgrowth. The intestinal flora produces propionic acid; which is a source of MMA. During antibiotic therapy MMA levels may be lower than normal. Patients suffering from these complaints were not included in this study (13).

According to current literature there is no consensus about the right schedule of IM vitamin B12 injections and the necessity of a loading dose. Table 10.7 gives an overview of the recommended vitamin B12 treatment according to several studies. Only a few studies have a loading dose of vitamin B12 injections in their recommendation. However, our study shows that IM injection regime with loading dose gives better results, in compare to a shorter and monthly regime without loading dose.

LIMITATIONS

Some limitations need to be addressed. First, it is a small-size retrospective cohort study. Second, bariatric patients use different types of vitamin supplements that may have influence on vitamin B12 or MMA values in general. The body's storage of vitamin B12 is approximately 2000 mcg/day in relation to the recommended daily requirement of 2,4 mcg/day. While most vitamin B12 in normal adults is absorbed in the ileum in the presence of IF, approximately 1% of supplemented vitamin B12 will be absorbed passively (by diffusion) along the entire length of the (non-bypassed) intestine after bariatric surgery given a high-dose oral supplement (8). Rhode et al. (11) found that a dosage of 350 - 600 mcg/day of oral vitamin B12 prevented vitamin B12 deficiency in 95% of patients and an oral dose of 500 mcg/day was sufficient to overcome an existing deficiency as reported by Brolin et al. [12] in a similar study. About the recommended amount of vitamin B12 after a sleeve gastrectomy is no consensus in the current available literature. However, a lot of our patients use over-the-counter supplements with a dosage of vitamin B12 of 2,5 or 5 mcg/day, for sleeve and gastric bypass, respectively. The body's storage will be depleted much faster in patients who using over-the-counter supplementation or no supplementation, in compare to patients who using high-dose WLS supplements.

In this study, a much faster and steeper rise in MMA levels was seen in patients who did not take their standard vitamin supplements regardless the injection regime. This is caused by the lack of a daily maintenance dose of vitamin B12 in combination with depleted liver stocks (1). Another important point is de absorption of the IM injections; about 10% of the injected dosage is retained (10).

A difference in follow-up MMA levels was also observed between patients who used high-dose WLS supplements and patients who used over-the-counter supplements. However, the groups of different kinds of supplements is too small to do statistical analysis. Besides that, these data are subjectively and it is unclear if patients take their supplements daily. Third, clinical aspects (complaints of vitamin B12 deficiency) are not included in this study because it is not clear which MMA values correlate with complaints. Despite these limitations, the results of the study have demonstrated that a shorter IM injection regime without loading dose is not sufficient for all patients in order to treat a vitamin B12 deficiency.

TABLE 10.7. Various literature references and their recommended vitamin B12 treatment

References	Conclusion vitamin B12 treatment
Levinson et al., 2013	Intramuscular vitamin B12 1000 mcg monthly or 3000 mcg every six moths
Bordalo et al. 2011	500 mg/day oral or 1000 mg/mol IM or 3000 mg/six monthly IM
Clements et al. 2006	1000 mcg IM every 3 months or intranasal 1000 mcg every week
Jeder et al. 2010	Treatment first phase: 350 mcg/dag oral crystalline B12 Treatment second phase: IM 1000-2000 mcg/2-3 months
Bozkurt et al 2014	350-600 mcg oral vitamin B12 per day is effective in correcting deficiency in 81 to 95% of the patients and IM monthly are another option in patient who have trouble adhering to daily oral supplement
Stacy et al. 2010	Neurologic symptoms: IM 1000 mcg/day for 5 days, followed by 1000 mcg per month. In patients who have had gastric bypass surgery: 1000 mcg IM every 3 months
Aills et al. 2008	Mild malabsorption: oral vitamin cyanocobalamin 500-1000 mcg or IM 1000 mcg daily or every other day for 1 week, then weekly for 4-8 week, and then monthly for life Severe malabsorption: IM 1000 mcg daily or every other day for 1 week, then weekly for 4-8 week, and then monthly for life
Sally et al. 2013.	Patients with severe deficiency should receive injections of 1000 mcg at least several times per week for 1 to 2 weeks, then weekly until clear improvement is shown, followed by monthly injections *

* This article is about a vitamin B12 deficiency in general. Not specifically for patients after bariatric surgery.

10.5 CONCLUSION

In this study, the 3 IM injection schedule without a loading dose is not sufficient to treat a vitamin B12 deficiency. A 5 IM injection regime with loading dose recovered all vitamin B12 deficiencies biochemically. MMA levels cannot recover spontaneously over time without IM injection regime. Compliance of intake of a standard vitamin supplementation and kind supplementation should be considered in decision-making to a certain injection regime. A randomised clinical trial is necessary to investigate different vitamin B12 supplementation regimes to define the most optimal one. Secondly, to examine potential placebo effects of IM vitamin B12 injections and cost effectiveness of the different IM injection regimes.

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11. IMPROVED AND MORE EFFECTIVE ALGORITHMS TO SCREEN FOR NUTRIENT DEFICIENCIES AFTER BARIATRIC SURGERY

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ABSTRACT

Background

Most bariatric guidelines recommend frequent lab monitoring of patients to detect nutrient and vitamin deficiencies as early as possible. The aim of this study was to optimize the cost effectiveness of the nutrient panel, by developing an algorithm, which detects nutrient deficiencies at lower costs.

Methods

In this retrospective study, 2055 patients who had undergone Laparoscopic Roux-Y Gastric Bypass (LRYGB) and Laparoscopic Sleeve Gastrectomy (LSG) surgery at Catharina Hospital Eindhoven between January 2009 and December 2013. Perioperative biochemical measurements (7 days before and 127 days after surgery) and measurements >549 days before surgery were excluded. For analysis, the most recent pre- and postoperative measurements were selected for each biochemical parameter separately. Firstly step the amount of moderate and severe deficiencies were calculated. Secondly, we investigated whether each variable (vitamins A, B_1, B_6, B_{12}, D, folate, ferritin, zinc and magnesium) could predict the presence of deficiency.

Results

In total, 561 (LRYGB) and 831 (LSG) patients had at least pre- and postoperative values of vitamin A, B_1, B_6, B_{12}, D, folate, ferritin, zinc or magnesium. The algorithm reduces vitamin D, B_{12}, B_6, B_1 and ferritin examinations by 15%, 11%, 28%, 28% and 38%, respectively, without missing clinically relevant deficiencies. The corresponding potential cost savings was 14%.

Conclusion

This study identified substantial cost savings in laboratory test for both LRYGB and LSG procedures. The potential cost reduction of 14% might even be increased to 42% when less frequent moderate deficiencies are not screened anymore, while >99.0 of moderate deficiencies will be detected.

11.1 INTRODUCTION

Patients undergoing bariatric surgery are subjected to possible adverse physiological, nutritional and metabolic changes (1). In order to detect these changes as early as possible, most bariatric guidelines recommend frequent monitoring with extensive laboratory panel (2-6). However, the recommended laboratory panels differ in these guidelines. Furthermore, the guidelines sometimes disagree with respect to cut-off levels to detect deficiencies and generally do not specify the corresponding biochemical assays. For example the prevalence of folate deficiency, which can be established in plasma and erythrocytes, varies between 6 and 65% (4).

In our hospital the most performed bariatric surgical procedures are the Laparoscopic Roux-Y Gastric Bypass (LRYGB) and Laparoscopic Sleeve Gastrectomy (LSG). These patients are extensively screened for numerous biochemical parameters including the nutrients/vitamins A, B_1, B_6, B_{12}, D, folate, ferritin, zinc and magnesium. Based on the Dutch national defined prices, the cost of this vitamin/nutrient panel is 72.60 euro. Since, the patient is monitored prior and up to 7 times after surgery the total costs of the follow-up period equals 580.80 euro. Since not all patients develop deficiencies and those who do, usually do not develop all deficiencies simultaneously, not all laboratory tests have clinical consequences. Reliable identification of the patients, which could be screened with less abundant laboratory panels, will result in a reduction of laboratory costs. Secondly, there is increasing governmental pressure to reduce healthcare costs and therefore this study was necessary.

The aim of this study was to optimize the cost effectiveness of the nutrient panel, by developing algorithms, which detect all nutrient deficiencies at lower costs. To develop these algorithms a retrospective analysis was performed on biochemical parameters of all LRYGB and LSG patients in our hospital in the past four years.

11.2 METHODS

DATA SELECTION

Patients who had undergone LRYGB or LSG surgery (n = 2055) at Catharina Hospital Eindhoven between January 2009 and December 2013 with at least one preoperative and one postoperative laboratory examination were included in this retrospective study. Patients who had emergency or revision interventions were excluded. Perioperative biochemical measurements (7 days before and 127 days after surgery) and measurements >549 days before surgery were excluded. For analysis, the most recent pre- and postoperative measurements were selected for each biochemical parameter separately. In total 561 LRYGB and 831 LGS patients were included. The Institutional Review Board approved this study and for this type of study formal patient consent is not required.

ALGORITHM DEVELOPMENT

All of our patients were screened for vitamins A, B_1, B_6, B_{12}, D, folate, ferritin, zinc and magnesium. We were interested whether the costs of lab testing in our center could be reduced. Therefore, the first step was to calculate the amount of moderate and severe deficiencies of the above mentioned (Table 11 S1).

TABLE 11 S1. Overview of the percentages of patients moderately and severe deficient prior and after surgery in LRYGB and LSG group

Variable	Type of surgery	% Moderate deficient preoperative	% Severe deficient preoperative	% Moderate deficient postoperative	% Severe deficient postoperative
Ferritin	LRYGB	20	5.2	16	3.9
	LSG	15	4.8	12	4.7
Folate	LRYGB	20	1.8	7.9	1.2
	LSG	21	2.3	14	2.2
Magnesium	LRYGB	3	0	3.5	0
	LSG	2.4	0	3.9	0
Vitamin A	LRYGB	0	0	0.5	0
	LSG	0	0	0	0
Vitamin B_1	LRYGB	0.2	0.2	0.6	0.2
	LSG	0.3	0.2	1.2	0.3
Vitamin B_6	LRYGB	1.4	0	0.2	0
	LSG	0.9	0	1.2	0
Vitamin B_{12}	LRYGB	7.1	7.1	3.6	3.6
	LSG	6.3	6.3	5.3	5.3
Vitamin D	LRYGB	70	21	22	3.1
	LSG	76	25	23	3.2
Zinc <10.7	LRYGB	22	0	35	0
	LSG	21	0	29	0.2
Zinc <8.4	LRYGB	0.5	0	3	0
	LSG	1	0	2.2	0.2

Abbreviations: LRYGB = Laparoscopic Roux-Y Gastric Bypass, LSG = Laparoscopic Sleeve Gastrectomy

Secondly, we investigated whether each variable (vitamins A, B_1, B_6, B_{12}, D, folate, ferritin, zinc and magnesium) could predict the presence of deficiency. This was done by calculating combination of deficiencies. For example in how many times is there a combined vitamin A and vitamin B_{12} deficiency? Or how many times are folate and vitamin B_{12} deficiencies present before and after surgery? These combinations were made for vitamins A, B_1, B_6, B_{12}, D, folate, ferritin, zinc and magnesium.

SUPPLEMENTATION REGIME

Patients were screened for vitamins A, B_1, B_6, B_{12}, D, folate, ferritin, zinc and magnesium preoperative and 6, 12, 18, 24, 36, 48, 60 months postoperative. Table 11.1 gives an overview of the definitions of deficiencies of the screened vitamins and minerals.

Most studies use one set of cut-off values to define nutrient deficiencies, which usually equals the method-specific lower reference limit (LRL). However, in literature also specific supplementation limits have been defined. Most supplementation limits are lower than LRL. In this study two sets of cut-off values were used to define nutrient deficiencies. Measurements below LRL are defined as moderate deficiencies and measurements below the supplementation limit as severe deficiencies. Only for ferritin and vitamin D the recommended supplementation limit is higher than our LRL.

After bariatric surgery, patients were instructed to take 200% (LRYGB) or 100% (LSG) of the daily recommend dose of vitamins and minerals. Specific nutrient deficiencies were additional supplemented. When iron was <10 nmol/L and ferritin was <20 µg/L ferrofumarate (200 mg) was administered twice a day, in combination with vitamin C (500 mg) once a day. Vitamin D < 50 nmol/L was supplemented with 1 mL colecalciferol (50,000 IU/mL) weekly during the first 4-6 weeks and subsequently monthly. Folate < 6.0 nmol/L was corrected with folic acid (5 mg/day) for 3 months. Vitamin B_{12} <145 pmol/L was supplemented with hydroxycobalamin injections of 500 µg/mL once per two weeks in the first 2 months and once per 3 months afterwards. Vitamin B_1 < 70 nmol/L was supplemented with 50 – 100 mg/day thiamine, for 3 months. There was no standardized supplementation protocol for vitamin A, B_6, magnesium and zinc.

TABLE 11.1. Definitions of moderate and severe deficiencies

	Moderate deficiency		Severe deficiency		Unit
Ferritin	< 30	(8-10)	< 13(□) < 23 (□)	(4, 9, 11-14)	µg/L
Folate (serum)	< 10.4	(10, 15)	< 6.7	(8, 9, 11, 13, 14, 16, 17)	nmol/L
Magnesium (plasma)	< 0.70	(8, 13, 17-19)	< 0.50	(8, 17)	mmol/L
Vitamin A (retinol)	< 0.70	(8, 17)	< 0.35	(8, 17)	µmol/L
Vitamin B_1 (TPP)	< 70	(8)	< 55	(20)	nmol/L
Vitamin B_6 (P5P)	< 35	#	< 20	(4, 8, 16, 17, 20)	nmol/L
Vitamin B_{12} (serum)	< 145	(4, 8, 11, 13, 14, 16, 17, 21)	<145	(4, 8, 11, 13, 14, 16, 17, 21)	pmol/L
Vitamin D (25-OH)*	< 50	(4, 8, 11, 13, 14, 16, 17)	< 25	(8, 10, 11, 13, 17)	nmol/L
Zinc (plasma)*	< 10.7	(8-10, 13, 17, 19)	< 5.0	(17)	µmol/L

Abbreviations: µg/L = microgramme per litre, nmol/L = nanomole per litre, mmol/L = millimole per litre, pmol/L = picomole per litre, µmol/L = micromole per litre

The underlined values are the method specific reference values. * The lower reference values for vitamin D and zinc are 17 nmol/L and 8.4 µmol/L, respectively. However, the cut-off levels 10.7 (zinc) and 50 nmol/L (vitamin D) are the most frequently mentioned levels in literature. #: Operating manual of vitamin B_6, chromosystems. *TPP:* thiamin pyrophosphate, *P5P*: pyrodoxal-5-phosphate.

