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The effect of non-alcoholic steatosis hepatitis on weight-loss and resolution of obesity-related comorbidities after bariatric surgery.

Dissertation

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1. Introduction

1.1 Obesity - Definition, BMI, Classification

Obesity is a chronic disease, which has been increasing worldwide (Strauss and Pollack 2001). The Incidence of Obesity has doubled in 70 countries since 1980, In 2015, a total of 107.7 million children and 603.7 million adults worldwide were obese (Collaborators, Afshin et al. 2017). In 2011 more than 50% of the population in Germany were overweight and 23% were obese (Mensink, Schienkiewitz, et al. 2013). The number of operations performed in Germany has steadily increased, reaching 10,000 procedures per year (Angrisani, Santonicola, et al. 2018).

Obesity is internationally measured using the body mass index. BMI is defined as the body weight in kilograms divided by the body height in meters and is universally expressed in units of kg/m^2, resulting from mass in kilograms and height in meters.

Many studies showed that BMI correlates with body fat proportion. That is why Micozzi et. Al. used BMI as an objective parameter to assess obesity (Micozzi, Albanes, et al. 1986). According to the WHO report, BMI classifies people according to the body habitus; namely underweight, optimal weight, overweight, and obese. Furthermore, it can indicate the increased risk of obesity-related diseases. Risk increases steadily after a BMI ≥ 25 and exponentially when BMI ≥ 40 (WHO, 2000).

Table 1: Weight classification according to BMI (WHO, 2000)

BMI Category	**kg/m^2**	**Risk of obesity-related diseases**
Underweight	< 18,5	Low
Optimal weight	18,5 – 24,9	Average
Overweight	≥ 25	Above average
Pre-Obese	25 – 29,9	Mildly elevated
Obese Stage I	30 – 34,9	Moderately elevated
Obese Stage II	35 – 39,9	Highly elevated
Morbidly Obese III	≥ 40	Very high

Legend: BMI; Body mass index, kg; kilogram, m^2; meter squared

Also, fat distribution plays an important role in obesity-related disorders. The first form is the gynoid form, in which the fat is more distributed over the lower limb and gluts compared to the android form, where the fat deposits in the abdomen, trunk, and neck. The type of fat distribution plays an important role in morbidity and mortality. Visceral fat deposition (android form) increases the risk of metabolic disorders, like diabetes type 2, which increases the risk of cardiovascular disease(Despres 2012). Another way to assess the risk of obesity-related disorders is to measure waist circumference (Lean, Han, et al. 1995).

Table 2: Waist circumference and risk for obesity metabolic-related disorders (Lean et al., 1995)

Risk of cardiovascular and metabolic complications	**Waist circumference Men**	**Waist circumference Women**
High	≥ 94	≥80
Very high	≥102	≥88

1.2 Prevalence of obesity

The incidence of obesity has increased steadily in the last decades, especially in developed and industrial countries (WHO, 2000).

In Germany, the incidence of obesity increased over time. In 1985 the prevalence of obesity was 16.2%. In 2008 the prevalence of obesity increased to 20.8% when considering BMI (≥ 30) and to 37.4% in the population with BMI (25-29.9). As result, 58% of the German population were overweight or obese in 2008 (Fontaine, Redden et al. 2003, Helmert and Strube 2004)

Robert Koch Institute reported in 2013, that 23% of men and 24% of women were obese (BMI ≥ 30) and 67% of men and 53% of women were overweight (Mensink, Schienkiewitz, et al. 2013). Just like England, Irland, Scottland, and Spain, Germany belongs to the european countries with the highest incidence of obesity. In the USA the incidence of obesity has reached 35%. Therefore, obesity has become one of the most serious global problems (Mensink, Schienkiewitz et al. 2013, Collaborators, Afshin et al. 2017). While 2.1 billion people worldwide are overweight (Ng, Fleming, et al. 2014), only 842 Million people are undernourished

(http://www.fao.org/hunger). In the last 33 years, no single country has achieved a reduction in the prevalence of obesity (Ng, Fleming, et al. 2014).

1.3 Mortality in Obesity

Many studies showed that obese people have reduced life expectancy compared to people of normal weight. (Fontaine, Redden, et al. 2003, McGee 2005, Lenz, Richter, et al. 2009). The morbidly obese; stage 3 (BMI ≥ 40) have a 200% increased mortality risk compared to people with normal weight (Lenz, Richter, et al. 2009).

Especially in the young population obesity influences the remaining life expectancy. Men and women between 20 and 30 years with BMI ≥ 45 have approximately, 13 and 8 years, respectively, shorter life expectancy compared to people with normal weight. In men, it means a 22% reduction of the remaining life expectancy (Fontaine, Redden et al. 2003).

1.4 Etiology of obesity

Obesity is multifactorial, usually due to a positive energy imbalance. This means, that over a long period of time more energy has been stored from food intake as consumed, leading to fat deposition and an increase in weight (Hall and Guo 2017).

The most common cause of this positive energy imbalance is the sedentary lifestyle in developed countries (WHO, 2000). Another factor is the easy access to high caloric food, especially carbohydrate- and fat-rich diet, which leads to an increase in body fat (Dreon, Frey-Hewitt, et al. 1988).

Another important issue is the decreased mobility in the era of technology, it is thought that the increase in available technology is a contributor to obesogenic environment, like using cars, escalators, elevators, which lead eventually to a positive energy imbalance (Gilmore, Duhe, et al. 2014).

Another important cause of obesity is genetic predisposition. In 1956, P.J. Clark observed in a study of twins, the presence of shared genetic components, that determine the height, weight, and pelvic circumference in 70% of the cases (Clark 1956). In 1994 Carmelli et al confirmed that even twins, that grow separately, show a high concordance in weight (Carmelli, Cardon, et al. 1994).

Obesity genes were discovered in the USA in 1949. Ingalls et al. reported a recessive phenotype in obese mice (Ingalls, Dickie, et al. 1950). In 1994 Zhang isolated the obese gene. Leptin was thought to be the result of obese-gene, which played a role in a signalling pathway responsible for the regulation of fat deposition (Zhang, Proenca, et al. 1994). Leptin is a hormone secreted from adipocytes, which interacts with hypothalamic receptors to decrease the secretion of the neuropeptide Y. Neuropeptide Y increases appetite and increases plasma levels of insulin and corticosteroid. A decrease in fat depots leads to a decrease in Leptin concentration which increases appetite(Zarjevski, Cusin, et al. 1993).

The initial theory, that the obese suffer from Leptin deficiency, ended as Maffei et al. showed a linear correlation between BMI and Leptin concentration in plasma. (Maffei, Halaas, et al. 1995). Considine et al. proved that obesity is associated with high levels of leptin, which indicates that obesity rise from Leptin-resistance rather than deficiency (Considine, Sinha, et al. 1996).

Another signaling pathways with an association with obesity is the deficiency in Carboxypeptidase E, which leads to a defect in processing of proinsulin, which leads to obesity-diabetes syndrome (Naggert, Fricker, et al. 1995). Furthermore, Huszar D et al. discovered in 1997 that the inactivation of the Melanocortin-4 receptor leads to hyperphagia, hyperinsulinemia, and hyperglycemia syndrome (Huszar, Lynch, et al. 1997).

Obesity can also be caused by Prader-Willi syndrome (Laurier, Lapeyrade, et al. 2015), Cushing syndrome (Drey, Berr, et al. 2017), and Hypothyroidism(Portmann and Giusti 2007). Also, be a result of many psychiatric disorders like Binge-Eating syndrome and Bulimia nervosa. (Villarejo, Jimenez-Murcia et al. 2014, McCuen-Wurst, Ruggieri, et al. 2018). Also, The consumption of some pharmacological agents has been linked with obesity like Tricyclic antidepressants, Corticosteroids, and Neuroleptics (Verhaegen and Van Gaal 2017).

1.5 Obesity-related disorders

Obesity is highly associated with metabolic syndrome. Arterial hypertension, Hyperlipidemia, Type II Diabetes mellitus, and obstructive sleep apnea syndrome are common co-morbidities for Obesity (WHO, 2000).
Another manifestation of obesity and metabolic syndrome is non-alcoholic fatty liver disease, which ranges from simple steatosis to non-alcoholic steatohepatitis, eventually leading to fibrosis and cirrhosis (Fassio, Alvarez et al. 2004).

1.5.1 Arterial hypertension

Arterial hypertension is the most common comorbidity associated with obesity. Stamler et al. showed in 1978 a correlation between blood pressure and body weight. In a nationwide hypertension screening study in the USA, 1 million Americans were examined. Over-weight individuals between 20-39 years had twice the incidence of arterial hypertension when compared to the normal population. Among those aged 40 to 64 years, the overweight group had a 50% increased risk of hypertension compared to normal-weight individuals and 100% increased risk compared to the underweight group (Stamler, Stamler et al. 1978). In the nurses' health study, which included 80000 women over 16 years, concluded that every 1 unit increase in BMI increases the incidence of hypertension by 12% (Huang, Willett et al. 1998). Arterial hypertension is an important risk factor for coronary artery disease and myocardial infarction. According to the Interheart Study, Hypertension increases the risk of myocardial infarction by 20% (Assmann, Schulte et al. 1997). When combined with smoking and diabetes, it increases to 50% (Yusuf, Hawken et al. 2004).

1.5.2 Type 2 Diabetes mellitus

According to the international federation for diabetes, in 2013, 382 Million people have type 2 diabetes mellitus. They expect this number to increase by 50% by 2035. There is also a strong association between overweight and glucose intolerance. The nurses' Health study also demonstrated that the risk of diabetes mellitus type 2 increases significantly when BMI ≥ 22. The risk triples when BMI ≥ 30. About 90 % of diabetics are overweight and 44% of diabetics are obese (Colditz, Willett et al. 1990).

1.5.3 Hypertriglycermia

The typical dyslipidemia of obesity consists of increased triglycerides (TG) and FFA, decreased HDL with HDL dysfunction and normal or slightly increased LDL- accompanied with increased small dense LDL. The concentrations of plasma apolipoprotein (apo) B are also often increased, partly due to the hepatic overproduction of apo B containing lipoproteins(Franssen, Monajemi et al. 2011, Wang and Peng 2011).