BIOCHEMICAL ASSAY

The utilised laboratory for our study is certified by the Dutch Association of Clinical Chemistry Labs (CCKL, registration number R0125). Independent clinical chemists did the biochemical analysis of the vitamins and minerals. Vitamin A was determined as retinol in serum with a UPLC-TUV (Waters®) instrument using Repice® reagents. Vitamin B_1 (thiamin pyrophosphate) and vitamin B_6 (pyridoxal-5-phosphate) were determined in EDTA-whole blood with chromosystems® reagents on a UPLC – FLR (Waters®) device. Vitamin D (25-hydroxy vitamin D) was determined in serum by an immunometric competition assay on Liason® using Diasorin® reagents. Vitamin B_{12} (cobalamin) serum, folate serum and ferritin heparin plasma were analyzed by immunometric assays on the cobas E-module Roche®. Magnesium was determined in heparin plasma by a colorimetric endpoint assay on the cobas C-module Roche®. Zinc was determined in plasma on an atomic absorption spectrometer (PerkinElmer®). Reference values are shown in table 11.1.

STATISTICAL ANALYSIS

The pre and postoperative prevalence were analyzed with McNemar test. A p-value < 0.05 was considered as significant. IBM Statistical Package for the Social Sciences 22 (SPSS) was used for statistical analysis. The development of the algorithms was based on prevalence of deficiencies before and after bariatric surgery. For the determination of potential cost reduction and sensitivity, all laboratory values were included of LRYGB and LSG patients and secondly sensitivity analysis was performed used a random effects model. Sensitivity was determined by dividing the percentages of missing deficiencies by all known deficiencies of the biochemical parameter. The potential cost savings were calculated by using Dutch national prices.

11.3 RESULTS

The most common deficiencies were vitamin D, zinc, ferritin, folate and vitamin B_{12} (Figure 11.1). Follow-up ranged from 3 to 84 months postoperative for each nutrient and vitamin determined, with a mean of 32 months. For the development of the algorithms it was important to have an indication of the pre- and postoperative prevalences of deficiencies and the moment a deficiency was established for the first time. Vitamin D, ferritin and folate deficiencies decreased significant after both bariatric surgeries ($p<0.05$). Vitamin B_{12} deficiencies decreased significantly after LRYGB ($p= 0.017$) and not after LSG ($p=0.461$). Using the cut-off value of 10.7μmol/L zinc is the second frequent deficiency and increased after both surgeries ($p< 0.05$). However, when the lower zinc reference value of 8.4 μmol/L was used to define a moderate zinc deficiency, the postoperative prevalences of the zinc deficiency was only 3% and 2% for LRYGB and LSG, respectively. In figure 11.1 the percentages of newly developed deficiencies are shown. Unexpectedly, most deficiencies were already present before surgery. For example, more than 82% of all postoperative vitamin D deficiencies and 64% of ferritin deficiencies were diagnosed prior to surgery. Magnesium, vitamin B_1, B_6 and A deficiencies were rare and the pre and postoperative prevalence of these deficiencies were not significantly different ($p> 0.05$). Moreover, no severe deficiencies were found for these biochemical parameters.

We designed an algorithm for efficient screening for vitamin D deficiencies based on the observation that 1) the majority (82 – 90%) of vitamin D deficiencies are present prior to surgery and 2) that most newly diagnosed post-surgery deficiencies have a preoperative vitamin D sampled in the spring/summer with concentrations between 50 and 70 nmol/L. (27, 28) Therefore, we used the cut-off levels of 50 and 70 nmol/L (for measurements in the periods October – March and April – September, respectively) to determine whether subsequent post-surgery vitamin D measurements were necessary or not (figure 11.2). This algorithm resulted in a 15% reduction of vitamin D measurements at the expense that only 98.5% of the patients were correctly categorized between deficient and not-deficient. Except for two patients, all missed deficiencies (n=37) were moderate deficiencies.

Since folate (B_9) is the most frequent B-vitamin deficiency and is a useful marker for monitoring compliance of vitamin supplementation (7), we designed algorithms for vitamin B_1, B_6 and B_{12} based on the folate concentration in the same order. For the vitamin B_1 algorithm we also include the haemoglobin level to identify the clinically relevant vitamin B_1 deficiencies, which are not captured by the folate concentration alone. (2-7) Using these algorithms 11 – 28% unnecessary B-vitamin measurements could be avoided (see figure 11.2).

Since iron deficiency is reflected in lowered ferritin, MCV and haemoglobin levels, we designed an algorithm based on these parameters to decide whether ferritin testing is necessary or not. When ferritin is only measured when the preoperative ferritin is < 75 µg/L and when MCV < 80 fL or haemoglobin < 8.0 mmol/L, 38% of the ferritin measurements could be avoided without missing clinically relevant iron deficiencies.

By using the algorithms in combination with the exclusion of nutrients from the standard panel (e.g. vitamin A, B_1 and B_6), which have only moderate corresponding deficiencies and, moreover, (very) low prevalences, the potential cost savings are 23 – 42% at the expense of 0.5 – 1.0% missed deficiencies. When only severe deficiencies should be identified the potential cost savings run up to 60% (Table 11.2)

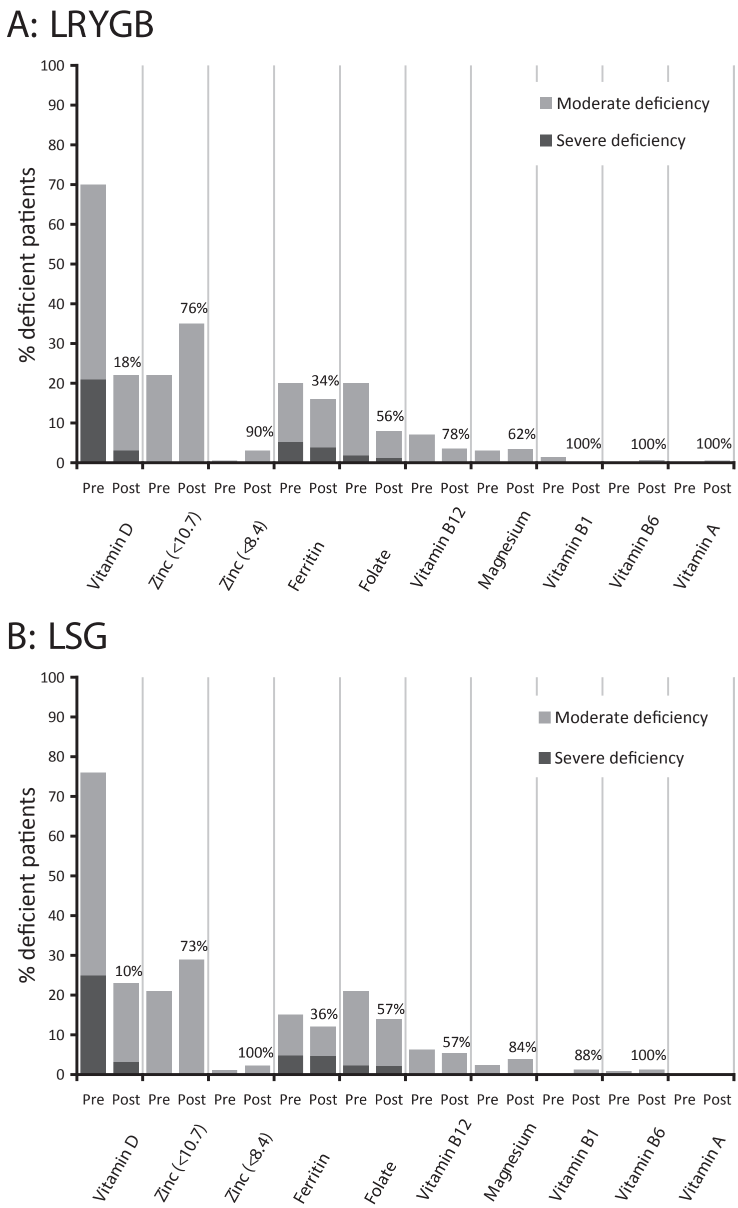

FIGURE 11.1. Pre- and postoperative prevalence of nutrient deficiencies undergoing A) LRYGB or B) LSG.

The bars indicate the total number of moderate deficiencies. The dark grey part represents the severe deficiencies. Mean follow-up ranged from 3 to 84 months. Above the bars the percentage of newly developed deficiencies post surgery are shown.

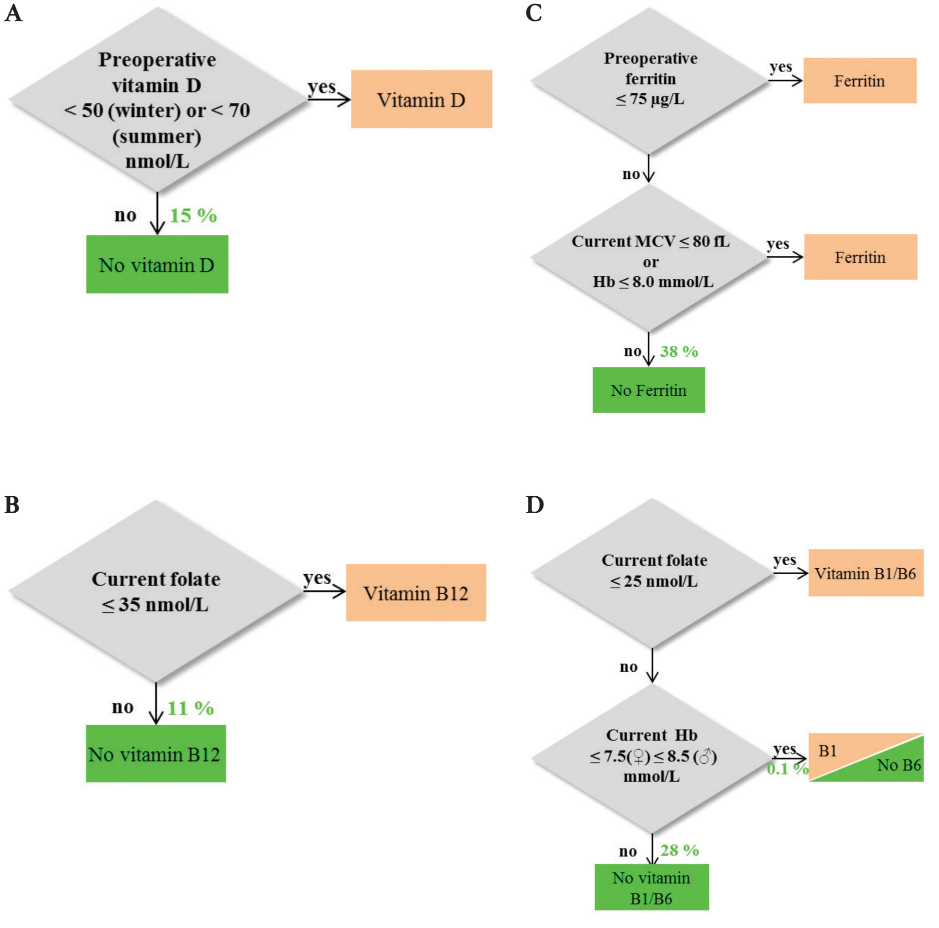

FIGURE 11.2. Algorithms for assessing A) vitamin D, B) vitamin B_{12}, C) ferritin and D) vitamin B_1/B_6 laboratory tests.

The criteria in the decision windows determine whether the corresponding parameter should be measured or not. The green percentage indicates the reduction of measurements. See text for addition information. Vitamin D (50 nmol/L equals 20 ng/ml), folate (35 and 25 nmol/L equals 15 and 11 ng/mL, respectively), ferritin (70 µg/L equals 70 ng/L) Hemoglobin (7.5, 8.0 and 8.5 equals 12, 12.9 and 13.7 g/dL, respectively.)
Hb: hemogloblin, Winter: October – March, summer: April – September

TABLE 11.2. Potential costs savings using the algorithm for A) LRYGB and B) LSG

A: LRYGB	Moderate			Severe		
	Cost (€)	Cost savings		Cost (€)	Cost savings	
Nutrient panel	508	-		508	-	
Algorithm	437	14 %		437	14 %	
99.9 % accuracy	437	14 %		250	51 %	M,A,B6,Z
99.5 % accuracy	388	23 %	B6	201	60 %	M,A,B1,B6,Z
99.0 % accuracy	293	42 %	A,B1,B6	201	60 %	M,A,B1,B6,Z

B: LSG	Moderate			Severe		
	Cost (€)	Cost savings		Cost (€)	Cost savings	
Nutrient panel	508	-		508	-	
Algorithm	437	14 %		437	14 %	
99.9 % accuracy	391	23 %	A	319	37 %	M,A,B6
99.5 % accuracy	391	23 %	A	201	60 %	M,A,B1,B6,Z
99.0 % accuracy	391	23%	A	201	60 %	M,A,B1,6B,Z

Costs are calculated by multiplying the Dutch national defined prices with the vitamins in the 7 phlebotomies post-surgery. The superscript letters indicate which nutrient were excluded from the labpanel, where M= magnesium, A=vitamin A, B_1= vitamin B_1, B_6= vitamin B_6 and Z= zinc.
Abbreviations: LRYGB = Laparoscopic Roux-en-Y Gastric Bypass, LSG = Laparoscopic Sleeve Gastrectomy

11.4 DISCUSSION

This study shows that substantial cost savings are possible in the detection of nutrient deficiencies under a standard supplementation regime after LRYGB and LSG surgery.

In our hospital we introduced one screening panel for both LRYGB and LSG patients, which consist of vitamin A, B_1, B_6, B_{12}, D, folate, ferritine, and magnesium and zinc (2-6). Although, some guidelines also recommend screening for vitamin E and K deficiencies, we did not include these vitamins in the panel, because these deficiencies occur more often after biliopancreatic diversion/ duodenal switch (BPD/ BPD-DS) and are rare after LRYGB and LSG (22). Moreover, vitamin K levels were not useful for patients using anticoagulants for any comorbidity.