Hypertriglyceridemia is defined as increased triglyceride concentration in serum ≥180 mg/dl (Sinning and Landmesser 2017). According to the American guidelines, the threshold is (≥150 mg/dl). Hypertriglyceridemia is also associated with lower HDL concentrations in serum ≤40mg/dl (Hegele, Ginsberg et al. 2014). The PROCAM Study concluded, that a BMI >30 kg/m² doubles and sometimes quadruple the risk of hypertriglyceridemia (Assmann, Schulte et al. 1997). The presence of hypertriglyceridemia significantly increases the risk of myocardial infarction (Nordestgaard, Benn et al. 2007, Cabrera, Sanchez-Chaparro et al. 2014).

1.5.4 Obstructive sleep apnea syndrome

Obstructive sleep apnea is defined as a respiratory arrest ≥ 10 seconds at least 5 times per hour during sleep. Overweight increases the risk of obstructive sleep apnea significantly (Degache, Sforza et al. 2013). Some studies report the prevalence of obstructive sleep apnea as high as 80% and 50% in morbidly obese men and women respectively(Salvador, Iriarte et al. 2004).

Untreated OSAS leads to other comorbidities like arterial hypertension, pulmonary hypertension, and worsening of heart failure(Hopps and Caimi 2015). It also increases the incidence of NAFLD (Weingarten, Mantilla ,et al. 2012).

1.5.5 Non-alcoholic fatty liver disease (NAFLD)

This is defined as an increase of > 5% of lipid content in the hepatocytes in the absence of excessive alcohol intake. This ranges from simple steatosis when >66% of hepatocytes show increased lipid content to non-alcoholic steatosis hepatitis, in which steatosis is combined with inflammation, which leads to fibrosis, cirrhosis, and occasionally hepatocellular carcinoma (Fassio, Alvarez et al. 2004, Albhaisi, Issa et al. 2018)

Histologically, NAFLD is similar to alcoholic fatty liver disease. However, NAFLD is characterized by the absence of alcohol or maximal alcohol consumption of 20g/day (Ludwig, Viggiano et al. 1980, Brunt, Janney et al. 1999).
The clinical course of NAFLD cannot be expected. 10-20% of the patients show a progression to NASH. 5% of NASH patients develop liver cirrhosis (Day 2006). HCC can develop in all stages of NAFLD, even in the absence of cirrhosis(Stine, Wentworth et al. 2018). In a long time follow up of patients with NAFLD-associated cirrhosis, 12 % developed HCC (Ascha, Hanouneh et al. 2010). The increased incidence of NAFLD-associated HCC has become a common indication for liver transplantation in the western world (Wong, Aguilar et al. 2015).

1.5.5.1 Prevalence of NAFLD

The prevalence of NAFLD in the western world is expected to lie between 25-33% of the population and only 2%(Bedogni, Miglioli et al. 2005)-3%(Browning, Szczepaniak et al. 2004) suffer from NASH. However, in bariatric surgery, the incidence of NAFLD increases to 91%, NASH to 33%, and NASH-related cirrhosis to 7%. This could be explained due to the high BMI in these populations and the association of NAFLD with BMI (Machado and Diehl 2016).

1.5.5.2 Pathogenesis of NAFLD

Day and James introduced the most widespread and prevailing model of the "two-hit hypothesis"(Day and James 1998), the "first hit" involves lipid accumulation in the hepatocytes (Duvnjak, Lerotic et al. 2007, Qureshi and Abrams 2007). Insulin resistance is suggested to be the key pathogenic factor for the development of hepatic steatosis. The "first hit" increases the vulnerability of the liver to many factors that constitute the "second hit" and promote hepatic injury, inflammation, and fibrosis.
Oxidative stress and subsequent lipid peroxidation, proinflammatory cytokines, adipokines, and mitochondrial dysfunction are included among these factors.
The role of oxidative stress is the main instigator triggering the progression of steatosis to steatohepatitis. Many studies demonstrate that oxidative stress is a prominent feature of NASH (Seki, Kitada et al. 2002, Albano, Mottaran et al. 2005, Begriche, Igoudjil et al. 2006). In addition, it has been proposed that genetic and environmental factors trigger the progression to NASH through the enhanced

production of reactive oxygen or/and nitrogen species (ROS/RNS) (Begriche, Igoudjil, et al. 2006). Furthermore, bacterial overgrowth, changes in gene expression, and renin-angiotensin system (RAS) are suggested as potential contributors to hepatic steatosis and inflammation. Adipose tissue, especially visceral adiposity, appears to play an important pathogenetic role. It is now recognized as an endocrine, autocrine, and paracrine organ that secretes adipokines.

NAFLD is associated with metabolic syndrome. Marchesini et al. postulated that 88% of their NASH patients suffer from metabolic syndrome. He also showed that patients with known metabolic syndrome had 3.5 times increased risk of developing liver fibrosis (Marchesini, Bugianesi, et al. 2003). In metabolic syndrome, type 2 diabetes mellitus and insulin-resistance play an important role in developing NAFLD. Chitturi showed that 95% of their NASH patients had a synchronous insulin-resistance, this was attributed to the increased free fatty acid concentration in the blood by increased lipolysis in the presence of insulin resistance, which contributed to lipid accumulation in the hepatocytes (Chitturi, Abeygunasekera, et al. 2002). Another complication of hyperinsulinemia is decreased synthesis of Apolipoprotein B 100, consequently decreased bound VLDL-associated lipid transport from hepatocytes, which leads to lipid accumulation within the hepatocytes (Charlton, Sreekumar, et al. 2002).

A population-based study in the USA showed that diabetes is an independent factor in the pathogenesis of hepatocellular carcinoma and it increases its risk in 2 to 3 folds (Davila, Morgan, et al. 2005).

1.5.5.3 Diagnosis of NAFLD

Given the substantial morbidity associated with NASH and the asymptomatic course of the disease, efforts were given in the last decades to identify patients with NASH. Nevertheless, a clear diagnostic approach is lacking(Sumida, Nakajima, et al. 2014).

Laboratory testing may show increased serum ALT or AST however, it is neither specific nor sensitive for the diagnosis of NAFLD (15 (Mofrad, Contos, et al. 2003). Some score systems were developed to predict the severity of NAFLD, like the NAFLD fibrosis score (Angulo, Hui, et al. 2007) and FIB-4 Score (Sterling,

Lissen, et al. 2006) in both tests AST, ALT, Thrombocytes, and patient's age are used in formulas to assess NAFLD severity.

An ALD/NAFLD index has been propagated to differentiate alcoholic liver disease from NAFLD(Conigrave, Degenhardt, et al. 2002). MCV, AST, ALT as well as the height and weight of the patient are used in the calculation. Another often used index in liver transplantation is the MELD score (Model of End-Stage Liver Disease), which uses Creatinine, Bilirubin, and INR to calculate the severity of the underlying liver disease (Chalasani, Younossi, et al. 2012).

Radiographic examination can detect fatty liver, but no modality can accurately distinguish simple steatosis from NASH (Saadeh, Younossi, et al. 2002). Ultrasound is a good modality to show hepatic steatosis, as well as ultrasound elastography, which tests stiffness of liver parenchyma. Some studies showed good results in identifying advanced liver disease (Bonekamp, Kamel, et al. 2009, Bril, Ortiz-Lopez, et al. 2015), but its sensitivity seems to decrease in the obese (Mottin, Moretto, et al. 2004). MRI and CT-scan are not always applicable, because of the body habitus. Many patients may not fit in the scanners and may exceed the table weight load limit (Fursevich, LiMarzi, et al. 2016). That is why, liver biopsy remains the gold standard in diagnosing NAFLD (Sheth, Gordon, et al. 1997). However, a minimum amount and depth are needed to accurately classify the disease(Arun, Jhala, et al. 2007).

1.5.5.4 Therapy of NAFLD

The initial therapy of NAFLD starts with lifestyle modification such as increased activity, mobility, healthy diet, and weight loss. Many studies showed that even a 7-10% decrease in body weight leads to significant improvement in NASH (Promrat, Kleiner, et al. 2010). Lifestyle modification prevents disease progression (McPherson, Stewart, et al. 2010) and increase insulin sensibility(Harrison, Fecht, et al. 2009).

Tendler et al. observed the effect of a low-carbohydrate diet over 6 months, this lead to significant weight loss and significant improvement in NAFLD Histology(Tendler, Lin, et al. 2007). A decreased insulin resistance by 40% and decreased fat deposition in the liver could be reached as soon as 6 weeks after starting the diet (Viljanen, Iozzo, et al. 2009).

Increased physical activity has proven to reduce intrahepatic triglycerides (Sullivan, Kirk, et al. 2012), this is due to increased insulin sensitivity in the liver (Van Der Heijden, Wang, et al. 2010) as well as the positive effect of increased kinetic activity on insulin resistance (Kirwan, Barkoukis et al. 2009) Although lifestyle modification is an effective therapy method, patient compliance is usually limited. (Centis, Marzocchi, et al. 2013).

Many studies reported improvement of liver histology after bariatric surgery. (Dixon, Bhathal et al. 2004, Klein, Mittendorfer, et al. 2006). Mathurin et al. observed 380 patients, in whom liver biopsies at 1 and 5 years after bariatric surgery, the liver biopsies showed improvement in simple steatosis and NASH but worsening of liver fibrosis. Histological improvement was seen mostly at 1 year after surgery. This was also evident 5 years after bariatric surgery (Mathurin, Hollebecque, et al. 2009). That is why the role of surgery in treating NAFLD is not clear. While some authors describe better histological findings after bariatric surgery (Stratopoulos, Papakonstantinou, et al. 2005), others describe the worsening of liver fibrosis (Chavez-Tapia, Tellez-Avila, et al. 2010).

Diabetes mellitus and Insulin resistance play an important role in the pathogenesis of NAFLD (Kotronen, Juurinen, et al. 2008). Mcpherson concluded that 80% of NAFLD patients, who had progression of liver fibrosis were diabetics (McPherson, Hardy, et al. 2015) That is why the treatment of T2DM could be a cornerstone in the therapy of NAFLD (Chen, Shieh, et al. 2013).

Pioglitazone is an Insulin sensitizer, improved hepatic inflammation and steatosis (Sanyal, Campbell-Sargent, et al. 2001, Belfort, Harrison, et al. 2006), however, this was not observed in non-diabetic patients. (Aithal, Thomas, et al. 2008).