In order to correctly recognize nutrient deficiencies, well-established cut-off values are required. However, there is no consensus in bariatric literature. Different cut-off values are used to define deficiencies, frequently without mentioning the matrix (e.g. serum/ plasma or whole blood) or method used (23, 24). The matrix is important since major changes might occur when sampling in different matrices. For example, vitamin B_1/B_6, can both be determined in whole blood or in plasma, where blood values are much higher since approximately 80% of vitamin B_1/B_6 is in the erythrocytes (8). Another example is zinc, where serum zinc levels are generally 5 to 15% higher than plasma values due to osmotic changes in the erythrocytes by the anticoagulant used (17). Specification of the analytical method used, is also important, since nutrients can be measured in different forms. For example vitamin B_1 can be determined as thiamine and as thiamine-pyrophosphate and vitamin A can be measured as retinol, retinal and retinoic acid, each with different reference and cut-off values. Furthermore, commercial nutrient methods are poorly standardized, resulting in differences up to 30% according to the Dutch external quality schemes, even when type of method and matrix are identical. Usage of lower reference values as cut-off value is not ideal to identify deficient patients. Firstly, by definition 2.5% of the healthy persons have values below the LRL and will be unnecessarily supplemented if the LRL is used as cut-off limit. Secondly, poor evidence exists that patients with mild or moderate deficiencies clinically benefit from nutrient supplementation. However, hard cut-off values for nutrient supplementation have been described (table 11.1). To avoid the discussion which cut-off level should be used, we have shown our data using two sets of cut-off values for both moderate and severe deficiencies.

The development of the algorithms was based on the prevalence of deficiencies. The prevalences of deficiencies in LRYGB and LSG patient groups were comparable (Table 11 S1). Therefore the algorithms were developed regardless the type of surgery.

All algorithms, except for the vitamin D algorithm, result in a major decrease in nutrient measurements without missing clinically relevant deficiencies. The percentage of missed vitamin D deficiencies, however, is low and most deficiencies are mild. However, in non-bariatric settings, multiple studies have shown that patients benefit from vitamin D supplementation when plasma levels are below 50 nmol/L. Therefore, one might argue that the algorithm is not clinically useful. On the other hand, 98.5% of the bariatric patients were correctly categorized between deficient and not-deficient, while in the general European population the prevalence of severe vitamin D deficiency (<25 nmol/L) is already 2-30% (25). Furthermore, due to the seasonal changes of vitamin D, in the winter period about half of healthy population have vitamin D levels <50 nmol/L while supplementation is not prescribed. (25, 27, 28) The study performed by Peterson et al., who found comparable results, supports our findings. (26) They found significant malnutrition prior to bariatric surgery in a cohort of 58 patients, especially Vitamin D (92.6% of their cohort was deficient) and Iron (36.2 to 56.9%). (26)

We have not designed an algorithm for zinc, magnesium and vitamin A, since no severe deficiencies are present in our study. Furthermore, none of the patients have magnesium and vitamin A levels below the recommended supplementation limit (8, 17). On the other hand, moderate zinc deficiencies are present depending on the cut-off limits used. According to ASMBS nutrient guideline of 2008 zinc should be supplemented below 10.7 μmol/L, while the LRL of zinc is 9.1 μmol/L. The LRL of our method is 8.4 μmol/L. Using the cut-off value of 10.7 μmol/L will result in unnecessary treatment of 10% of healthy persons, while in the general population persons with similar levels are not supplemented. A limit of 10.7 μmol/L seems therefore inappropriate.

When the prevalence of zinc deficiencies was calculated with the LRL of 8.4 μmol/L, the postoperative zinc deficiency is only 3% for LRYGB and 2% for LSG patients. This is not significantly different from the general population. Severe deficiencies under 5 μmol/L are extremely rare.

Our postulated algorithms result in reduction of laboratory costs of 14% without missing clinically relevant deficiencies, except for vitamin D. Because the prevalences of moderate deficiencies of vitamin A, B_1 and B_6 are relatively low, one might exclude these biochemical parameters from the standard nutrient panel. This will result in an additional cost reduction of 28%. Furthermore, the maximum of 1% missed deficiencies should be placed in perspective, since the prevalence of deficiencies is very high in the morbid obese population in general and the preoperative group in particular. (13, 14) The relative high preoperative prevalence of deficiencies and for some biochemical parameters the relative low percentage of newly developed deficiencies after surgery, suggest that the preoperative patient should be supplemented with higher doses of multivitamins.

LIMITATIONS

Of course, retrospective analyses have their limitations. For example, missing values might occur when labpanels were manually ordered. Furthermore, the adherence of multivitamin supplemention was not monitored. Also the dietary nutrient and vitamin intake might differ between patients after LRYGB and LSG and might result in under- and/or over-reportation of deficiencies in these populations. However in a larger sample retrospective analysis, we were not able to adjust for this confounder. Possibly the cost savings might be higher when only non-compliant persons are screened for deficiencies. Since we have no information about compliance, only prospective studies might determine the true accuracy and reduction in costs.

Secondly, problems arise because of inconsistency in the definition of the deficiency according to several guidelines and lack of consensus of the appropriate way to measure the level of a particular nutrient. Thirdly, this is a single site study and there might be differences in outcomes when our algorithm is used in other laboratories. Our algorithm is only applicable for primary LRYGB and LSG patients (our included study population) and might not be suitable for other bariatric (revisional) procedures. Also we have to consider that our algorithm might not be appropriate for patients >7 years after bariatric surgery. Further validation studies need to determine this.

11.5 CONCLUSION

This study shows that there are substantial cost savings possible in laboratory tests in LRYGB and LSG patients. With our algorithms, 14% of costs might be saved, without missing relevant deficiency. The cost savings can be up to 42%, when biochemical parameters with a low prevalence of nutrient deficiencies are removed from the nutrient panel. In light of our findings we have to take into account that this study has variability in follow-up and this is a single center/laboratory study.

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12. TIME TO GLYCEMIC CONTROL: AN OBSERVATIONAL STUDY OF 3 DIFFERENT OPERATIONS

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ABSTRACT

Background

Medical treatment fails to provide adequate control for many obese patients with type 2 diabetes mellitus (T2DM). A comparative observational study of bariatric procedures was performed to investigate the time at which patients achieve glycemic control within the first 30 postoperative days following sleeve gastrectomy (SG), mini-gastric bypass (MGB), and diverted sleeve gastrectomy with ileal transposition (DSIT).

Methods

Included patients had a body mass index (BMI) ≥30 kg/m^2; T2DM for ≥3 years, HbA_{1C} >7% for ≥3 months, and no significant weight change (>3%) within the prior 3 months. Surgical procedures performed were SG (n=49), MGB (n=93), and DSIT (n=109). The primary endpoint was the day within the first postoperative month on which mean fasting capillary glucose levels reached <126 mg/dL. Multivariate logistic regression analysis was used to identify predictors of glycemic control.

Results

The cohort included 251 patients with a mean BMI of 36.04±5.76 kg/m^2; age, 52.84±8.52 years; T2DM duration, 13.09±7.54 years; HbA_{1C}, 8.82±1.58%. On the morning of surgery, mean fasting plasma glucose was 177.63±51.3 mg/dL; on day 30, 131.35±28.7 mg/dL ($p<0.05$). Mean fasting plasma glucose of <126 mg/dL was reached in the DSIT group (124.36±20.21 mg/dL) on day 29, and in the MGB group (123.61±22.51 mg/dL), on day 30. The SG group did not achieve the target mean capillary glucose level within postoperative 30 days.

Conclusion

During the first postoperative month, glycemic control (<126 mg/dL) was achieved following DSIT and MGB, but not SG. Preoperative BMI and postprandial C-peptide levels were independent predictors of early glycemic control following DSIT.

12.1 INTRODUCTION

Obesity and type 2 diabetes mellitus (T2DM) have become global problems during recent decades. Unfortunately, medical treatment fails to provide adequate glycemic control in obese diabetics (1-5). A growing body of literature shows that bariatric surgery achieves favorable metabolic outcomes, is associated with a reduction in cardiovascular events and mortality, and can provide effective treatment for T2DM in obese patients (6-16). Bariatric surgical outcomes include improved glycemic control, reduction of required medications, fewer complications, remission of T2DM, and prevention of diabetes in non-diabetic patients (17). However, T2DM is a heterogeneous and dynamic disease. Despite evidence that glycemic control is achieved rapidly following bariatric surgery (sometimes within days), its relationship to a low-calorie perioperative diet and to weight loss is not linear (18,19).

Although diabetes remission after bariatric surgery is a well-recognized phenomenon, evidence reporting the time frame of remission is sparse, as is the best means of managing diabetes in patients who do not experience rapid remission. Briatore and Scopinaro and colleagues and Fenske et al have reported on treatments with insulin analogues that produced a long-lasting effect for up to one year (11-13). This effect may be explained by the period of pancreatic regeneration stimulated in the early postoperative period. A healthy glucose environment is beneficial for beta cell function not only in the short, but also in the long term.

Our group investigated the glycemic regulation patterns of type 2 diabetics following 3 different surgical procedures. Postoperative glucose levels were measured twice a day by patients treated by either sleeve gastrectomy (SG), mini-gastric bypass (MGB), or diverted sleeve gastrectomy with ileal transposition (DSIT). Short-term diabetic outcomes could be examined in a mainly restrictive (SG) and mainly malabsorptive (MGB) procedure, as well as in a novel surgical technique with combined effects but without significant malabsorption (DSIT). DSIT is a relatively new metabolic surgical procedure that has been shown to be effective for diabetes control in lower BMIs, with favorable nutritional outcomes. It is associated with high rates of diabetes remission and a marked decrease in the use of medications after one year (14).

We report findings of a retrospective comparative observational study to investigate the time required for patients to achieve glycemic control after three different surgical options within the first 30 postoperative days. The association of glycemic control with patterns of weight loss in these groups was also analyzed.

12.2 METHODS

STUDY DESIGN

The independent ethics committee of our Institutional Review Board approved this prospective comparative cohort study (14/10/2011, no. 08/2011). The study took place between November 2011 and March 2015. This study was designed in accordance with our Center of Excellence in Bariatric and Metabolic Surgery guidelines and followed principles of the Declaration of Helsinki and Good Clinical Practices. Patients were informed about the purpose of the study and gave informed consent prior to surgery. The study was conducted according to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement. Diagnosis of T2DM was established based on the criteria of the American Diabetes Association (15). Study design was based on the retrospective analysis of prospectively collected data from patient follow-up charts.

INCLUSION CRITERIA

Inclusion criteria for surgery were: duration of T2DM under continuous medical treatment for at least 3 years, HbA_{1C} >7% for more than 3 months, weight stability (defined as no significant change [>3%] within the prior 3 months), and body mass index (BMI) ≥30 kg/m^2. Specific inclusion criterion for the present study was a fasting glucose level <200 mg/dL during the hospital stay, before discharge. All patients received oral and written information about the surgical options, and decisions were made with the medical team. CONSORT diagram that demonstrates patient flow is presented in Figure 12.1.

EXCLUSION CRITERIA

Patients were excluded from surgical treatment if they had a fasting C-peptide level <0.5 ng/mL or anti-GAD positivity. Other exclusion criteria included: previous major gastrointestinal surgery, pregnancy, intolerance to anesthesia, severe eating problems, and/or the use of psychopharmacological drugs for eating problems. Patients requiring oral anti-diabetic and/or insulin treatment during discharge were excluded from the present study.

OUTCOME MEASURES

The numbers of patients in SG, MGB, and DSIT groups were 49 (19.5%), 93 (37.1%), and 109 (43.4%), respectively. Age, BMI, HbA_{1C}, fructosamine, one-month weight loss, fasting and one-hour postprandial plasma, C-peptide, and total insulin levels of all patients were measured and recorded. For this purpose, all patients when presenting for the first time underwent a one-hour mixed-meal tolerance test. High-density lipoprototein (HDL), low-density lipoprotein (LDL), triglycerides (TG), comorbidities, and T2DM duration were also examined. During their stay in the hospital, blood glucose levels were measured in the morning (before breakfast) and night (before dinner), and weight was measured during the fasting state in the morning and recorded. Weight was measured by the nursing staff (not self-reported). Normoglycemia was defined as fasting plasma glucose ≤126 mg/dL without medication.

PATIENT CARE

Patients received the same preoperative preparation, including two days of liquid diet and hospitalization the day before surgery. Discharged patients were given forms for post-operative follow-up (Figure 12.4). Their glucometer calibrations were controlled before discharge. Patients were asked to record their blood glucose levels, blood pressure levels and weight during the fasting state in the morning, and also in the evening, and to bring the forms with them to the first month control visit.

STATISTICAL ANALYSIS

Statistical analyses were performed using SPSS software (IBM SPSS Statistics, ver. 19, Somers, NY, USA). Data for continuous variables are presented as means ± standard deviations, and categorical variables as frequencies or percentages. Differences in the baseline values of surgery types were analyzed using analysis of variance (ANOVA) followed by Tukey's HSD test, as appropriate. Multivariate logistic regression analysis was used to determine the independent relationships between surgery type and changes in weight and plasma glucose levels. P values <0.05 were considered statistically significant.

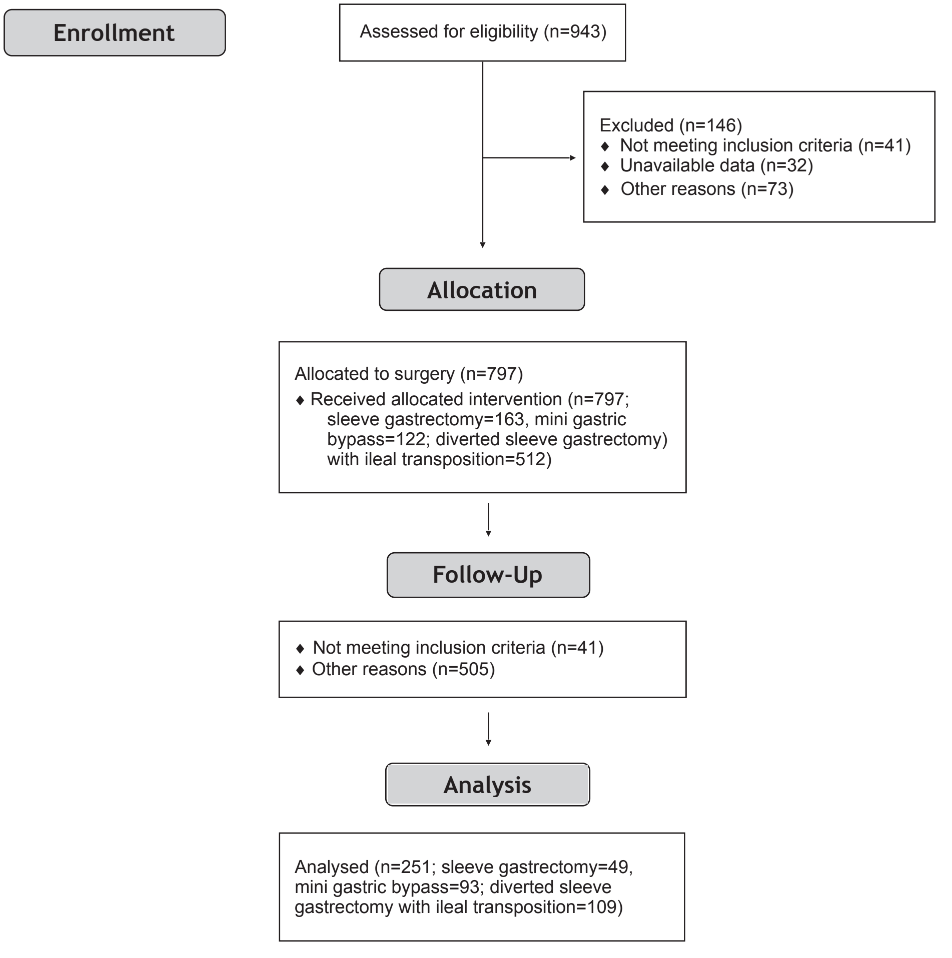

FIGURE 12.1: CONSORT flow diagram for recruitment of patients in this study

12.3 RESULTS

The study groups consisted of 251 patients (111 females, 140 males) with a mean age of 52.84 ± 8.52 years and a mean preoperative BMI of 36.04 ± 5.76 kg/m^2. All patients had poorly controlled diabetes as shown by a mean HbA_{1C} of 8.82 ± 1.58%, and a mean fructosamine level of 324.2 ± 69.95 (μmol/L). Mean diabetic duration was 13.1 ± 7.54 years.

All patients had T2DM, demonstrated by mean fasting C-peptide of 2.69 ± 1.09 ng/ml and mean postprandial C-peptide of 3.94 ± 1.84 ng/ml. Mean fasting and postprandial plasma insulin levels were 19.12 ± 23.3, and 36 ± 34.16, respectively. Hypertension, as defined by values exceeding 140/90 mm Hg, was noted in 145 individuals (57.8%). Mean levels of total cholesterol, HDL cholesterol, LDL cholesterol, and triglyceride were 212.16 ± 47.82, 40.58 ± 13.14, 132.32 ± 36.49, and 223.44 ± 180.87 mg/dL, respectively. Mean weight loss during the first month was 12.23 ± 4.74 kilograms. Table 12.1 provides an overview of baseline characteristics.

TABLE 12.1. Baseline parameters of surgery groups ([a] and [b] refer to statistical significance)

	DSIT (mean±SD)	SG (mean±SD)	MGB (mean±SD)	*P-value*
Age (years)	51.89±8.4	54.2±8.2	53.23±8.78	0.247
BMI	33.98±4.81[a]	39.32±6.87[b]	36.72±5.2[c]	**<0.001**
First month weight loss (kg)	12.17±3.9	13.22±7.39	11.56±3.35	0.249
HbA_{1C} (%)	9.09±1.73[a]	8.24±1.71[b]	8.82±1,23[ab]	**0.007**
Fructosamine (μmol/l)	343.69±63.13[a]	300.71±80.9[b]	313,72±65.94[b]	**<0.001**
Fasting C-peptide (ng/ml)	2.49±0.8[a]	3.35±1.51[b]	2.57±0.99[a]	**<0.001**
Postprandial C peptide (ng/ml)	3.57±1.13[a]	5.39±2.81[b]	3.61±1.48[a]	<0.001
Δ C-peptide (ng/ml)	1.12±0.28	2.09±0.97	1.24±0.56	**<0.001**
Fasting insulin (IU)	15.04±9.46[a]	21.72±18.71[ab]	22.54±33.94[b]	**0.049**
Postprandial insulin (IU)	30.33±20.01[a]	51.46±43.96[b]	34.5±39.04[a]	**0.001**
Δ Insulin (IU)	14.93± 11.05	28.16±20.44	18.27±9.12	<0.001
Total cholesterol (mg/dl)	213.52±52.25	209.04±44.24	212.21±44.5	0.863
HDL (mg/dl)	39.71±8.4	39.5±11.53	42.17±17.69	0.340
LDL (mg/dl)	133.42±38.66	127.52±33.37	133.54±35.59	0.593
Triglyceride (mg/dl)	237.16±221.91	227.78±185.07	205.07±112.44	0.448
Vitamin D (ng/ml)	12.79±9.23	11.86±7.63	13.42±7.71	0.569
Diabetes duration (years)	12.99±6.54[a]	10.87±6.75[b]	15.12±9.46[b]	**0.024**

DSIT = Diverted sleeve gastrectomy with ileal transposition; SG = Sleeve gastrectomy; MGB = Mini-gastric bypass; BMI = Body mass index; HbA_{1C} = Hemoglobin A_{1C},; HDL = High-density lipoprotein; LDL = Low-density lipoprotein.

a-b-c: Different superscripts indicate statistically significant difference. Groups having the same superscripts are associated with similar results.

TABLE 12.2: Type of medications used in all groups before surgery

Medication	DSIT (n= 109)	SG (n= 49)	MGB (n= 93)
OAD only	21 (19.2%)	28 (57.1%)	17 (18.3%)
Insulin only	17 (15.6%)	4 (8.2%)	9 (9.7%)
OAD + insulin	71(65.2%)	17 (34.7%)	67 (72%)

DSIT = Diverted sleeve gastrectomy with ileal transposition; SG = Sleeve gastrectomy; MGB = Mini-gastric bypass.
80.8% of patients in DSIT, 42.9% of patients in SG, and 81.7% of patients in MGB group were using insulin with/without oral antidiabetics (OAD) ($p<0.001$ for SG vs. MGB and DSIT, $p=0.426$ for DSIT vs. MGB). Note: 1 patient in the DSIT, and 4 patients in the MGB group were using OAD + insulin + GLP-1 analogue (Liraglutide).

GLYCEMIC CONTROL AFTER SURGERY

Group analysis showed that 13 of 109 patients (11.92%) undergoing DSIT, 16 of 93 patients (17.2%) undergoing MGB, and 11 of 49 patients (22.44%) undergoing SG had normal plasma glucose levels on the morning of surgery. On postoperative day 30; 81 of 109 patients (74.31%) treated by DSIT, 66 of 93 patients (70.96%) treated by MGB, and 29 of 49 patients (59.18%) treated by SG had normal glucose levels (<126 mg/dL) at least once, within 30 days after surgery. Graphical demonstration of the percentage of patients reaching normoglycemia, comparing the first and 30th days is shown in Figure 12.2.

Figure 12.3 provides an overview of the daily (morning/evening) glucose measurements in the first 30 days after surgery. On the first day after surgery, 40 patients (15.93%), and on the 30th day, 176 patients (70.11%), achieved normoglycemia defined as a blood glucose level of ≤126 mg/dL. The mean plasma glucose level of all patients was 177.63 ± 51.3 mg/dL on the morning of surgery, and 131.35 ± 28.7 mg/dL on postoperative day 30. When type of surgery was assessed, the SG group never achieved a mean plasma glucose level <126 mg/dL. Although 29 of 49 patients (59.18%) in this group had blood glucose level <126 mg/dl, at least once during this period, the average glucose value remained above 126 mg/dl.

The lowest mean fasting plasma glucose level in the SG group was 132.84±42.4 mg/dL, occurring on the 30th day. A mean fasting plasma glucose level of <126 mg/dL was achieved on the evening of day 29 for DSIT (124.36 ± 20.21 mg/dL), and on the evening of day 30 for MGB (123.61 ± 22.51 mg/dL).

MULTIVARIATE ANALYSIS

Multivariate logistic regression analysis was used to determine the independent relationship between surgery type and changes in weight and plasma glucose levels. When performing a multivariate logistic regression analysis on glycemic control after DSIT (compared with the

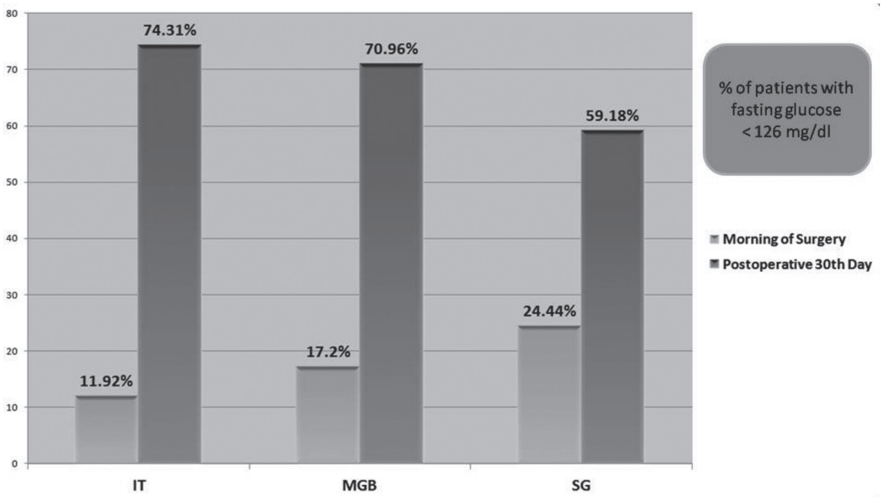

FIGURE 12.2. Percentage of patients who achieved normoglycemia.

(blood glucose level ≤ 126 mg/dL) with different surgical modalities, both on the morning of surgery and on POD 30 Patients treated by DSIT had the highest rate of glycemic improvement, followed by MGB and SG. In the SG group, 29 of 49 patients (59.18%) had blood glucose level <126 mg/dl, at least once during this period. However, the average glucose value for this group persisted above 126 mg/dl.

DSIT = Diverted sleeve gastrectomy with ileal transposition; MGB = Mini-gastric bypass; SG = Sleeve gastrectomy.

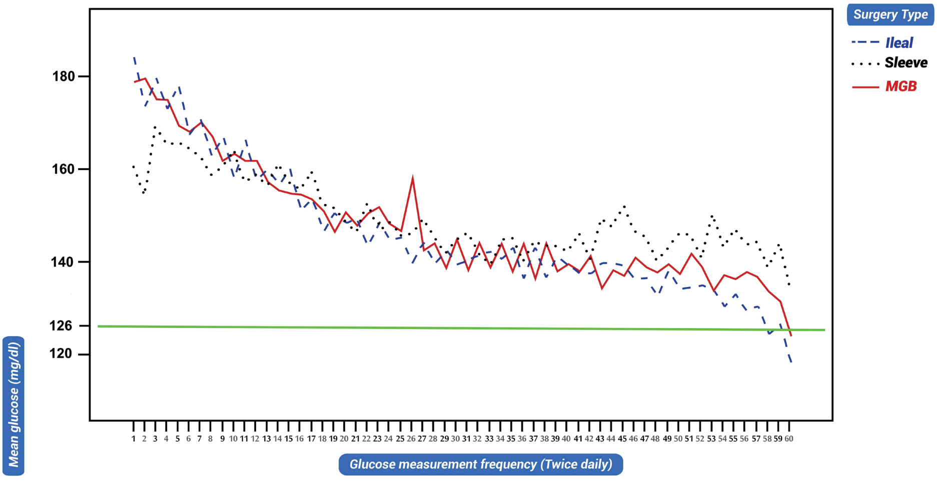

FIGURE 12.3. Daily follow-up mean glycemic level in all groups.

Horizontal green line indicates normoglycemia (126 mg/dl). Duplicate measures per day were obtained in all groups. Glucose levels were significantly lower in the SG compared to DSIT and MGB groups (SG, 161.82 ± 44.2 mg/dL; DSIT, 183.97 ± 47.39 mg/dL; MGB, 178.52 ± 57.58 mg/dL) on postoperative Day 1. Starting from day 27, DSIT and MGB groups experienced significantly lower glucose levels compared to the SG group. Within the first 30 days, the DSIT and MGB groups had mean glucose levels <126 mg/dL. Group effect: $p=0.828$; Time effect: $p<0.001$; Group x Time effect: $p<0.001$. Repeated measures ANOVA.

SG group as reference), preoperative BMI (OR = 0.855; 95% CI [0.753 – 0.957]; p = 0.003) and postprandial C-peptide (OR = 0.542; 95% CI [-0.036 - 1.120]; p = 0.038) were found to be independent predictors for glycemic control after surgery. When performing a multivariate logistic regression analysis on glycemic control after MGB (compared with the SG group as reference), no significant independent predictors were found.

Patient Follow-up Chart

Name and Surname: Starting Date: / / 20

Day	Fasting Blood Sugar (Morning)	Fasting Blood Sugar (Evening)	Weight	Blood Pressure (Morning)	Daily Water Intake	Number of Urination	Breakfast + Snack	Lunch + Snack	Dinner + Snack
1									
2									
3									
4									
5									
6									
7									
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FIGURE 12.4. Postoperative follow-up chart

12.4 DISCUSSION

In the present study, we aimed to analyze how soon patients achieve glycemic control after different bariatric surgical options. Our results demonstrated that the SG group did not achieve a mean fasting plasma glucose level <126 mg/dL within the first 30 postoperative days. A mean plasma glucose level below 126 mg/dL was achieved on postoperative day 29 for DSIT and on postoperative day 30 for MGB. Also, multivariate logistic regression analysis identified preoperative BMI and postprandial C-peptide in the DSIT group as independent predictors for postoperative glycemic control. To our knowledge, this is the first study to compare short-term (first 30 days) glycemic control in three different types of surgery (DSIT, MGB and SG).

Many studies have investigated the metabolic outcomes of surgical treatment, but most have not focused on the short-term glycemic changes in obese T2DM patients with relatively newer surgical procedures such as DSIT (16,17) and MGB (18). A recent systematic review and meta-analysis investigated whether remission of T2DM depends on the surgical procedure or BMI. The authors had three main findings regarding anthropometric variables: *i*) bariatric surgery improves T2DM to the same extent in patients with a BMI of greater versus less than 35 kg/m^2, *ii*) improvement in HbA_{1C} was independent of baseline BMI, and *iii*) improvement in HbA_{1C} was inversely related to waist circumference (19). In the current study, preoperative BMI was found to be an independent predictor of glycemic control in patients after the DSIT. According to the same article, biliopancreatic diversion with a duodenal switch (BPDDS) had the strongest effect on diabetic remission (89%), followed by Roux-en-Y gastric bypass (RYGB) (77%); whereas, both SG and laparoscopic adjustable gastric banding (LAGB) had similar remission rates (60% and 62%, respectively) (19). The effects of BPDDS and RYGB on diabetic remission were also confirmed by a systematic review and meta-analysis conducted by Buchwald et al (6).