Vitamin E has a positive effect on the oxidative stress in hepatocytes. Sanyal et al. studied its effect on NASH and showed that patients taking Vitamin E had better histological results compared to patients in the placebo group (Sanyal, Chalasani, et al. 2010). Similar results were reported in other publications (Hasegawa, Yoneda, et al. 2001, Harrison, Torgerson, et al. 2003)

In conclusion, new therapies are being developed to treat NAFLD. To date, Lifestyle modification and weight loss are still the cornerstones in treating NAFLD(Chalasani, Younossi et al. 2012). In those, were conservative therapy fails, offering bariatric surgery may affect positively on NAFLD through weight loss (Mathurin, Hollebecque et al. 2009).

1.6 Therapy of obesity

According to S3-German guidelines in bariatric surgery. Therapy is indicated for overweight and obesity when BMI 25-30 kg/m² if one of the following were met:

- An obesity-related disorder such as arterial hypertension, Type 2 Diabetes mellitus, etc.
- Abdominal obesity
- High psychosocial impact

Patients with a BMI ≥ of 30 kg/m² have an indication for therapy. In the presence of a consuming disease (e.g. cancer or AIDS) or pregnancy, there is no indication to treat obesity.

1.6.1 Conservative Therapy

The conservative treatment of obesity includes exercise, diet, and behavioral therapy. Weight management is divided into a weight reduction phase and weight maintenance phase. The keys to weight loss and maintenance are low-fat and low-calorie nutrition, constant nutritional behavior, and an active lifestyle (Klem, Wing, et al. 1997). Curioni and Lourenço described great success in weight loss when combining diet and exercise compared to diet alone. The combined group showed 20% more weight loss at the start and the 1-year follow-up (Klem, Wing, et al. 1997). The results of the National Weight Control Registry (NWCR) which included 2700 individuals, showed that a low-calorie diet with low-fat consumption prevented increases in body weight at follow-up (Phelan, Wyatt, et al. 2006). According to the German Nutrition Society is the intake of carbohydrates irrelevant for body weight (Hauner, Bechthold, et al. 2012). Furthermore, fast food (Phelan, Wyatt, et al. 2006), high-calorie drinks, and alcohol should be avoided for weight loss and weight maintenance(Breslow and Smothers 2005). A randomized control trial showed that regular consumption of food with low energy density (kcal/g) like soups, vegetables, and fruits, leads to greater weight loss compared to a normal diet(Rolls, Roe, et al. 2005).

In order to lose weight due to physical activity, it is required >150 min of exercise per week (Donnelly, Blair, et al. 2009) and to maximize loses in body fat, BMI, and waist circumference, a moderate-to-vigorous intensity aerobic activity is recommended (McTiernan, Sorensen et al. 2007). Increasing daily physical

activity in driving a bicycle to work and taking the stairs instead of the elevator leads to similar results to rigorous sport-programs (Anderson, Reynolds, et al. 2011).

Aside from diet and physical activity is behavioral therapy an essential part of a weight loss program. Behavioral therapy is divided into lifestyle interventions and cognitive-behavioral interventions, prevention of weight gain, Stimulus-control are part of these interventions (Anderson, Reynolds, et al. 2011).

The Achille's heel of conservative therapy is the high recurrence rate. According to Wing and Phelan, only 20% of obese can maintain their weight after undergoing weight loss programs. The risk of recurrence decreases after 2-5 years of stable weight (Wing and Phelan 2005).

The following are the recommendations of the American Association of Liver Disease (Chalasani, Younossi et al. 2012, Spengler and Loomba 2015) :

1. Recommend lifestyle modification:
    a. Weight loss of at least 5–10% of total body weight
    b. Aerobic exercise 3–5 times a week
    c. Minimization of alcohol use (no more than 1 drink/day for women, or 2 drinks/day for men)
2. Assess cardiovascular risks: lipid profile, fasting glucose and/or Hgb A1c, waist circumference, BMI
3. Manage comorbidities, including diabetes, dyslipidemia, hypertension, cardiovascular disease
4. Discontinue medications that may worsen steatosis: corticosteroids, amiodarone, methotrexate, tamoxifen, estrogens, tetracyclines, valproic acid
5. Obtain baseline liver evaluation, including liver ultrasound, CBC, liver panel (AST, ALT, bilirubin, alkaline phosphatase), INR, and creatinine
6. Consider referral for liver biopsy, if:
    a. The patient has risk factors for NASH and advanced fibrosis, including diabetes and/or metabolic syndrome

b. The patient has findings concerning for cirrhosis, such as thrombocytopenia, AST>ALT, or hypoalbuminemia

c. Patients are undergoing cholecystectomy or bariatric surgery and intraoperative biopsy is low risk

7. Consider pharmacotherapy if the patient has biopsy-proven NASH without cirrhosis and no absolute contraindications

8. Obtain appropriate screening if the patient has known cirrhosis:

    a. Right upper quadrant ultrasound every 6 months for HCC screening

    b. EGD screening for esophageal varices

    c. Referral to transplant center when appropriate

1.6.2 Surgical therapy of obesity

Surgical therapy is an important option in the treatment of obesity. In Germany, the indications for surgical intervention are according to S3-Guidelines (Runkel, Colombo-Benkmann, et al. 2011)

1.6.2.1 Indication and contraindication of bariatric surgery

According to patients BMI and the presence of obesity-related comorbidities, surgery is indicated.

If the patient has a BMI ≥ 35 kg/m² with simultaneous obesity-related disorders, or has a BMI ≥ 40 kg/m², surgical therapy is indicated by weight stagnation (<10% of weight loss) after 6 months of conservative therapy. In case, conservative therapy has no prospect of success, for example by complete immobility, surgical therapy is primarily indicated.

If the patient's BMI ≥ 50 kg/m², surgical therapy can be offered regardless of the presence of obesity-related comorbidities and without trying conservative therapy. In chronic diseases, unstable psychopathological status or consuming and neoplastic diseases, where the postoperative catabolic metabolic state can worsen, bariatric surgery is not recommended (Runkel, Colombo-Benkmann, et al. 2011)

1.6.2.2 Bariatric operations

In general, bariatric operations are either restrictive, malabsorptive, or a combination of both. The operations differ in their reversibility, complications rate, and their short-term and long-term outcome. We included only two types of operations in our study, namely SG and RYGB.

1.6.2.2.1 Restrictive Procedures

Restrictive operations aim to reduce the stomach volume. This leads to a decrease in the storage capacity of the stomach and produces an early feeling of satiety, which eventually leads to decreased food intake and weight loss. The restrictive procedures include sleeve gastrectomy (SG), gastric balloons, laparoscopic gastric banding.

1.6.2.2.1.1 Sleeve Gastrectomy

Sleeve gastrectomy is an irreversible restrictive procedure. This is usually done laparoscopically. This starts resecting the great omentum off the greater curvature, Great care should be taken to free the left crus of the diaphragm and the posterior wall of the stomach from retroperitoneal structures. For Calibration of gastrectomy, a 38 French bougie is introduced to control the diameter of the remaining stomach. Gastric transection starts 6 cm proximal to pylorus and continues up to the angle of his using a stapler device, we begin with two Black 45-mm reloads, followed by violet 60-mm reloads. After completion of transection, we oversew the stapled line using PDS 3.0.

Besides the restrictive effect of sleeve gastrectomy, it influences the production of gastric acid and Ghrelin after resecting the fundus and body of the stomach. Decreased Ghrelin levels in Plasma lead to a decrease in appetite(Karamanakos, Vagenas, et al. 2008).

After 1 year about 60%, excess weight loss can be achieved (Nocca, Krawczykowsky, et al. 2008, El Chaar, Hammoud, et al. 2015). Sometimes, SG is the first stage procedure to support a major second-stage procedure such as biliopancreatic diversion/duodenal switch when the health of the super-obese is fragile (Milone, Strong et al. 2005), this decreases the overall risk of the major operation compared with 1 stage operation in the super obese (Regan, Inabnet et al. 2003). Complications of this procedure include anastomotic leak, gastric

ischemia, bleeding, stenosis, and prolonged postoperative vomiting (Himpens, Dapri, et al. 2006).

1.6.2.2.2 Malabsorptive procedures

Malabsorptive procedures aim to decrease the absorption of nutrients. This can be achieved using, Roux-Y gastric bypass, Mini-bypass, single anastomosis duodenoileal bypass, and duodenal switch procedure. In our cohort, we only included patients who had RYGB.

1.6.2.2.2.1 Laparoscopic Roux-Y gastric bypass (RYGB/LRYGB)

The Roux-Y gastric bypass is the most common bariatric operation worldwide (Welbourn, Pournaras, et al. 2018). This is performed by creating a 30-ml pouch (Wittgrove and Clark 2000). In our center, we use 1 violet 45-mm reload, followed by two violets 60-mm reloads. The jejuno-jejunostomy is then performed using one white 45-mm reload with over-sewing of the remaining defect, creating a 50-cm biliary and a 150-cm alimentary limb. The gastro-jejunostomy is performed with a transoral assisted-anvil with a 25-mm green circular stapler.
The common limb is where the digestive juice mixes with food, breaking it into absorbable nutrients. The shorter the common limb is, the greater is the achieved malabsorption (Brolin, LaMarca, et al. 2002). RYGB can lead to a 70% EWL after 1 year (DeMaria, Sugerman, et al. 2002).

RYGB and SG are the most common bariatric operations in Germany (RYGB 46,8%, SG 43,7%) (Stroh, Weiner, et al. 2014).

2. Aim of the study

Obesity is an expanding pandemic that is increasing in prevalence worldwide (Collaborators, Afshin et al. 2017). NAFLD is associated with obesity and metabolic syndrome (Marchesini, Bugianesi, et al. 2003).

While many obesity-related disorders have fixed standards for the diagnostic and treatment. NAFLD is still not clearly understood, therefore lacks standardization. The primary aim of this study is to evaluate the influence of non-alcoholic fatty liver disease on weight loss and resolution of obesity-related comorbidities after bariatric surgery.

3. Methods and Materials

3.1 Collection of Data

3.1.1 Patient Selection

Using the prospective Database of “Adipositascentrum des Universitätsklinikums Hamburg-Eppendorf”, we identified patients who had an intraoperative liver biopsy due to abnormal liver appearance during bariatric surgery. The indication for bariatric surgery was according to S3 German Guidelines (Runkel, Colombo-Benkmann, et al. 2011). Only patients undergoing either SG or RYGB were included.