As reported by Fried et al in an integrative review of metabolic surgery for the treatment of T2DM in patients with BMI <35 kg/m^2, the resulting excessive weight loss was clinically meaningful, but not drastic (from a BMI of 29.4 to 24.2 kg/m^2). In spite of that, 85.3% of patients were free off T2DM medications and had a fasting plasma glucose level and HbA_{1C} approaching normal values. In a subgroup analysis, the authors found that BMI reduction and T2DM resolution were the greatest in malabsorptive procedures (20).

These results show that restrictive gastric procedures have lower diabetic remission rates than the procedures involving intestinal diversion in the long run. Also, procedures based on intestinal re-routing of the distal ileum provided more effective control than RYGB. In our study, both DSIT and MGB provided more effective glycemic control than SG despite yielding lower excessive weight loss than SG.

As an explanation of these results, the pathophysiology of T2DM may be revisited: Excessive weight and adipotoxicity issues are suggestive as only a single group of mechanisms leading to T2DM. In the novel paper, by De Fronzo, eight mechanisms have been pointed out to regulate the natural progression of T2DM, and among those, incretin resistance / insufficiency and alpha cells (glucagon activity) play major roles (21). In our study, we found that better glycemic control was achieved with intestinal re-routing procedures added to a mechanical restriction despite less excessive weight loss. Our findings may be reflecting the role of incretins and alpha cells.

In a population-based cohort study performed by Yska et al, T2DM remission rates after bariatric surgery were compared with those of a matched control group receiving medical therapy. Per 1,000 person-years, 94.5 T2DM remissions were found in the surgical group, compared with 4.9 in the control group. The surgical group of patients had an 18-fold increased chance of T2DM remission, compared with matched controls. The greatest effect was observed in RYGB patients (adjusted RR = 43.1), followed by SG (adjusted RR = 16.6) and gastric banding (adjusted RR = 6.9) [22]. These findings were further supported in studies by Zanghelini et al and Gagner, et al (23-26).

The efficiency of surgical options based on mechanical restriction depends mainly on weight loss, which is expected to exert a positive effect on glycemic control. But, according to meta-analysis results, clinical success seems to be limited with surgical procedures like SG and LAGB, which are based on mechanical restriction. Long-term results obtained from diabetic patients who underwent SG showed that diabetic remission rates deteriorated in time, approaching 20% in five-year follow-up (27).

Major metabolic operations such as BPD, BPDDS, RYGB, duodenal-jejunal bypass (DJB) and IT are known for rapid postoperative glycemic control (28). Procedures based on intestinal re-routing of ileum, like BPD, have documented effects on reduction of hyperglycemia and improvement of insulin sensitivity as early as one month after surgery (29). RYGB, which is another type of metabolic surgery, promotes rapid improvement in T2DM irrespective of weight loss. Elevations in postprandial GLP-1 have been shown to be the triggering factors for increased insulin production within one week after surgery (30), and improved oral glucose tolerance one month after surgery (31).

A paucity of literature exists regarding T2DM remission after MGB. Musella et al. conducted a comparative study of MGB and SG in terms of T2DM remission. They found that T2DM was in remission in 85.4% of the MGB patients and 60.9% of SG patients in the first postoperative year ($p<0.001$) (32). High diabetic remission rates after MGB have been confirmed in a study by Kular et al (18).

The DSIT is a relatively new surgical procedure with promising outcomes. In a recent report, our group demonstrated that, at one year following surgery, DSIT had good metabolic outcomes in terms of T2DM remission, with a significant decrease in HbA_{1C}, from 9.24% to 6.14% (17), and with a significant reduction in diabetic medication costs (14).

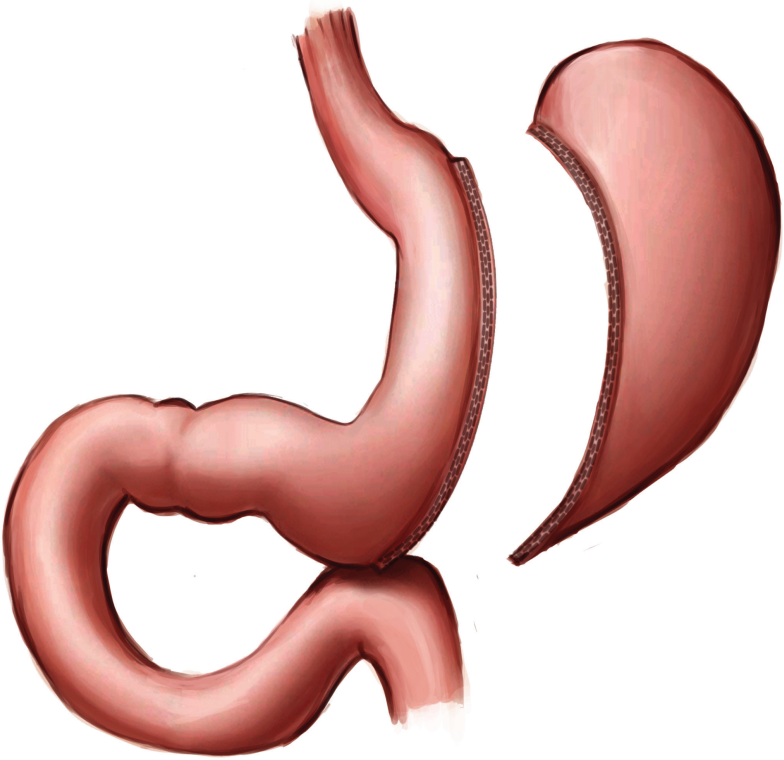
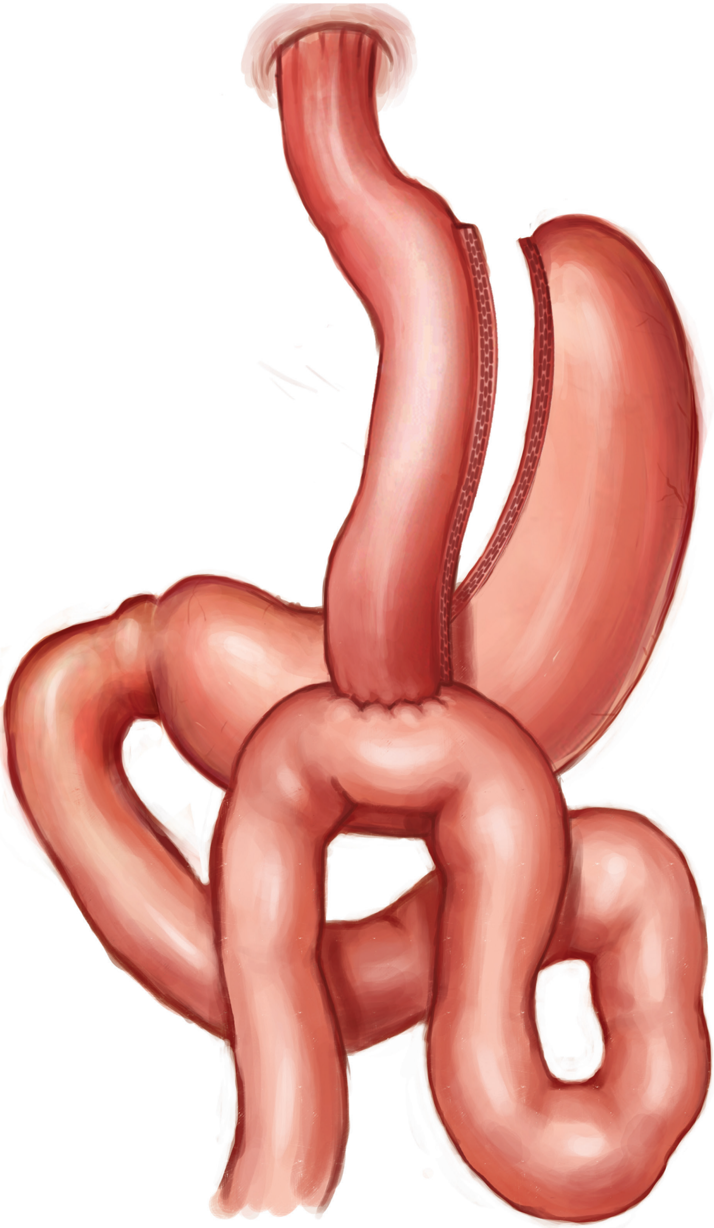
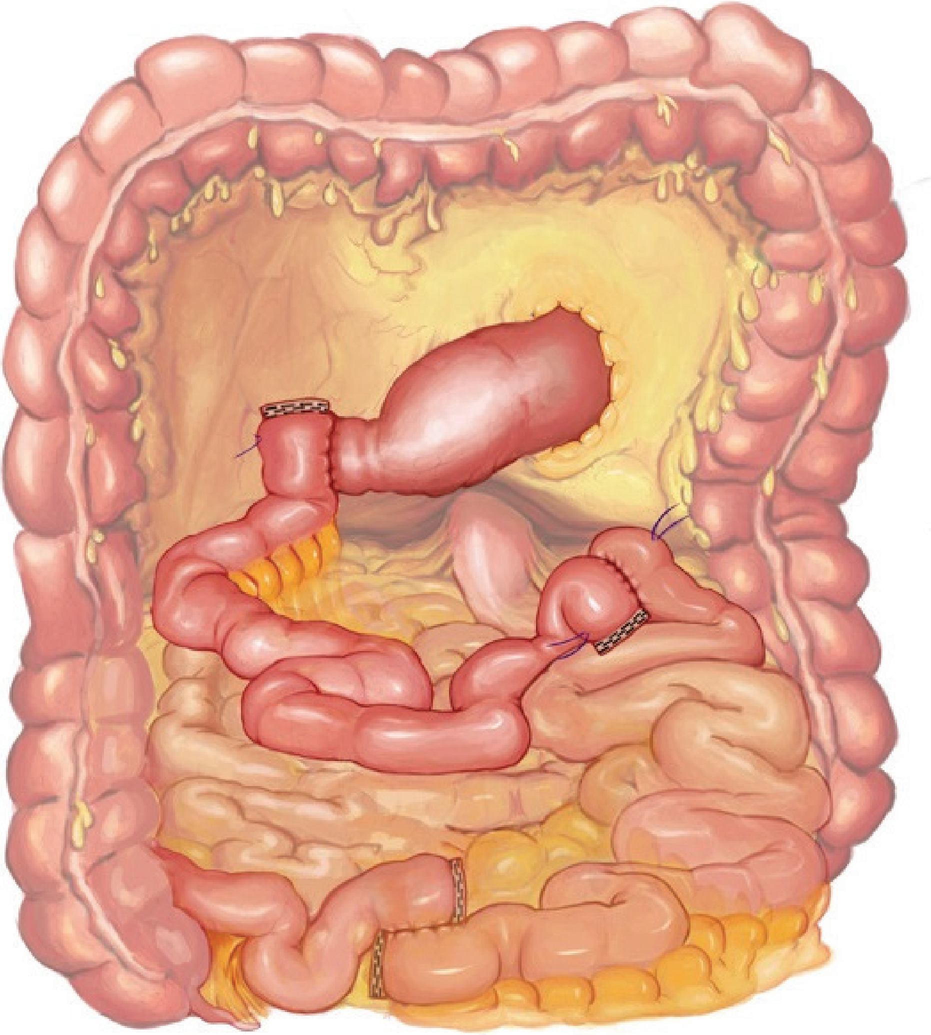


FIGURE 12.5. Types of included surgical procedures. **A: Sleeve gastrectomy**



B: Mini Gastric Bypass (MGB)



C: Diverted Sleeve Gastrectomy and ileum transposition (DSIT)

Results of the current study demonstrated that, initially, the SG group had a markedly lower mean fasting glucose level on the morning of surgery. This outcome might result from lower HbA_{1C} and fructosamine levels, higher fasting, postprandial and Δ C-peptide, and insulin values, demonstrating a slightly lower disease severity, and better beta cell functions in this group. Furthermore, the rate of SG insulin users was markedly lower than that of the DSIT and MGB groups (42.9% vs. 80.8% and 81.7%), (Table 12.2). Despite these differences in baseline characteristics, the degree of weight loss was similar in all groups. While statistically not significant, the SG group had the highest level of weight loss. But, the change in plasma glucose levels was the lowest in the same group. The DSIT and MGB groups had almost identical weight loss patterns, but disease severity and beta cell functions were markedly better in the MGB group. Although the baseline characteristics reflected a higher disease severity and patients had a lower mean BMI in the DSIT group, the mean glucose level showed better improvement. Duodenal exclusion was performed in both DSIT and MGB groups. The distinctive efficiency in the DSIT group may be due to the early contact of food with ileal mucosa, and a more potent activation of the ileal hormones.

At the end of first month, 29 of 49 patients that underwent SG had blood glucose level <126 mg/dl at least once in the postoperative period. However, the average glucose value for the group persisted above 126 mg/dl. Therefore, it would be better to mention an improvement in glycemia rather than a frank glycemic control.

Apart from the type of surgical method, several scoring systems have been used to predict T2DM remission after bariatric surgery. The Dia-Rem score, for instance, includes factors such as insulin use, age, HbA_{1C} and type of antidiabetic medication (33). In another report, a diagnostic system that includes recent T2DM diagnosis, absence of insulin therapy regardless of weight loss, and definition of the remission were employed as the main predictors (34). The ABCD score (Age, BMI, C-peptide, duration) and weight loss have been reported to have a major influence on the outcomes (35). Although these scoring systems are used to determine long-term diabetic remission rates, when adapted to the current cohort of patients, there was no difference in age. The remaining determinants of diabetic remission favored SG, followed by MGB, and DSIT. Despite this fact, we observed better glycemic control in the DSIT group, followed by MGB, and SG.

This study has some limitations. First, the criteria for T2DM remission are quite different among different countries and also among other studies investigating T2DM remission after bariatric surgery. These definitions range from simple withdrawal of diabetes medication to fasting glucose levels <100 mg/dL or <126 mg/dL and/or final levels of HbA_{1C} ranging from <6% to <7% (6,15,19). Such different definitions can create bias in interpreting results. A second limitation was that blood glucose controls were performed with a glucometer (glucose [mg/dL] = 0.102 + [19.295 X capillary blood glucose (mg/dL) / 18]) in accord with International

Federation of Clinical Chemistry and Laboratory Medicine (IFCC) recommendations for devices measuring glucose levels in capillary blood samples after calibrated to plasma glucose levels.

Even though the calibrations of the devices used by the patients were controlled prior to their discharge, patient- or device-related errors could occur. Also, patients checked their weight at home using their own scales; biases related to this variable may have occurred. To minimize this, patients were weighed before surgery and on the same day of their control visit with the same scales, while their weight on the discharge was written on their charts as the baseline. For some patients with poorly controlled DM, poor glycemic control can be attributed to suboptimal glucose monitoring and treatment (Reviewer #3, comment #2). Furthermore, differences between initial BMI and oral/insulin dependent mix values in different groups and lack of long term follow-up may bring about remarkable restrictions on our results.

The sleeve gastrectomy patients in the present study had the lowest Hb A1c levels, despite the highest average BMI values initially. This may indicate that their compliance might be better before surgery and in such a case, this may be another factor which may influence our results. Notwithstanding these potential limitations, we observed the highest improvement of glucose levels in the DSIT group. Initially, this group had the highest mean glucose levels, but by the end of the 30^{th} day, they presented the lowest levels of mean blood glucose. A similar outcome was also evident for the MGB group. Since the mean number of manipulations and the procedure time were higher in the DSIT group, this group might also have had a greater inflammatory reaction and exaggerated surgical stress hormones. Although we did not evaluate the levels of these hormones, it is possible that restoration of the incretin effect due to intestinal re-routing might have been delayed, causing their effects to manifest by the end of the fourth week.

12.5 CONCLUSION

In conclusion, in this study, we observed differences in glycemic control following three types of surgery within the first 30 postoperative days. Patients in the sleeve gastrectomy group did not achieve a mean plasma glucose level <126 mg/dL. Mean plasma glucose levels <126 mg/dL were achieved on the evening of day 29 following diverted sleeve gastrectomy with ileal transposition, and on the evening of day 30 after the mini-gastric bypass. Multivariate logistic regression analysis identified preoperative BMI and postprandial C-peptide as independent predictors of postoperative glycemic control in the diverted sleeve gastrectomy with ileal transposition group. Intestinal rearrangement may provide an important component of diabetes control following bariatric surgery. Weight loss was not the only or perhaps primary contributor to early achievement of glycemic control. More research on this topic is needed.

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13. SUMMARY, DISCUSSION AND FUTURE PERSPECTIVES

Walter Pories made game-changing statements in 1992 (1) and 1995 (2). He suggested that bariatric surgery has more beneficial effects than solely weight loss. The statement that type 2 diabetes mellitus (T2DM) might be a surgical disease was a visionary one during that time. (1) By now the benefits of bariatric surgery for cardiovascular, pulmonary and metabolic diseases can be added. (3-7) The purpose of this thesis was to provide more insight in perioperative cardiopulmonary and metabolic physiology in bariatric surgery.

PART I: CARDIAC AND PULMONARY PHYSIOLOGY

An overview of the current literature about cardiac structure and function changes before and after bariatric surgery is provided in Chapter 2. In summary, irrespective of the type of bariatric surgical procedure, it seems that bariatric surgery is beneficial for myocardial structure, systolic and diastolic function. (8) Pre-existing hypertension and left ventricular hypertrophy seem to be a prerequisite for reverse remodelling after bariatric surgery. However the question remains whether cardiac pathology can be considered an indication for bariatric surgery. According to the guidelines of the International Federation of Surgery for Obesity and Metabolic disorders (9) cardiac pathology solely is not an indication for bariatric surgery, but several case series have demonstrated the positive effect of bariatric surgery on left ventricular ejection fraction (LVEF) and the New York Heart Association functional class (of heart failure). (10-14) Ristow et al. (15) reported on two patients who no longer required heart transplantation after successful weight reduction and improvement of LVEF.

The responsible mechanism(s) of cardiovascular changes after bariatric surgery are not fully clarified. (8) There might be a combination of weight-dependent (e.g. weight loss, circulating volume) and also weight-independent mechanisms (inotropic hormones, like GLP-1) that induce cardiac remodelling. This includes that there is a possibility of direct gut hormonal inotropic action on the myocardium through an enterocardiac axis. (8, 16) Manipulation of enteric gut hormones has been shown to have beneficial effects on cardiovascular function through the enterocardiac axis. (16, 17) The classical hemodynamic weight-dependent effect of bariatric surgery is no longer thought to be the only one responsible for reverse remodelling seen after bariatric surgery, as the beneficial effects can be independent from changes in blood pressure. (18, 19) Although these mechanisms are only understood partially, changes in blood pressure (e.g. remission of hypertension) can be beneficial for the burden of disease.

Hypertension, one of criteria for the metabolic syndrome, is a major contributor for the development of congestive heart failure. (20) In assessing the blood pressure (BP) of obese subjects several challenges exist. Nowadays, we have the standard auscultatory sphygmomanometry, widely used in clinical practice, based on the principles of Riva-Rocci/

Korotkoff (RRK). (21) However, RRK BP measurements can lead an overestimation of the BP of obese patients due to the cuff size and the circumference of the upper arm. (22, 23) This could induce misdiagnosing and over-treating hypertension in this population. (22-24) The increasing prevalence of obesity makes validation of finger blood pressure measurements for this group clinical valuable, because blood pressure cuff readings as well as intra-arterial catheter placement in (morbid) obese individuals can be challenging or even impossible. (25) Fingers remain relatively thin in obesity, which may imply that finger blood pressure measurements using the volume clamp methodology may be feasible. The difficulty to assess, both invasive and non-invasive blood pressure in morbid obese individuals makes an alternative technique very valuable.

Therefore in chapter 3, the Nexfin® non-invasive continuous hemodynamic monitoring device was validated against blood pressure measurement according to Riva-Rocci/Korotkoff in obese patients scheduled for bariatric surgery, using the original and the revised protocol of the European Society of Hypertension. This protocol consisted of two phases. The first phase determines how accurate the device will be for individual measurements and second phase 2.2 determines the accuracy for individual measurements. Determining the number of differences (between the Nexfin® device and RRK BP measurements) within 5, 10 and 15 mmHg, and then determining the accuracy will do this. (26)

It was found that the Nexfin® device passed phase 1 and 2.1 of the original validation protocol developed by the European Society of Hypertension. (27) When comparing the obtained data with the revised protocol (26), the Nexfin® device was not able to pass part 1 and 2 of the validation (the former phase 2.1 and 2.2). Notwithstanding these results, the Nexfin® device could be suitable as a non-invasive monitoring device. This because the systolic BP recorded at the wrist may better reflect 'true' systolic BP prevailing in the artery than the systolic BP measured at the arm. (28) This possibility is supported in the study by de Senarclens et al. (28) by the observation that the ratio of width (the decimal log arm of circumference calculated in obese patients) was higher than the optimal value originally validated by Marks et al. (24) This basically means that in our study the arm systolic blood pressure is an overestimation of the 'true' blood pressure. Secondly, the reference method used could be another reason for not passing the validation protocol, because of the possible overestimation of the BP of our study population (as RRK BP measurements were used as a reference). This also explains why there is less differences between the Nexfin® measurements and other reference methods (such as radial artery blood pressure, used in a recent study by De Wilde et al. (29)) Thirdly, both protocols (26, 27) do not make any recommendations for special groups like patients with obesity.

Despite not passing validation completely, the Nexfin® device is a valuable tool for assessing hemodynamic changes. Therefore in the follow-up study short-term hemodynamic changes before and three months after bariatric surgery were assessed using this device (chapter 4). It was found that irrespective of the type of bariatric surgery, that heart rate; mean arterial pressure (MAP), systolic and diastolic BP significantly decreased after bariatric surgery. And stroke volume significantly increased. These results are in line with the current literature, which shows that bariatric surgery has positive effects on cardiovascular hemodynamics. (30)

In addition to cardiovascular effects of bariatric surgery the effects on the pulmonary function were investigated. Chapter 5 gave an overview of the current literature regarding pulmonary physiology in patients with obesity and its considerations for perioperative care in bariatric surgery. Physiologically, obesity is associated with an altered lung function, characterised by a reduction of lung volumes, mostly a restrictive pattern. The pathogenesis is multifactorial, however an increased truncal fat load is one of the possible mechanisms. (31)

Because of affected respiratory physiological parameters such as compliance, neuromuscular strength, work of breathing, lung volumes and spirometric measurements (32, 33), obese subjects are prone to develop pulmonary complications after bariatric surgery. Several strategies are present to improve perioperative care, such as fast track (ERAS) programs. However, the most optimal perioperative care needs to be evaluated on a case-to-case basis. Regarding the link between the impaired lung function, postoperative complications and the necessity of pulmonary function screening prior to bariatric surgery, conflicting results exist and future studies need to determine whether preoperative pulmonary function screening is useful in bariatric practice.

One of the most important pulmonary function parameters is the maximum inspiratory pressure (MIP). It is known that a decreased MIP has a significant effect on postoperative pulmonary complications after cardiac surgery. (34-37) To investigate if this also applies after bariatric surgery, a study was performed to assess the MIP changes and a possible relationship between the MIP and postoperative pulmonary complications following bariatric surgery. In chapter 6, the maximum inspiratory pressure (to assess inspiratory muscle strength) before and after bariatric surgery was determined. The maximum inspiratory pressure significantly decreased three months after bariatric surgery. After six and 9 months a gradual recovery/increase was seen. Morbidly obese patients have increased metabolic demands due to a deposition of fat in the chest wall, which results in an increased mass to move and therefore a higher work of breathing (WOB). This elevated WOB results in reduced chest wall compliance. Also there is an elevation of the diaphragm, which (upon contracting) acts under pressure of a distended abdomen. (38-40) This pathophysiological mechanism is known as the ‘overload’ hypothesis and it is thought that the ‘overload’ triggers a variety of mechanisms in the activity of the respiratory muscles and causes a long-term training effect, which can increase muscle strength. (38, 39, 41) In the postoperative period, weight reduction may promote an improvement in respiratory mechanics and compliance, improving the efficiency of the respiratory muscles. (42) The decrease in muscle strength (e.g. MIP) after three months is due to 1) a loss of fat free mass after surgery, roughly 10% (43) 2) a more efficient cellular working mechanism shortly after bariatric surgery. (43) After six months a new cellular setpoint (in energy metabolism) will be achieved and therefore will increase inspiratory muscle strength.

Changes in maximal inspiratory muscle strength are one of the important pulmonary function alterations after bariatric surgery. Training goals to optimize the MIP before surgery are important as seen in cardiac surgery (34-37). In the current literature there are several predictive equations available, although not tailored for the obese/bariatric population and therefore difficult to predict changes in inspiratory muscle strength.

Chapter 7 gives a critical appraisal of the utility and adequacy of the currently available predictive equations. The equations of Harik-Khan, Neder, Costa, Wilson and Enright were studied.

In the preoperative period, the predicted maximum inspiratory pressure (MIP) according to the Harik-Khan, Neder, Costa and Wilson equation were significantly different compared to the Actual MIP ($p<0.05$). The predicted MIP according to the Enright equation was not significantly different ($p>0.05$). Bland Altman analysis showed that the Enright equation was best suitable for predicting the MIP. In bariatric surgery, these equation are not often used, but as a preparation for cardiac surgery, these MIP equations can be suitable to determine adequate training goals. Inspiratory muscle training is effective in reducing postoperative pulmonary complications in patients scheduled for elective coronary artery bypass grafting. (34) In general, obesity is an increasing problem. (44) To determine the adequate training goal, there is increasing need for a mathematical equation which can adequately predict the respiratory muscle strength and therefore to set achievable training goals. According to this study, the equation of Enright et al. is the most adequate to predict MIP changes and therefore should be used in clinical practice.

Future research must get more insight in the respiratory function of the morbidly obese and the influence of bariatric surgery on respiratory muscle function several function parameters have to be studied. Spirometry is the first step for testing pulmonary function. A comparative analysis between spirometric variables and maximal inspiratory/expiratory pressures can provide more insight in the pulmonary physiology of the morbidly obese.

To integrate energy metabolism, cardiac and pulmonary physiology, an overview of the current evidence regarding perioperative exercise in bariatric surgery was given in chapter 8. Considering the great value of exercise, very limited number of prospective studies addressed perioperative exercise in bariatric surgery. To simplify our findings, an exercise program with a median of 12 weeks, an intensity of 65% peak heart rate/VO_2max, with partial supervision, seems to be to most effective. However the literature regarding different perioperative exercise regimens is very sparse. Considering the earlier mentioned 'overload' hypothesis on pulmonary muscles, we can state that a same sort of 'overload' exists on skeletal muscles. This indicates a training effect of being obese on skeletal muscles and therefore high intensive interval training (HIIT) or resistance training with heavy weights should be beneficial to achieve adequate results. Regarding the timing of exercise regimens, controversies exist. (34, 45-48) Preoperative exercise seems more suitable because the effects of the training do not interact with the effects of bariatric surgery.

PART II: METABOLIC PHYSIOLOGY

The second part of this thesis focused on metabolic physiology, in particular nutritional deficiencies and type 2 diabetes (T2DM). An algorithm is suggested in Chapter 9 to improve and optimize the screening for nutrient deficiencies in patients admitted for bariatric surgery. In the development process of this algorithm the data of 561 Roux en-Y Gastric Bypass (RYGB) and 831 Sleeve Gastrectomy (SG) patients were included. These patients had to had at least pre- and postoperative values of vitamin A, B1, B6, B12, D, folate, ferritin, zinc or magnesium (with a mean follow-up ranging from 3 to 84 months postoperative. The algorithm reduces vitamin D, B12, B6, B1 and ferritin examinations by 15%, 11%, 28%, 28% and 38%, respectively, without missing relevant deficiencies. The corresponding potential cost savings was 14%. This algorithm shows us that we do not have to determine every vitamin and mineral in a preoperative laboratory screening to catch relevant deficiencies. It can be used until at least 84 months postoperative for RYGB and SG patients. Whether this algorithm is suitable for other bariatric procedures and for a follow-up of >84 months is subject for further research.

Chapters 10 and 11 focussed on the specific supplementation strategies for vitamin B12 deficiencies. In chapter 10, the variations in supplementation regimes to treat perioperative vitamin B12 deficiencies were systematically reviewed and analysed. Vitamin B12 supplementation has an effect on the intracellular vitamin B12 content and in the correct dosage it can prevent a vitamin B12 deficiency. There is no consensus about the correct dosage of vitamin B12 after bariatric surgery worldwide, as shown in the results of this study. (49-51)

In chapter 11 is a study described wherein the effectiveness of three different intramuscular vitamin B12 supplementation regimes was assessed in a retrospective matched cohort study. One group received 6 intramuscular vitamin B12 injections with a loading dose; one group received 3 intramuscular vitamin B12 injections without loading dose and the third group received no vitamin B12 injections. Of these supplementation regimes, the 6 injections regime recovered all vitamin B12 deficiencies biochemically.