Anthropometric measurements and laboratory studies were collected preoperatively and at follow-up. Follow up was performed at our center or by expert external medical providers. Before the study, we obtained *informed consent from all subjects.*

3.1.2 Liver Histology

Formal consent was obtained from all patients preoperatively for the liver biopsy in case of abnormal macroscopic appearance. A wedge-shaped resection of the left lobe of the liver was performed at the end of Bariatric surgery in case of macroscopic abnormal appearance of the liver. All histologic specimens were reviewed by our pathologist. The liver biopsies were classified according to the NASH-CRN from Kleiner et al. scoring which postulated that a NAS score ≥ 5 is diagnostic for NASH (Kleiner, Brunt et al. 2005) According to NAFLD Score: NAS <3 (No NASH), NAS 3-4 (Borderline NASH) and NAS ≥ 5 (NASH) (Rastogi, Shasthry et al. 2017). All patients were additionally categorized into four histological groups: normal liver tissue with less than 5% steatosis, steatosis without a sign of fibrosis, fibrosis without a sign of cirrhosis, and cirrhosis.

3.1.3 Obesity-related diseases

All the associated diseases were extracted from the patients’ records, which were taken at the presentation in our bariatric surgery center, as well as at follow-up. Relevant metabolic associated diseases like type 2 diabetes mellitus, obstructive sleep apnea, arterial hypertension, and hyperlipidemia were documented.

Psychiatric evaluation for eating disorders and alcohol addiction was conducted preoperatively. Their presence was a contraindication for bariatric surgery.

3.2 Inclusion criteria

A retrospective evaluation was conducted for patients undergoing bariatric surgery at Adipositascentrum des Universitätsklinikum Hamburg-Eppendorf between September 2011 and October 2014. Only patients who received an intraoperative biopsy were included. Only those receiving sleeve gastrectomy or Roux-Y gastric bypass were included. All patients were adults ≥18 years. Written consent was received from all patients preoperatively. Histologies showing alcohol-induced liver disease were excluded.

3.3 Statistical analysis

The Data was collected in tables using *Microsoft Office Excel* then was analyzed using *IBM SPSS 24*. According to the NAFLD activity score, patients were divided into 3 groups: No NASH (NAS<3), Borderline (NAS= 3-4), and NASH (NAS>4). For categorical variables, Chi-square or Fisher exact tests were to show differences between groups. A *p-value* < 0.05 was considered significant.

For numerical variables Shapiro-Wilk test assessed normality. Because of abnormal distribution in our cohort, Wilcoxon Test was used to compare patient characteristics for the whole cohort preoperatively and postoperatively. Kruskal-Wallis test was used to compare the differences between these variables according to liver histology groups. A *p-value* ≤ 0.05 was considered significant. Lastly, the late outcome of patients with NASH (NAS>=5) was assessed according to operation (SG vs. RYGB) using the Mann-Whitney Test.

4. Results

4.1 Patient characteristics at baseline

Using our prospective Database, we identified 306 Patients, in whom a liver biopsy was conducted at the time of operation between September 2011 and October 2014. Ten patients were excluded because they underwent different types of bariatric surgery than SG and RYGB. 8 Patients were excluded due to other forms of liver disease (n=2, one patient with a primary biliary cirrhosis, one patient with hepatitis), absence of consent for research enrolment (n=3), or due to inadequate liver biopsy (n=3).

Table 3: Patient demographics at baseline

Patients	n= 288
Female sex, n (%)	200 (69.4 %)
Mean age, n (%)	43 y
Mean BMI, n (%)	52 ± 10.2 kg/m^2
Diabetes mellitus type II, n (%)	103 (35.7%)
Hyperlipidaemia, n (%)	179 (62.3%)
Hypertension, n (%)	180 (65.6%)
OSAS, n (%)	108 (37.5%)
GERD, n (%)	45 (15.6%)

Legend: n (%); number of subjects (Percentage), y; years, BMI: Body mass index, OSAS; obstructive sleep apnea, GERD; gastroesophageal reflux disease.

4.2 Liver histology at baseline

Out of 288, seventy patients (24.3%) had no signs of non-alcoholic fatty liver disease in their histology. 218/288 had histological evidence of NAFLD and 117 Patients had evident liver fibrosis in the histology (Table 3). Liver cirrhosis was diagnosed in 11 (3.8%) patients (Table 2).

Figure 1: NAFLD scores across the whole population at baseline

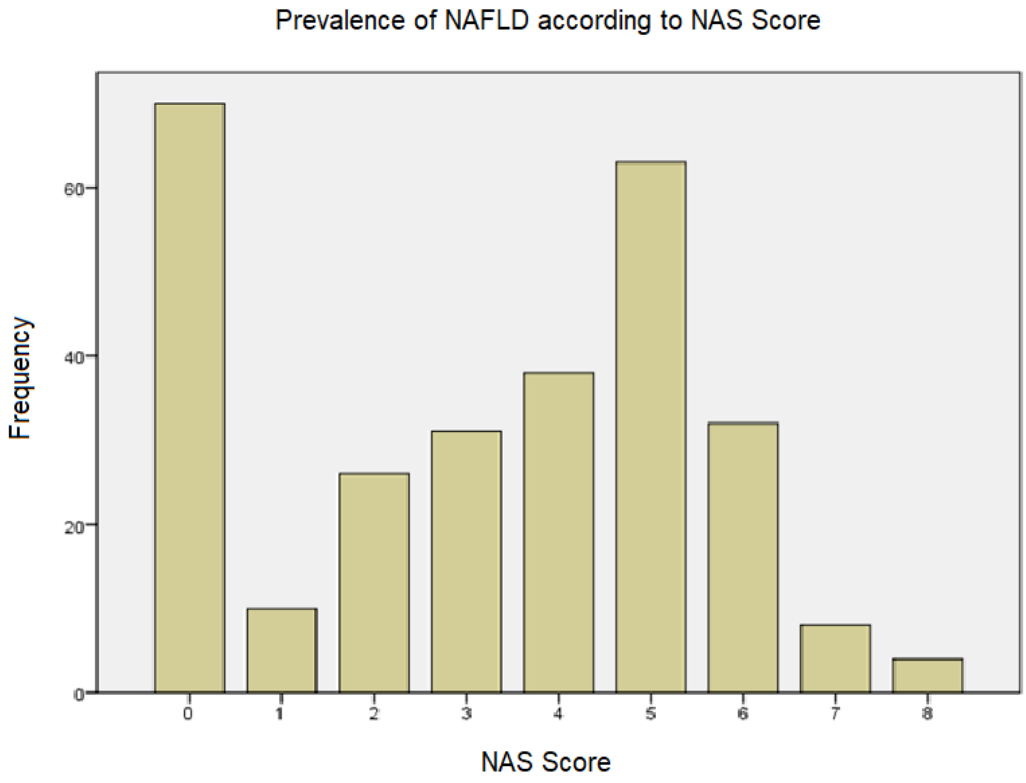


Table 4: Distribution of liver cirrhosis

	n=	Percentage %
No Cirrhosis	277	96,2%
Cirrhosis	11	3,8%
Total	288	100

Legend: n=, number of subjects.

Table 5: Distribution of liver fibrosis

Grade of Fibrosis	n=	Percentage %
0	171	59.4%
1	91	31.6%
2	11	3.8%

3	5	1.7%
4	10	3.5%
Total	288	100%

Legend: (n=), number of patients

Using the NAFLD activity score classification of Brunt et al (Brunt, Janney, et al. 1999). The liver biopsies were classified into 3 groups: NASH (NAS<3), Borderline (NAS= 3-4), and NASH (NAS>4) (Table 4 and Graph 2)

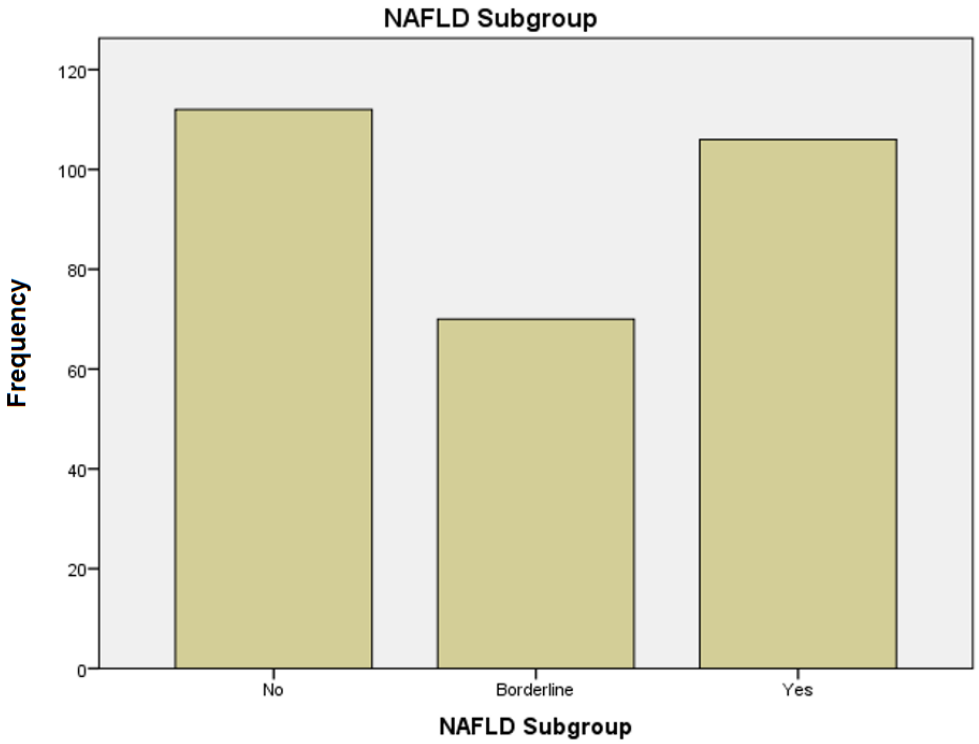
According to the NAFLD activity score (NAS) Brunt, et al. 106 (36.8%) Patients had NAS ≥ 5, which is the definitive criteria for diagnosing non-alcoholic steatohepatitis (NASH). 112/288 (38.9%) had NAS 0-2 which ruled out NASH. 70/288 (24.3%) had NAS 3-4, defined as borderline NASH.

Table 6: Distribution of NAFLD according to severity:

	N	Percent %
No NASH	112	38,9%
Borderline NASH	70	24,3%
NASH	106	36,8%
Total	288	100%

Legend: n; number of subjects, NASH; non-alcoholic steatohepatitis

Figure 2: Distribution of NAFLD according to severity:



Legend: (No); No NASH , (Borderline); Borderline NASH, (Yes); NASH.

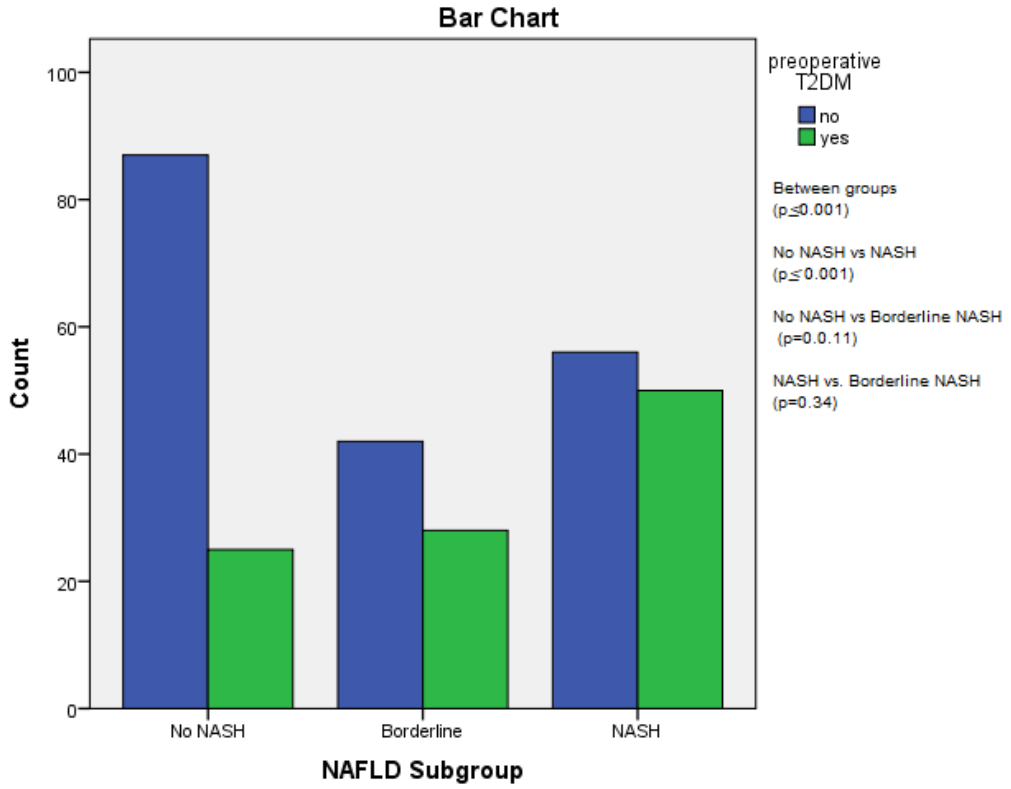
4.3 Obesity-related diseases at baseline

The frequency of arterial hypertension, type 2 diabetes mellitus, hyperlipidemia, obstructive sleep apnea syndrome and gastroesophageal reflux disease was collected preoperatively using our prospective Database.

Essential hypertension was the most associated disease with obesity preoperatively n=180 (65.6%), followed by hyperlipidaemia n=179 (62.3%), OSAS n=108 (37.5%) and diabetes mellitus n=103 (35.7%).

Preoperatively Diabetes mellitus type 2 was associated with NASH *p-value* ≤ *0.001* and Borderline NASH *p-value* = *0.011* compared to No NASH. All other obesity-related disorders were similar among all NAFLD groups.

Figure 3: Bar Chart showing the association of T2DM to different NAFLD groups preoperatively



Legend: T2DM, type 2 diabetes mellitus. NASH; non-alcoholic steatohepatitis, *p;* p-value according to x^2 test.

Table 7: Relation of obesity-associated disorders to NAFLD

Obesity-related disorder	**Association to NAFLD *p-value***	**NASH vs No NASH *p-value***
Type 2 Diabetes Mellitus	≤ 0.001	≤ 0.001
Hypertension	= 0.153	
Hyperlipidemia	= 0.138	
OSAS	= 0.968	
GERD	= 0.980	

Legend: GERD; gastroesophageal reflux disease, OSAS; obstructive sleep apnea syndrome, NASH; non-alcoholic steatohepatitis, *p;* p-value according to x^2 test.

4.4 Laboratory parameters at baseline

The following table shows the mean of the most relevant biochemical parameters of our cohort at baseline. Tests were performed according to the recommendations of S3-German Guidelines.

Comparison of the Laboratory parameters at baseline according to liver histology, shows worse HbA1c, AST, ALT, HDL, Triglyceride, and Vitamin D levels in the NASH group (Table 8).

Table 8: Laboratory parameters at baseline and their relation to NASH

Biochemical parameters	Results	*Association to NASH p-value*
HbA1c %	6.4 ± 1.4	<0.001
AST U/L	25.9 ± 18	<0.001
ALT U/L	33.4 ± 20	<0.001
CRP mg/dl	13.5 ± 11	0.16
LDL mg/dl	105 ± 32	0.80
HDL mg/dl	43.8 ± 12	<0.002
Triglyceride mg/dl	209 ± 108	<0.001
Total Cholesterol mg/dl	189 ± 38	0.68
Folic acid µg/l	7.9 ± 5	0.10
Vitamin B12 ng/l	522.5 ± 234	0.17
Vitamin D µg/l	12.2 ± 7	<0.01

Legend: p-value indicates significance according to Wilcoxon Test, HbA1c (normal < 6.5%), ALT alanine aminotransferase (normal, 10–35 U/L), AST aspartate aminotransferase (normal, 10–35 U/L), CRP C-reactive protein (normal <5 mg/L), serum triglycerides (normal, 70–180 mg/dL), Total Cholesterol (normal,

150-200 mg/dl), HDL high density lipoprotein (normal 45-65 mg/dl), LDL low density lipoprotein (normal <150mg/dl), Folic acid (normal, 4.6-18.7 µg/l), Vitamin B-12 (normal, 270-730ng/l), 1,25(OH)-D-Vitamin D (calcitriol) (normal > 30 pg/ml).

4.5 Type of operation

Only patients, who underwent SG or RYGB were included in this study. One hundred and forty-nine Patients 149 (51.7%) underwent SG. The rest of the patients 139 (48.3%) underwent RYGB.
The type of Operation was performed according to S3- German Guidelines and patient preference.

Table 9: Types of operation

	N	Percent
Sleeve Gastrectomy	149	51,7%
Roux-Y Gastric Bypass	139	48,3%
Total	288	100%

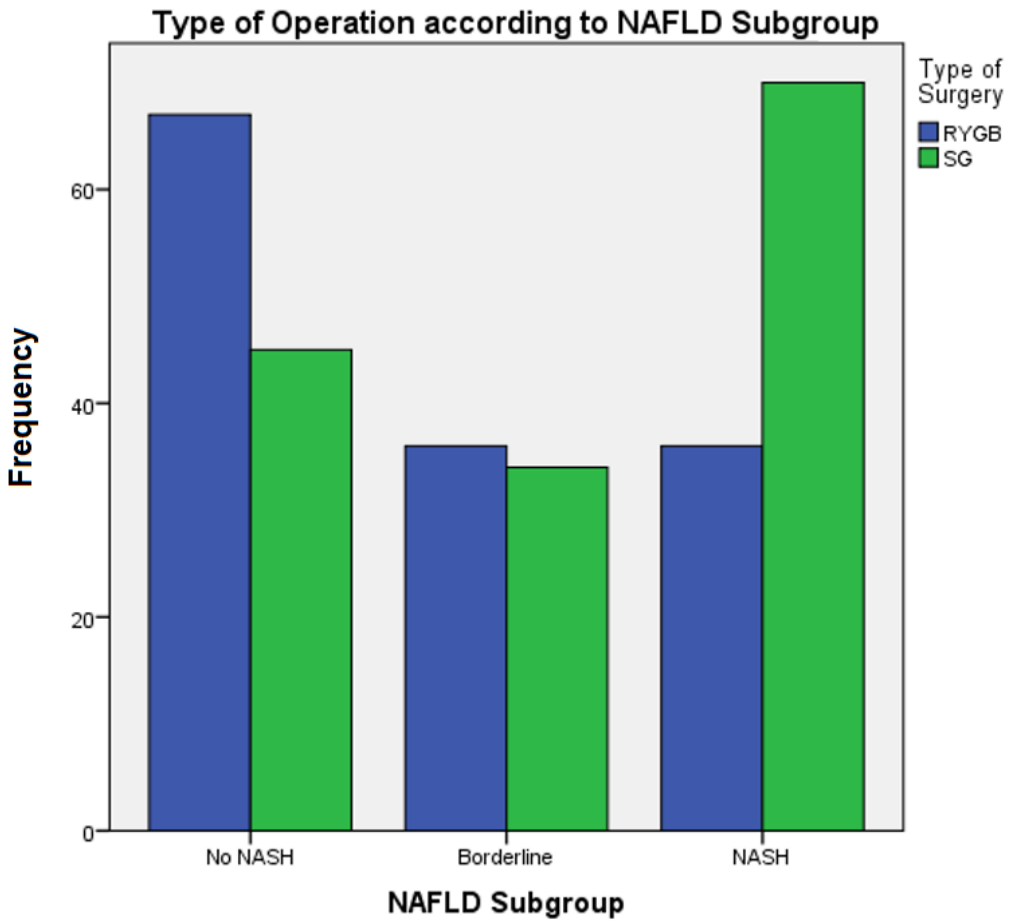
Legend: n; number of patients.

Table 10: Type of Operation according to histology

	RYGB	SG	Total
No NASH	67 (60%)	45 (40%)	112
Borderline	36 (51%)	34 (49%)	70
NASH	36 (34%)	70 (66%)	106
Total	139 (48%)	149 (52%)	288

Legend: RYGB; Roux-Y gastric bypass, SG; sleeve gastrectomy, NASH; non-alcoholic steatohepatitis.