Following these two studies no optimal protocol of vitamin B12 supplementation can be suggested. Currently a lot of research is done to show with different supplementation regimens that vitamin and mineral deficiencies can be biochemically corrected after bariatric surgery, but somehow the clinical relevancy of 'correcting' these deficiencies is lost in the cause. In terms of reducing potential health risks, there is lack of evidence that a supplementation of vitamin B12 is beneficial. Therefore difficulties arise in defining hard endpoints in these supplementation trials. Secondly, especially for vitamin B12, we do not know whether a low or high dose supplementation has beneficial long terms effects. Current lacks in evidence comprise basically the link between deficiency and clinical relevancy, and the long-term effects of different supplementation regimens.

In terms of metabolic diseases studied, apart from vitamin and mineral physiology, there is great interest in the remission of T2DM after surgery. Especially the comparison between the well-established surgical procedures and the newer ones is an important subject nowadays. Therefore, in the final chapter of part II (chapter 12) assessed the time to glycemic control after several bariatric surgical procedures. In this study we aimed to determine how soon after bariatric/metabolic surgery patients achieve glycemic control (defined as a mean plasma glucose level < 126 mg/dl) in different types of surgery. Our results demonstrated that in the first 30 days after surgery, the SG group never achieved a mean plasma glucose level < 126 mg/dl. Mean plasma glucose level reaching below 126 mg/dl was achieved on 29th day evening for Diverted Sleeve Gastrectomy and Ileal Transposition (DSIT), and 30th day evening for Mini Gastric Bypass (MGB) patients.

Many studies have investigated the metabolic outcomes of surgical treatment, but most of them do not focus of the short-term glycemic changes in type 2 diabetes mellitus obese patients in relatively new surgical procedure like the DSIT (52-54) and MGB (55). Two problems arise interpreting results like type 2 diabetes remission; is the mechanism weight dependent or weight independent, and secondly how do you define remission of type 2 diabetes mellitus? A recent systematic review and meta-analysis by Panunzi et al. (56) investigated whether remission of T2DM is surgical procedure dependent or BMI dependent. They had three main findings regarding anthropometric variables: 1) bariatric surgery improves T2DM to the same extent in patients with a BMI of more or less than 35 kg/m^2; 2) improvement of Hb1Ac is independent of baseline BMI; 3) improvement of Hb1Ac is inversely related to waist circumference. (56) It seems that regarding the type of surgical procedure, there is a superiority of malabsorptive procedures in terms of type 2 diabetes mellitus remission. This was also shown by the meta-analysis of Panunzi et al. (56). They found that the biliopancreatic diversion with duodenal switch (BPD) has the strongest effect (89% remission of T2DM), followed by the Roux en Y Gastric Bypass (RYGBP, 77%), whereas both the SG and laparoscopic adjustable gastric banding (LAGB) had similar remission rates (60% and 62% respectively). These results were confirmed by the systematic review and meta-analysis conducted by Buchwald and colleagues. (3)

FUTURE PERSPECTIVES

Many of the worlds leading bariatric surgeons stated (57) that we are ready for a change in the current guidelines regarding bariatric surgery. Secondly with the increased understanding of the remission of type 2 diabetes, we might even consider a change of name to metabolic surgery. A recent report by David Cummings and Ricardo Cohen support these earlier mentioned statements. (57)

According to the guidelines of the International Federation of Surgery for Obesity and Metabolic disorders (IFSO) (9) surgery is warranted to patients with a BMI greater than 40 kg/m^2, or greater than 35 kg/m2 with serious comorbidities such as type 2 diabetes mellitus. Although these recommendations were clinically valuable, nowadays these guidelines have possible significant limitations and new scientific insights came to light. One of the limitations is the fact that only open operations were considered, whereas most procedures are now undertaken laparoscopically, which is safer with a ten-times lower operative mortality. (58, 59) A second limitation is that there were only moderate recommendations for diabetes, but nowadays increasing knowledge exists about the mechanisms responsible for improvement of type 2 diabetes. Thirdly no recommendations were made about the effects of bariatric surgery on cardiac and pulmonary diseases. This goes way beyond just reducing food intake and bodyweight. (57, 60) Therefore future research must focus on elucidating the mechanisms responsible for the remission of metabolic diseases and to clarify the gaps in current hypotheses.

We have to gain more insight in the effects of bariatric and metabolic surgery on the remission of cardiac and pulmonary diseases. Secondly bariatric and metabolic surgery can be of aid in preventing chronic pulmonary and cardiac diseases. Especially, chapters 2 – 8 of this thesis give a basic insight in the effects of obesity and weight loss (due to bariatric surgery) on cardiac and pulmonary physiology. Furthermore, one of the future challenges lies in defining which imaging modality to assess the cardiac structure and functional parameters in patients with obesity. Currently there is no study available to assess the differences between echocardiography and cardiac magnetic resonance imaging (MRI). A recent study by Patel et al. (61) showed that the diagnostic performance of echocardiography might be inferior to cardiac MRI. In this study the diagnostic performance was tested in finding (para) cardiac masses, but the same diagnostic inconsistencies might occur in determining functional cardiac parameters in patients with obesity. Therefore the differences between cardiac MRI and echocardiography need to be assessed. Secondly as proposed in the chapter 2 of this thesis, the presence of left ventricular hypertrophy (LVH) and/or hypertension are a prerequisite for cardiac remodelling. It seems obvious that a these features are prone to change after bariatric surgery, but what happens with the functional and structural parameters of patients who do not have left ventricular hypertrophy (LVH) and/or hypertension. Comparative studies between these patient groups can give us direction in different features of cardiac remodelling after bariatric surgery.

Also a research field that needs to be investigated is the influence of bariatric surgery cardiac rhythm disorders. It is well known that weight loss has a positive effect on the treatment of rhythm disorders such atrial fibrillation, but the literature on the effects of bariatric surgery on these rhythm disorders are sparse. (62, 63) Also we do not know what the coexistence of features like LVH/RVH and (pulmonary) hypertension does on treatability of rhythm disorders in obese patients. The effects of bariatric surgery on cardiac physiology need to be investigated in more specific patient subgroups to determine adequate benefits.

Regarding pulmonary physiology in the obese and after bariatric surgery, more research is showing at we need to determine adequate subgroups prone for postoperative complications. In chapter 6 was stated that the maximum inspiratory pressure does not have an influence on postoperative complications in bariatric surgery. In recent studies by Van Huisstede et al. (4, 5, 64) the interaction between pulmonary diseases, pulmonary physiology, obesity and bariatric surgery were investigated. One of the main findings of these studies was that patients with abnormal spirometry; an $FEV_1/FVC <70\%$ and a $\delta FEV_1 \geq 12\%$ have an increased risk of postoperative complications. (64) With these identified groups, future research can focus on training these specific patient populations with the goal to decrease this risk of postoperative complications. Secondly we need to look at the burden of comorbidities and the risk of postoperative complications. Patients with more comorbidities (e.g. heart failure, COPD) have an increased risk of postoperative complications compared to patients with one comorbidity. This enables researchers to look at the interaction between different comorbidities and its relationship with the postoperative period.

Finally, the remission of T2DM will be point of discussion in the next few years. Basically which surgical procedure is the most suitable for patients with T2DM. Chapter 11 showed that in terms of glycemic control the Diverted Sleeve Gastrectomy with Ileal Transposition (DSIT) is superior compared with the Mini Gastric Bypass (MGB) and the Sleeve Gastrectomy (SG) in the first 30 days after surgery. These improvements in glycemic control after DSIT find their basis in the Forgut-Hindgut hypothesis. (52-54) By transferring the distal ileum just below the pylorus, digested food stimulates the production of satiety hormones like GLP-1, PYY and oxyntomodullin. (54) These hormones are also known for their anti-diabetogenic properties and also increased blood levels are found after other surgical procedures, like the Roux en-Y Gastric Bypass (RYGB), Laparoscopic Adjustable Gastric Banding (LAGB) and Biliopancreatic Diversion with or without duodenal switch (BPD-DS). However in current literature, there is lack of studies comparing surgical models and conventional models in terms of production of these hormones. Therefore Celik et al. (66) recently started with the HIPER-1 project to investigate the production of hormones GLP-1 and PYY in different surgical and non-surgical models.

In conclusion, as stated by Cummings and Cohen (57), we are ready for a change in our current guidelines, mainly to broaden the indications for bariatric and metabolic surgery. (57) With a landmark study like the Swedish Obese Subjects study (that has generated the foremost evidence base in the speciality) we were able to change current guidelines, but still the indications for bariatric and metabolic surgery need to be broadened. Therefore the challenges lie in designing high-quality randomised controlled trials and to design population based studies by combining national and international databases. Eventually this will lead to new guidelines and indications for bariatric and metabolic surgery.

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GÖTHEBORG

14. VALORISATION

Since the mid-twentieth century, the influence of surgical procedure into metabolic disease became clearer. Starting with a report of Friedman and colleagues wherein they demonstrated in 1955 that a gastrectomy resulted in resolution of type 2 diabetes mellitus (T2DM). In the 70's and 80's, Bosello and colleagues demonstrated the key mechanisms and interplay between morbid obesity and T2DM. They observed that after a jejunoileal bypass weight loss was the primary factor in lowering hyperglycemia and decreasing insulinemia. Ackerman and Halverson found that immediately after malabsorptive bariatric surgical procedures T2DM patients became euglycemic and were freed from diabetes medication.

Nowadays, with the obesity pandemic reaching epic proportions, there is an ever-increasing need for change. More than 30% of the world population has obesity and associated comorbidities. Scientific research of the last decade has shown that bariatric surgery has effect on metabolic diseases apart from the impact of weight loss. For this reason several bariatric organisations have changed their names into societies for 'bariatric and metabolic surgery'.

RELEVANCE OF THE SCIENTIFIC RESULTS IN THIS THESIS

This thesis contains two parts, both with the purpose of understanding perioperative physiology in bariatric and metabolic surgery. The first part describes cardiopulmonary physiology before and after bariatric and metabolic surgery. Regarding cardiac physiology, specifically cardiac structure and function, patients with pre-existent left ventricular hypertrophy (LVH) and/or hypertension benefit the most from bariatric surgery. According to the available literature, bariatric and metabolic surgery will induce short-term cardiac remodelling in these patients (chapter 2).

Several methods are available to assess cardiovascular hemodynamics (e.g. blood pressure (BP)). One example is the intra-arterial BP measurement, mostly measured of the radial artery, as considered the most accurate one. Because of its invasiveness and its risk for infection it is not suitable for BP measurement in obese patients scheduled for bariatric surgery. Another measurement tool is the auscultatory sphygmomanometry, widely used in clinical practice, based on the principles of Riva-Rocci/Korotkoff. However these measurements can give an overestimation of the BP (when using the correct blood pressure cuff). The measurement device used in this thesis is the Nexfin®. This device continuously measures the pressure waveform in the finger and calculates the beat-to-beat brachial BP through an algorithm. The Nexfin® device was used in the bariatric population to determine its relation with Riva-Rocci/Korotkoff BP measurement (chapter 3) and to assess cardiovascular hemodynamics before and after bariatric and metabolic surgery (chapter 4). The Nexfin® device appeared to be easy to use and capable to determine a trend in cardiovascular hemodynamics. It is less dependent on brachial blood pressure variations in relation to the circumference of the upper arm and cuff size. Therefore the Nexfin® device can be easily used for clinical and research purposes in obese individuals.

Regarding pulmonary physiology chapters 5 and 6 showed that the altered pulmonary function as a result of obesity could give potential challenges in perioperative care. Changes in pulmonary function are not solely a change in muscle function, but are interplay between muscle function, intrinsic function of the lungs and thoracic compliance (chapter 5 and 6). However predicting inspiratory muscle function might not be useful in bariatric surgery, in other specialties (such as cardiac surgery) it is standard practice (chapter 7).

The final chapter of the first part of this thesis demonstrates the integrative aspect of cardiopulmonary physiology in perioperative exercise. In chapter 8 is shown that perioperative exercise in bariatric surgery is beneficial in terms of weight loss and the reduction of cardiovascular risk factors. However, the optimal exercise regimen for which patient remains unclear. Based on the results found, we recommended an exercise regimen ideally pre- and postoperative. These exercise regimens should last for a median of 12 weeks, has an intensity of either 65% peak heart rate or 65% VO2 max and is at least partially supervised. When implemented these exercise regimens should give additional benefit for patients before and after bariatric surgery.

The second part of this thesis focussed on two aspects of metabolic physiology; vitamin deficiencies and type 2 diabetes mellitus (T2DM) remission. Screening for nutritional deficiencies is costly. Trying to reduce the costs, an algorithm was developed (Chapter 9), to improve and optimize the screening for nutrient deficiencies after bariatric surgery. We have found that our algorithm is able to reduce vitamin D, B12, B6, B1 and ferritin examinations by 15%, 11%, 28%, 28% and 38%, respectively, without missing clinically relevant deficiencies. Also this corresponds with a potential cost savings of 14%.

The supplementation regimen of vitamin B12 deficiencies after bariatric and metabolic surgery was the focus of chapters 10 and 11. The literature review in chapter 10 showed that to treat a vitamin B12 deficiency with oral multivitamin supplements, a minimum dosage of 350 microgram was necessary. Oral supplements with lower dosages were not able to recover vitamin B12 deficiencies biochemically. Chapter 11 showed us that in a retrospective study a 6 intramuscular vitamin B12 injection regime was able to recover all vitamin B12 deficiencies. According to these two studies an oral supplement must have at least 350 microgram of vitamin B12. Secondly, an intravenous supplementation regimen should at least contain 6 intramuscular injections with a loading dose (one injection). Each injection should contain 1000 μg of hydroxocobalamin.

In the final chapter of part II (chapter 12) we have assessed the time to glycemic control after several bariatric surgical procedures. T2DM is a major burden and therefore the faster remission is achieved, the better it is for patients but also it reduces healthcare costs significantly. Our results demonstrated that in the first 30 days after surgery, patients who had a Diverted Sleeve Gastrectomy and Ileal Transposition (DSIT), or a Mini Gastric Bypass (MGB) achieved glycemic control after respectively 29 and 30 days.

POPULATION OF INTEREST

The results of this thesis are relevant for several groups of patients. Firstly, patients who were recently operated or patients who want to undergo a bariatric surgical procedure. Secondly, this thesis emphasises that bariatric surgery might be beneficial for more than just weight loss. Patients with metabolic, cardiac and/or pulmonary diseases can benefit from bariatric/metabolic surgery.