Figure 3: Illustration of type of operation according to NAFLD



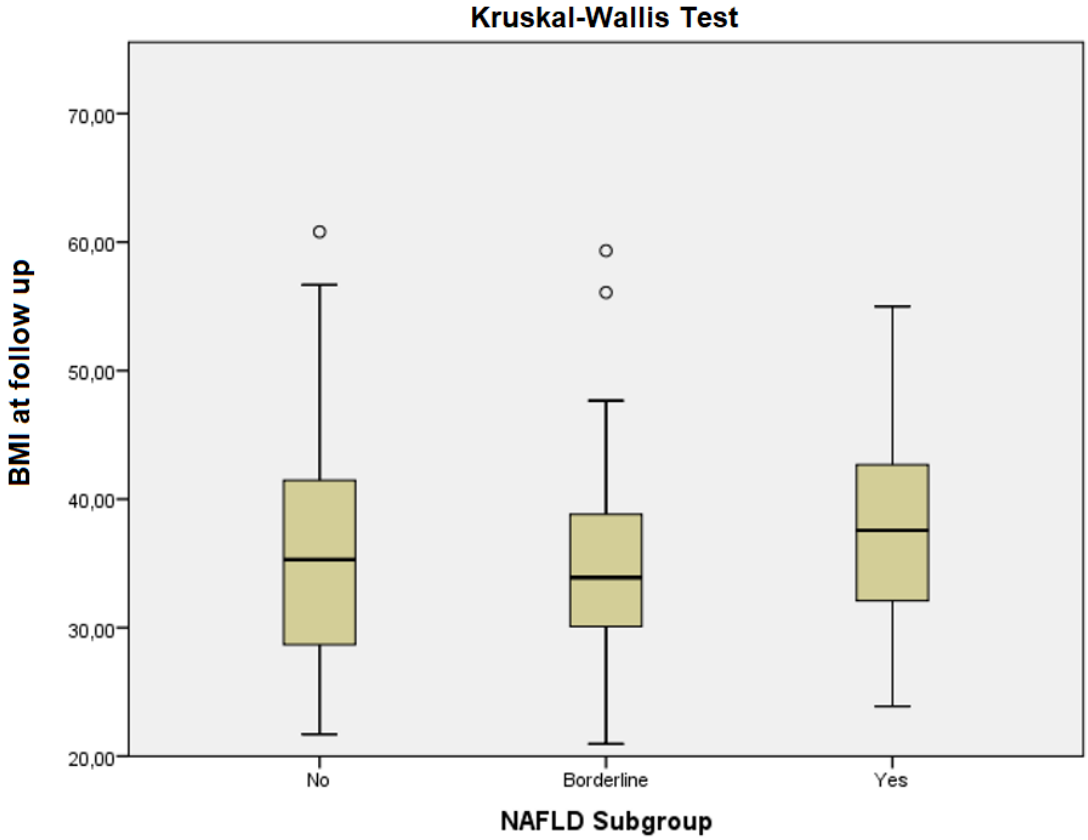
Legend: RYGB; Roux-Y gastric bypass, SG; sleeve gastrectomy, NASH; non-alcoholic steatohepatitis.

4.6 Patient characteristic at follow up and relation to NAFLD:

The follow-up was available for 234 patients (81.2%). The mean follow-up time was 24.9 months (± 13.6) and was carried out at our Institution or by external medical providers following the S3-German Guidelines.

At the time of follow up, the mean weight decreased to 105.5 ± 24. The mean BMI was 36.6 ± 8. Although there was a tendency for the NASH group to have higher BMI, it did not reach statistical significance (*p-value 0.056).*

Figure 5: Box-Plot showing relation of BMI at follow up to liver histology



Legend: (x) axis shows the three groups of NAFLD (No NASH, Borderline NASH, NASH), (y) axis shows BMI values at follow up.

Table 11: Patient Demographics at follow up

Patients	n= 234
Follow-up time	24.9 months (± 13.6)
Mean Weight kg	105.5 ± 24
Mean BMI, n (%)	36.6 ± 8 kg/m^2
Diabetes mellitus type II, n (%)	25 (11.4%)
Hyperlipidaemia, n (%)	69 (33%)
Hypertension, n (%)	79 (36.7%)
OSAS, n (%)	32 (14.9%)
GERD, n (%)	9 (4.2 %)

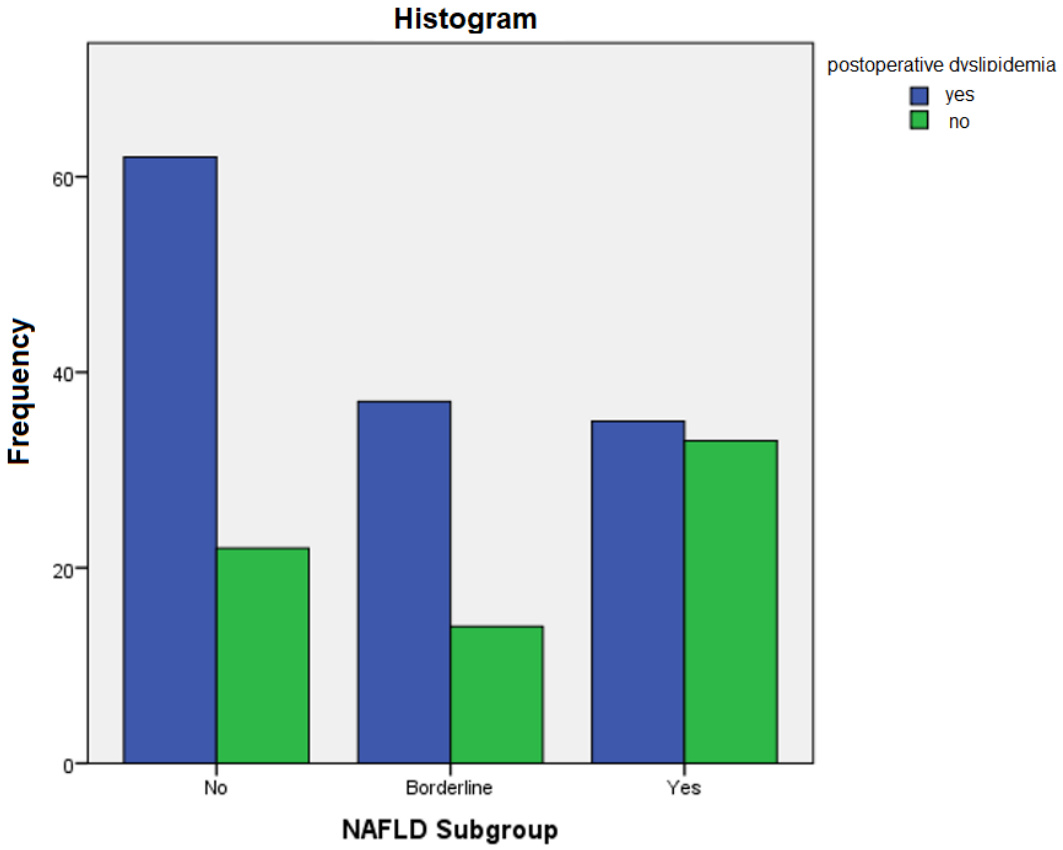
Legend: n (%); number of subjects (Percentage), BMI; body mass index, OSAS; obstructive sleep apnea, GERD; gastroesophageal reflux disease

4.7 Obesity-related disorders at follow up and relation to NAFLD

The frequency of arterial hypertension, diabetes mellitus type 2, hyperlipidemia, obstructive sleep apnea syndrome and gastroesophageal reflux disease was assessed at follow-up.

After bariatric surgery, the incidence of associated disease dropped drastically: arterial hypertension from n=180 (65.6%) to n=79 (36.7%), Hyperlipidaemia from 179 (62.3%) to n=69 (33%), OSAS from 108 (37.5%) to n=32 (14.9%) and diabetes mellitus type 2 from 103 (35.7%) to n=25 (11.4%). When analyzing the prevalence of obesity-related disorders to NAFLD subgroups, only hyperlipidemia was associated with NASH compared to No NASH and Borderline NASH *p-value (0.002)* and *(0.04)* respectively. All other obesity-related disorders showed no significance concerning NASH at follow up.

Figure 6: Association of hyperlipidemia at follow up according to liver histology



Legend: No; No NASH (NAS<3), Borderline; Borderline NASH (NAS= 3-4), Yes; NASH (NAS≥ 5)

4.8 Laboratory parameters at follow up

Table 12: Comparison between laboratory parameters at baseline and follow up

	Baseline	At follow up	*Before/After Association p-value*
HbA1c %	6.4 ± 1.4	5,5 ± 1	<0.001
AST U/L	25.9 ± 18	22.5 ± 24.3	<0.001
ALT U/L	33.4 ± 20	25.8 ± 27.1	<0.001
GGT U/L	68.8 ± 80	29.3 ± 30	<0.001
CRP mg/dl	13.5 ± 11	7 ± 6	<0.001
LDL mg/dl	105 ± 32	93.9 ± 33	<0.001
HDL mg/dl	43.8 ± 12	59.3 ± 18	<0.001
Triglyceride mg/dl	209 ± 108	149.8 ± 99	<0.001
Cholesterol mg/dl	189 ± 38	180.5 ± 36.2	0.006
Folic acid µg/l	7.9 ± 5	10.4 ± 6.1	<0.001
Vitamin B12 ng/l	522.5 ± 234	564.5 ± 297	0.29
Vitamin D µg/l	12.2 ± 7	25.8 ± 11.6	<0.001

Legend: p-value indicates significance according to Wilcoxon Test, HbA1c (normal < 6.5%), ALT alanine aminotransferase (normal, 10–35 U/L), AST aspartate aminotransferase (normal, 10–35 U/L), CRP C-reactive protein (normal <5 mg/L), serum triglycerides (normal, 70–180 mg/dL), Total Cholesterol (normal, 150-200 mg/dl), HDL high density lipoprotein (normal 45-65 mg/dl), LDL low density lipoprotein (normal <150mg/dl), Folic acid (normal, 4.6-18.7 µg/l), Vitamin B-12 (normal, 270-730ng/l), 1,25(OH)-D-Vitamin D (calcitriol) (normal > 30 pg/ml).

The Wilcoxon test was used to assess the before and after results of laboratory parameters in the whole population. There was a significant improvement in all the above parameters (Table 11), except Vitamine B12 with a *p*-value 0.2

4.9 Laboratory parameters at follow-up and its relation to NASH

The Kruskal-Wallis test was used to identify the relevance of different NAFLD subgroups on the laboratory parameters at follow-up. Lower HDL, higher Triglyceride, and Cholesterol levels were associated at follow up with NASH with a *p-value 0.03, 0.04, and 0.03* respectively.

Table 13: The laboratory parameters at follow-up and its relation to NASH.

Biochemical parameters	results	Relation to NASH p-value
HbA1c %	5,5 ± 1	0.41
AST U/L	22.5 ± 24.3	0.27
ALT U/L	25.8 ± 27.1	0.14
GGT U/L	29.3 ± 30	0.89
CRP mg/dl	7 ± 6	0.17
LDL mg/dl	93.9 ± 33	0.057
HDL mg/dl	59.3 ± 18	0.03
Triglyceride mg/dl	149.8 ± 99	0.041
Cholesterol mg/dl	180.5 ± 36.2	0.039
Folic acid µg/l	10.4 ± 6.1	0.98
Vitamin B12 ng/l	564.5 ± 297	0.69
Vitamin D µg/l	25.8 ± 11.6	<0.001

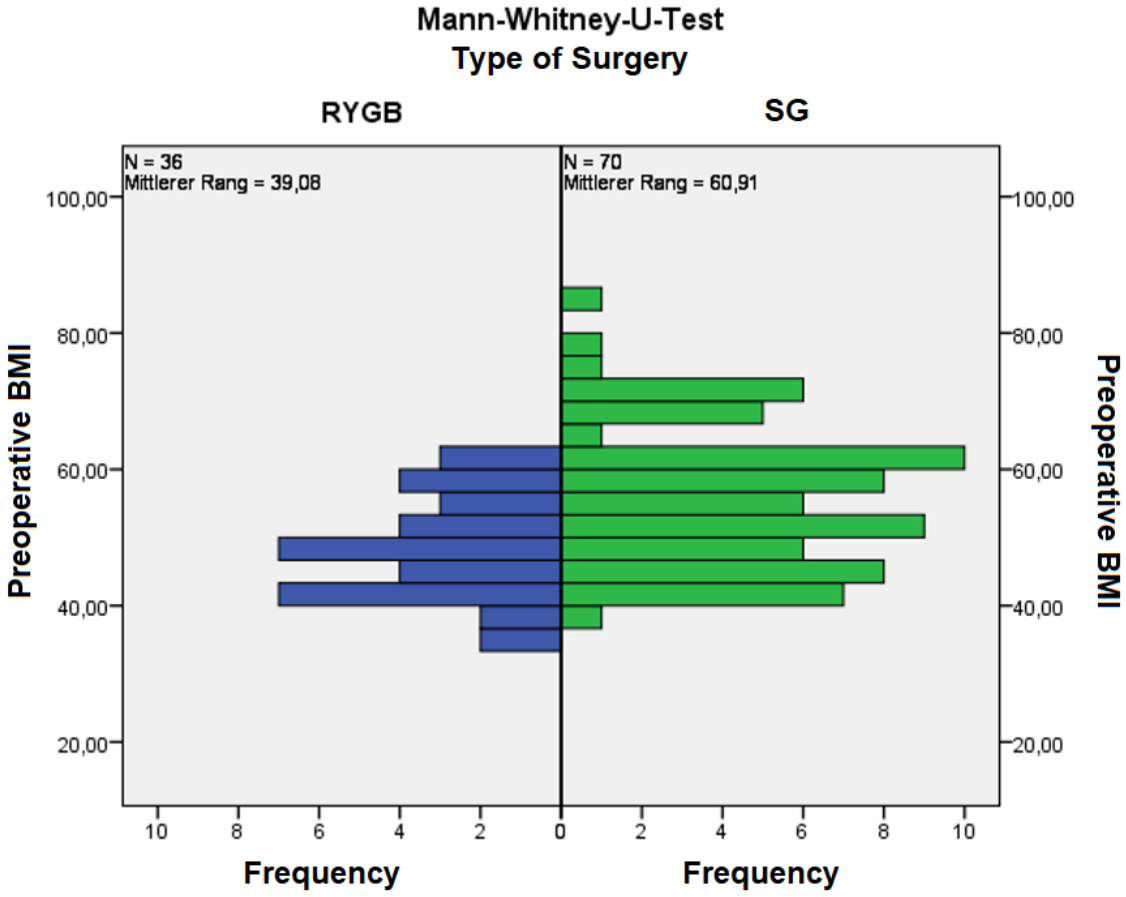
Legend: p-value indicates significance according to Wilcoxon Test, HbA1c (normal < 6.5%), ALT alanine aminotransferase (normal, 10–35 U/L), AST aspartate aminotransferase (normal, 10–35 U/L), CRP C-reactive protein (normal <5 mg/L), serum triglycerides (normal, 70–180 mg/dL), Total Cholesterol (normal, 150-200 mg/dl), HDL high density lipoprotein (normal 45-65 mg/dl), LDL low density lipoprotein (normal <150mg/dl), Folic acid (normal, 4.6-18.7 µg/l), Vitamin B-12 (normal, 270-730ng/l), 1,25(OH)-D-Vitamin D (calcitriol) (normal > 30 pg/ml).

4.10 Late outcome of NASH group at follow up according to the type of operation

In a subgroup analysis for patients with NASH only, BMI and laboratory parameters were assessed at follow-up and compared according to the type of surgery (Sleeve Gastrectomy vs. Roux-Y Gastric Bypass). There was no difference in BMI at follow-up between both groups p-value 0.07, although at baseline the SG group had a higher BMI p-value 0.001.

Further analysis showed lower levels of ALT, AST, GGT in the SG group, *p-value 0.029*, *0.06,* and *0.04* respectively compared to the RYGB group. However; better levels of LDL *p-value 0.002* and Cholesterol *p-value 0.01* at follow-up were associated with RYGB.

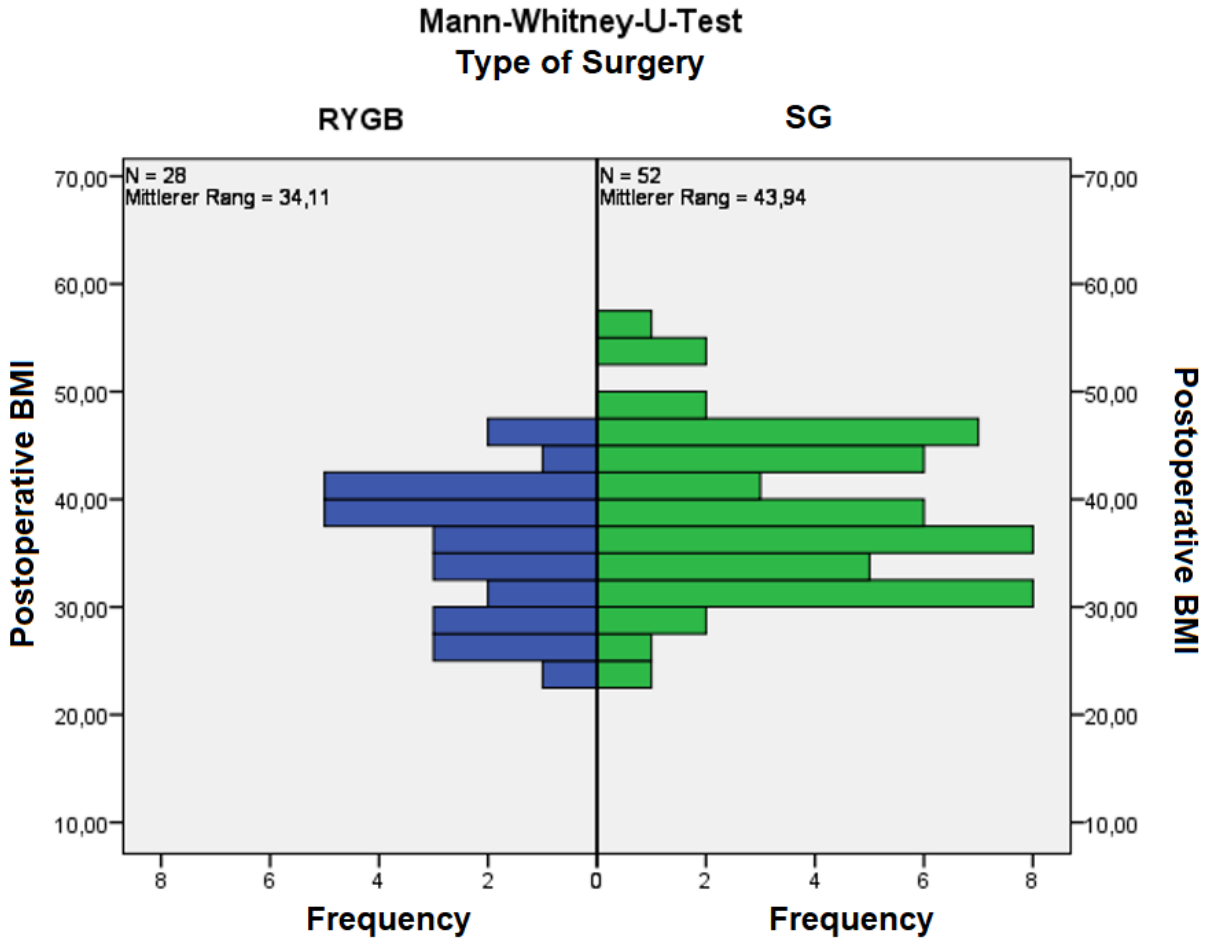
Figure 7: BMI at baseline according to operation using the Mann-Whitney Test:



Legend: Preoperative BMI; Body Mass Index at baseline, SG; Sleeve Gastrectomy, RYGB; Roux-Y Gastric Bypass. Patients with NASH who

underwent SG had significantly higher BMI compared to RYGB patients **p≤0.001** at baseline.

Figure 8: BMI of patients at follow up according to operation using Mann-Whitney test



Legend: SG; Sleeve Gastrectomy, RYGB; Roux-Y Gastric Bypass. Patients with NASH who underwent SG tended to have higher BMI at follow up than patients with RYGB **p=0.074**

5.Discussion

5.1 Patient characteristics

This retrospective study was conducted for patients undergoing bariatric surgery at Adipositascentrum des Universitätsklinikum Hamburg-Eppendorf between January 2012 and June 2014.