This thesis is also of interest of clinicians who treat patients with therapeutic resistant cardiac, pulmonary of metabolic diseases. Also, the contents of this thesis are of interest for expert panels, responsible for the development of national and international guidelines.

INNOVATION AND FUTURE

The impact of bariatric surgery on cardiac, pulmonary and metabolic diseases apart from its weight loss effect is becoming clearer. This is not yet reflected by the current guidelines regarding bariatric surgery.

The guidelines of the International Federation of Surgery for Obesity and Metabolic disorders (IFSO) state that surgery is warranted to patients with a BMI greater than 40 kg/m^2, or greater than 35 kg/m^2 with serious comorbidities such as type 2 diabetes mellitus. These guidelines were carefully written at that time, but nowadays these guidelines have increasing limitations. Among these limitations are that there were only moderate recommendations for diabetes and metabolic disorders, and that these guidelines are based on only open operations, whereas most procedures are now undertaken laparoscopically, which is safer with a ten-times lower operative mortality. One of the most important goals for future research is elucidating the mechanisms responsible for the remission of metabolic diseases. We have to gain more insight in the effects of bariatric and metabolic surgery on the remission of cardiac and pulmonary diseases. And so, we can help more patients with metabolic diseases.


SOL

15. NEDERLANDSE SAMENVATTING

In dit proefschrift worden twee domeinen van de perioperatieve fysiologie in de bariatrische en metabole chirurgie besproken. Het eerste onderwerp is de cardiale en pulmonale fysiologie. In het tweede onderwerp de metabole fysiologie, met een nadruk op de vitamine en mineralen suppletie en de remissie van type 2 diabetes mellitus na bariatrische en metabole chirurgie. In beide domeinen worden tevens optimalisatie strategieën besproken.

In **hoofdstuk 2** wordt een overzicht gegeven van de literatuur met betrekking tot de verandering in cardiale functie en hemodynamiek voor en na bariatrische chirurgie. Hieruit blijkt dat bariatrische chirurgie gunstige effecten heeft op de functie van het hart. Teven blijkt dat patiënten met pre-existente hypertensie dan wel linker ventrikel hypertrofie het meeste baat hebben bij bariatrische en metabole chirurgie op basis van de huidige literatuur.

Hoofdstuk 3 beschrijft de resultaten van de validatiestudie van het Nexfin® hemodynamiek monitoring apparaat, afgezet tegen de reguliere bloeddrukmeting bij obese patienten voorafgaand aan bariatrische chirurgie. **Hoofdstuk 4** omschrijft de verandering in de hemodynamiek voor en na bariatrische chirurgie gemeten middels de

Nexfin®. Het blijkt dat na bariatrische en metabole chirurgie er een significante daling optreedt van de systolische en de diastolische bloeddruk en tevens het slagvolume. Ook heet bariatrische en metabole chirurgie gunstige effecten op de cardiac output.

Een overzicht van de invloeden van obesitas op de pulmonale fysiologie en zijn implicaties voor de klinische praktijk worden gegeven in **hoofdstuk 5**. In **hoofdstuk 6** worden de verandering van de maximale inspiratoire druk beschreven voor en na bariatrische chirurgie. In de eerste drie maanden postoperatief treedt er een significante daling op in maximale inspiratoire druk, maar na negen maanden stijgt de maximale inspiratoire druk wordt er een stijgend trend waargenomen, waarschijnlijk het gevolg van het 'wennen' aan de nieuwe lichaamssituatie. **Hoofdstuk** 7 is een logisch gevolg en kijkt derhalve of de verandering in maximale inspiratoire druk bij obese patiënten voorspeld kan worden aan de hand van voorspelformules. **Hoofdstuk 8** geeft een kritisch overzicht over de meerwaarde van perioperatieve bewegingsinterventies bij bariatrische en metabole chirurgie.

Hoofdstuk 9 is het eerste hoofdstuk in het gedeelte 'metabole fysiologie' en beschrijft de variaties in suppletie strategieën van patiënten met een vitamine B12 deficiëntie. De retrospectieve studie in **Hoofdstuk 10** onderzocht de effecten van drie verschillende vitamine B12 suppletie regimes. In **hoofdstuk 11** wordt een algoritme beschreven om de screening naar vitamine en mineralen deficiënties voor en na bariatrische chirurgie te optimaliseren en het blijkt dat dit algoritme een significant kostenreductie teweeg kan brengen. Het laatste hoofdstuk (**hoofdstuk 12**) van dit proefschrift heeft onderzocht welke van de drie typen bariatrisch chirurgische operaties het snelste kan zorgen voor het in remissie treden van diabetes mellitus type 2 in de eerste 30 dagen postoperatief. Hieruit blijkt dat de ‘diverted sleeve gastrectomy and ileal transposition (DSIT)’ mogelijk superieur is aan de ‘mini gastric bypass (MGB)’ en de ‘sleeve gastrectomy (SG).’

16. DANKWOORD

And we are done...

Een promotieonderzoek, dat klinkt heel simpel en eenvoudig, maar niets is minder waar. Het is de ultieme beproeving op wetenschappelijk, psychisch en lichamelijk niveau. Gedurende een periode van een aantal jaar deel je lief en leed, ergernis, depressies en vreugde momenten met een selecte groep mensen, waarvan een ieder direct of indirect een steentje heeft bijgedragen. Die mensen wil ik heel graag bedanken.

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Graag wil ik alle medeauteurs bedanken voor hun waardevolle bijdragen en commentaren. In het bijzonder veel dank aan **prof. dr. Frank Smeenk**, voor alle vakkundige ondersteuning bij de pulmonaal georiënteerde stukken. Ook als opleider heb ik veel van je geleerd en jij bent degene geweest die me mee heeft genomen naar de wereld 'achter het artikel', anders gezegd hoe moet een lezer jouw artikel lezen en wat voor boodschap je wil uitdragen. Ook hoop ik dat ons gezamenlijke project met de Cliniques Universitaire Saint-Luc in Brussel mooie resultaten gaat opleveren. Daarnaast speciale dank aan **dr. Arthur Bouwman**. Ik heb nog nooit iemand gezien die artikelen zo kritisch nakijkt, bestudeert en letterlijk elke steen omdraait. Voor mijn gevoel duurde het altijd een eeuwigheid voordat ik commentaar van je terugkreeg, maar altijd tot in de puntjes verzorgd en het bracht het artikel altijd naar een hoger niveau. Ook **dr. Lukas Dekker** en **dr. Patrick Houthuizen** wil ik heel hartelijk bedanken voor hun input bij de cardiologisch georiënteerde artikelen in dit proefschrift. Als laatste bijzondere waardering voor data wizard en klinische chemicus/endocrinoloog **dr. Arjen-Kars Boer** en de enige echte epidemioloog/ spraakwaterval **dr. Saskia Houterman**.

Arts-assistenten en arts-onderzoekers Heelkunde/IC van het CZE
De afgelopen jaren heb ik met veel plezier met jullie mogen samenwerken en natuurlijk mogen feestvieren. In het bijzonder wil ik mijn bariatrie broeder **Martin van Wezenbeek** bedanken. Weet zeker dat de lokale Weense bevolking nog lang napraat over ons bezoek aan het IFSO congres…

Chirurgen en Intensivisten van het CZE

In de afgelopen jaren heb ik het genoegen gehad om veel van jullie te mogen leren, zowel in de kliniek als daarbuiten. Daarvoor mijn oprechte dank. In het bijzonder wil ik **Frans Smulders** bedanken. Van vliegende flessen wijn in een club in Wenen en diepgaande gesprekken met een berg hamburgers in een Zweedse McDonalds, tot in recordtijden een gastric sleeve doen (en in recordtijd bepaalde Franse chirurgen figuurlijk laten ontploffen), de bijnaam 'opperbaas' misstaat je absoluut niet. Ook de 'rollator PhD's' **Ingeborg Herold**, **Marco Haanschoten** en **Herman Kreeftenberg** verdienen een eervolle vermelding. Er is niets leukers om tussen de operaties, de SIT oproepen en het acht uur journaal, nog even de statistische ergernissen van de dag door te nemen.

Mijn Franciscus SEH en Chirurgie collega's

Toen ik de parel van Brabant verliet, had ik nooit gedacht dat het in Rotterdam minstens net zo gezellig zou zijn. Wat moet ik zonder mijn lieftallige collega's in het turbulente Rotterdam en Schiedam. Speciale dank aan de man die sneller arteriële (of veneuze) bloedgassen prikt, dan Lucky Luke op zijn schaduw schiet. En ook nog mensen red, terwijl hij zelf met een halve anafylactische shock rondloopt **Chris Nijdam**, wat hebben wij een aantal gekke diensten gehad. Ook KNO koning **Djazz van der Heijden** is zonder twijfel een echte baas, Merocel hier, Rapid Rhino daar, zelf knie reconstructies kan deze man in een handstand. Echt een waar genoegen om jullie als vrienden en collega's te hebben. #vlietlandlife

Marieke Smelt

Mijn opvolgster. Je ziet maar zelden mensen die zo'n motivatie en drive hebben om verder te komen in hun carrière. Daarom kijk ik met veel plezier uit naar jou promotie die zeer snel zal gaan plaatsvinden.

Robin, Rémondo en Mila

Mijn Rotterdamse buurtjes (echter een paar wijken verderop). Wat is het toch altijd een plezier om jullie als vrienden te hebben. Jullie zijn het bewijs dat hard werken loont en dat bewonder ik zeer.

Mijn paranimfen Ben en Sanne

Wat een groot genoegen dat jullie tijdens mijn promotie aan mijn zijde staan. Als ex-collega's, stapmaatjes en mijn allerbeste vrienden staan jullie naast me. Ik weet het nog als de dag van gisteren, dat we in de lokale Albert Heijn te Arnhem onze handen vol hadden aan 'boefjes' die de winkel leeg probeerde te jatten. Dat waren me nog eens tijden.

Mijn 010 en 020 maatjes: Martin, Mark, Kirby, Rudi, Barry, Tamara en Marianna
Wij hebben in de loop der jaren menig discotheek/festival/club/strandtent onveilig gemaakt en geen muziekgenre is ontsnapt aan onze visie. Van chagrijnig lopen door het Amsterdamse bos na afloop van '909' festival tot vliegen staan meppen bij Hernan Cattaneo op Loveland, wij hebben bewezen dat 'raven' topsport is. Nu alleen het Olympisch Comité nog even overtuigen.

Zamir, Muhamad, Besir, Sjerionda, Erik, Marga, Bjorn, Jens en Manon
Mijn maatjes, mijn steun en toeverlaat in donkere dagen, mijn beste vrienden. Ik wil jullie nogmaals laten blijken hoe veel ik jullie vriendschap waardeer. Zonder jullie, had ik dit promotieonderzoek niet kunnen doen. Dank voor jullie interesse, wijze raad en af en toe harde woorden die mij met beide benen op de grond hebben laten staan.

Familie Elhatri,
Elke keer is als kwam trainen na een dag hard werken, viel ik in een warm bad. Zelden zie je een familie bedrijf wat zo goed functioneert. Ieder met zijn eigen specifieke doelen en op die manier complementeren jullie elkaar. Appie, Farah, Fatima en Hayad hartelijk dank voor jullie vriendschap, gastvrijheid en jullie hebben mijn interesse voor vechtsporten nieuw leven ingeblazen in een tijd dat ik het privé erg moeilijk had. Dat heeft mij zeer goed gedaan.

Johan van de Vliet,
Johan, ik weet eigenlijk niet zo goed waar ik moet beginnen. 'Krav Maga heeft me gegrepen!' En dat is in de loop der tijd wel duidelijk geworden. Ook je wijze raad en discipline hebben mij zeer goed gedaan. En ja, wij gaan nog een keer voor een seminar naar Polen. Afgesproken?

My Mexican friends Cindy and Manuel,
We met in Philadelphia during the 'Weight Loss and Fitness Expo' and since then we became friends. It's a true honour to have you guys present at my thesis defence. It means a lot to me.

Dear dr. Gupta, dear Adarsh,
Together with Alper Çelik and a lot of our foreign colleagues we have started a research group investigating the physiological mechanisms of type 2 diabetes remission after bariatric and metabolic surgery. The result of a diner we had together in Philadelphia with pizza and cheese-steak. Thank you for your friendship and collaboration. I'll see you soon!

Dear prof. dr. Çelik, dear Alper,
As you have said it before, that meeting in Philadelphia was a game changer for us. Since then we became good friends and colleagues. Thank you for your trust, your good advice and your

hospitality. It was really nice to visit you guys in Istanbul a few months ago and I'm looking forward to the Metabolus Istanbul meeting in 2018. Also I have noticed that Wing-Chun Kungfu and Krav Maga have a lot of similarities. Let's keep on rocking!

Sjaak, Nina, Martin en Marcel
Jullie steun is onbeschrijfelijk en eigenlijk niet in woorden uit te drukken. Daar waar mijn eigen ouders en mijn broertje me in de steek lieten, hebben jullie mij opgevangen in de meest donkere tijden van mijn korte leven. Bij jullie voel ik mij thuis, gewaardeerd, geliefd en kan ik mijzelf zijn. Mijn oprechte dank voor het feit dat jullie altijd in mij hebben geloofd en mij hebben gesteund.


ESTADIO MARIO FILHO
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17. CURRICULUM VITAE

Jacobus Hendrikus (Sjaak) Pouwels werd op 11 december 1989 geboren in Amsterdam. Na het behalen van zijn Gymnasium diploma aan het Lorentz Lyceum te Arnhem, begon hij met de studie Geneeskunde aan de Radboud Universiteit in Nijmegen. Tijdens zijn studententijd was Sjaak actief als onderzoeker bij het Centrum voor Plastische Aangezichtschirurgie, waar hij onderzoek deed naar de cosmetische aspecten van de perifere aangezichtsverlamming, alvorens hij in Eindhoven terecht kwam. Gedurende het vierde jaar Geneeskunde is Sjaak gestart met zijn promotieonderzoek. In 2014 behaalde hij zijn arts-examen, na een afsluitende klinische en onderzoeksstage van negen maanden op de afdeling Vaat- en Transplantatiechirurgie van het Radboudumc te Nijmegen. Na het ontvangen van de artsenbul startte Sjaak als arts-onderzoeker in het Catharina ziekenhuis te Eindhoven. Gedurende een jaar verrichte hij onderzoek naar de perioperatieve fysiologie bij bariatrische en metabole chirurgie. Daarna heeft hij een periode als ANIOS Intensive Care gewerkt en sinds 1 augustus 2016 is Sjaak werkzaam als ANIOS Chirurgie in het Franciscus Gasthuis en Vlietland in respectievelijk Rotterdam en Schiedam.

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