In our cohort, a female predominance was noted at 69.4%. According to the report of Robert Koch Institute for the prevalence of Obesity in Germany 2012, Obesity is in males and females comparable 23.3% vs 23.9%.

Many publications in the field of bariatric surgery with similar patient numbers show similar female proportions (Sjostrom, Lindroos, et al. 2004), some papers show female proportion as high as 78% (Mathurin, Hollebecque, et al. 2009, Kleiner, Berk, et al. 2014). This could be explained because female patients seek help more than male patients. The causality for this phenomenon has not yet been explained (Kolotkin, Crosby, et al. 2008).

The mean age in our cohort was 43.4 years (± 11.9). This was comparable to other publications (Mathurin, Hollebecque, et al. 2009, Kleiner, Berk, et al. 2014).

The mean preoperative BMI in our cohort was 52 (± 10) kg/m². This was similar to other cohorts (Mathurin, Hollebecque, et al. 2009), on the other side, the Swedish study, which examined 4047 patients undertaking bariatric surgery, had a lower mean BMI of 42 kg/m² (Sjostrom, Lindroos et al. 2004).

5.2 Obesity-related disorders

As previously stated bariatric surgery is related to several comorbidities, namely, diabetes mellitus, arterial hypertension, hyperlipidemia, OSAS and NAFLD.

The most common obesity-related disorder in our patient collective was arterial hypertension n=180 (65.6%) of the 288 included patients at baseline. Our results are similar to Biertho et al. and Costa et al (Biertho, Lebel et al. 2014, Costa, Yamaguchi, et al. 2014). Another common comorbidity in obese is type 2 diabetes mellitus. In our cohort was the prevalence as high as 35.7%. In a study of the anti-diabetic effects of bariatric surgery which included 17670 patients, showed a similar prevalence of diabetes (31.2%) to our cohort (Weiner, El-Sayes, et al. 2014).

In terms of hypertriglyceridemia, the prevalence of the disease varies according to the definition. When defined as >150 mg/dl in serum, the prevalence was 67,6%, but when defined as >180mg/dl the prevalence dropped to 49.7%.
When comparing our results to similar studies from Andrade-Silva et al. (Andrade-Silva, Caranti, et al. 2014) and Visockiene et al. we had a higher Incidence of Hypertriglyceridemia. Andrade-Silva et al. reported a prevalence of 47.8%, whereas Visockiene reported only 52,4%. In both studies 150 mg/dl, the cut off for defining hypertriglyceridemia.
In our cohort, the mean of triglyceride level in serum was 209 ± 108, which was pathologic for both cut-off levels. The maximum detected triglyceride level was 771. Very severe hypertriglyceridemia, which is defined as triglyceride levels in serum between 1000-1999 mg/dl (Hegele, Ginsberg, et al. 2014), that could precipitate acute pancreatitis(Valdivielso, Ramirez-Bueno et al. 2014) was not detected in our cohort.
Another common comorbidity related to obesity is obstructive sleep apnea. In our cohort was the prevalence of OSAS (35.7%) at baseline. According to Martí-Valeri et al. 44% of his bariatric patients suffered from OSAS(Marti-Valeri, Sabate, et al. 2007). Biertho et al. reported an even higher prevalence of OSAS (63%) in his 378 bariatric patients (Biertho, Lebel, et al. 2014). In conclusion, our cohort included a typical patient collective for bariatric surgery at baseline.

5.3 Liver Histology and NAFLD

In our cohort, (75.6%) patients had histological signs of NAFLD. This is similar to other publications (Kroh, Liu, et al. 2007). Also, 36.8% of our patients suffered from non-alcoholic steatosis hepatitis (NASH), which is an inflammatory asymptomatic advanced liver disease, that could lead to extensive liver fibrosis, cirrhosis, and eventually hepatocellular carcinoma (Day 2002). However, it is important to recognize that our biopsies were done, only when a macroscopic abnormality was intraoperatively detected. Which could mean, that the true prevalence of NAFLD, NASH, and liver cirrhosis is lower.
In the western world, the prevalence of NASH is 2-3% in adults (Neuschwander-Tetri and Caldwell 2003). However, in bariatric patients the prevalence of NASH is higher and varies in the literature, it lies between 26% (Total patient collective n=212) (Ong, Elariny, et al. 2005) and 98% (Total patient collective n=51). Kleiner

et al. reported the prevalence of NASH to be 16,2% in 693 Patients (Kleiner, Berk, et al. 2014). According to Machado et al. the mean prevalence of NASH in bariatric patients is about 37% (Machado and Diehl 2016), which is similar to our results (36.8%).

Moreover, we identified 11 Patients who suffered from liver cirrhosis (3.8%), The incidence is higher compared to other publications, this may be attributed to the high BMI in our patients. In the other studies, the rate of cirrhosis ranged from 0% (Total collective n=106) to 1.2% (Total collective n=693)(Fassio, Alvarez, et al. 2004, Kleiner, Berk, et al. 2014). Also Machado et al. reported in a review of 10 studies, that the mean prevalence of liver cirrhosis is almost 1.4% in bariatric patients (Machado, Marques-Vidal, et al. 2006).

Nevertheless, higher rates of cirrhosis were also reported. For example in a study from Shalhub et al., the rate of newly diagnosed liver cirrhosis was as high as 7%(Shalhub, Parsee, et al. 2004).

In our patients, a correlation between liver cirrhosis and BMI could not be found. This was also shown in retrospective analysis from Younus et al. In their cohort patients with liver cirrhosis had even lower BMI levels than non-cirrhotic patients (46 kg/m^2 vs. 52 kg/m^2) (Younus, Sharma et al. 2019).

NASH-associated Liver cirrhosis has become one of the most common indications for liver transplant (Wong, Aguilar, et al. 2015). Important is to identify patients with advanced liver disease, in order to provide timely treatment and surveillance. It is alarming that in our cohort 11 patients suffered from asymptomatic NAFLD-associated liver cirrhosis, these patients are at high risk of developing Hepatocellular carcinoma.

Hepatocellular carcinoma, which has been rising in incidence in the last decade, is now the second leading cause of cancer death worldwide (Wallace, Preen, et al. 2015).

In the absence of periodic control in patients with NAFLD, the incidence of non-curable hepatocellular carcinoma increases (Pocha, Kolly, et al. 2015). Hepatocellular carcinoma can also rise in NASH without the presence of cirrhosis. Stine et al. reported in a metanalysis of 19 studies that the incidence of HCC was seen in up to one-third of non-cirrhotic NASH patients (Stine, Wentworth, et al. 2018). This is driven through lipotoxicity and insulin resistance leading to fibrogenesis, inflammation, and abnormal proliferation and alteration of cell death

(Baffy, Brunt et al. 2012). Non-cirrhotic NASH patients also have inferior outcomes, decreased survival rates, and increased Mortality after the diagnosis of HCC compared with other non-cirrhotic liver disease etiologies of HCC (Younossi, Otgonsuren et al. 2015, Hassan and Gane 2019). That is why the S3 German guidelines for HCC recommend screening ultrasound and Alpha-fetoprotein levels every 6 months in patients with NASH. This recommendation was based on the good outcome and higher survival rates in screened asymptomatic HCC patients, in whom the 5-year survival exceeded 50% (Bruix, Sherman et al. 2011) unlike diagnosing HCC after appearance of symptoms, which is associated with a worse 5-year survival rate of 0-10% (Llovet, Burroughs et al. 2003). Based on these observations stated Dhanasekaran et al. that HCC screening can be extended to all patients with morbid obesity and not confine it to NASH patients. Howell et al. suggested that, this could eventually lead to a decrease in liver transplantation due to decreased incidence NAFLD associated liver failure and cirrhosis (Howell, Balderson et al. 2016).

We also detected in our cohort a high incidence in liver fibrosis 40.6%. This high incidence of liver fibrosis was also reported in a similar publication. It ranged between 36.1%(Kleiner, Berk, et al. 2014) and 40% (Machado, Marques-Vidal, et al. 2006).

The high incidence of liver disease in patients undergoing bariatric surgery leads to the question if routine liver biopsy should be implemented during bariatric surgery as recommended by some authors (Shalhub, Parsee, et al. 2004, Kleiner, Berk, et al. 2014), which could lead to early disease recognition and control.

The high incidence of liver cirrhosis 3.8% and fibrosis 40.6% in our study, emphasizes the importance of close surveillance in these patients. According to some authors, the progression of liver fibrosis is seen in up one-third of the patients at 4 years (Fassio, Alvarez, et al. 2004).

5.4 NAFLD and macroscopic examination

Globally, the incidence of obesity increases steadily over time, so that more patients suffering from liver diseases will be encountered in the future. A drawback is the limited ability of the surgeons in recognising liver disease based on its macroscopic appearance.

In a clinical trial including 51 patients undergoing bariatric surgery, the surgeon assessed the liver macroscopically for the presence of NASH. Clinical and histological assessments were compared. This study showed that macroscopic examination had a sensitivity of 14%, a specificity of 56%, and that macroscopic examination is a poor tool to identify NASH (Teixeira, Bellodi-Privato, et al. 2009).

5.5 NAFLD and current diagnostic methods

Due to the high number of individuals with NAFLD worldwide, great efforts are done for establishing cost-effective strategies for the screening of NASH, advanced fibrosis, and cirrhosis (Castera, Friedrich-Rust, et al. 2019). Reliable non-invasive methods for diagnosing and following up on NASH are still not available. There is no serum marker with high sensitivity and specificity that distinguishes simple steatosis from NASH (Helling, Helzberg, et al. 2008). Like in our cohort, generally serologic liver function tests are not specific, since many patients with NASH have normal levels of ALT and AST (McPherson, Stewart, et al. 2010). AST and ALT are general markers for cellular liver damage, so increased levels of AST and ALT cannot differentiate between different causes of liver damage and are not specific for NASH. Using AUROC (Area under Receiver Operating Characteristic) analysis, Subasi et al. reported that different non-invasive panel scores like FIB-4, NAFLD fibrosis score did not reach significant sensitivity or specificity (AUROC> 0.75) for NASH and that these non-invasive panels have similar efficacy in detecting NAFLD (Subasi, Aykut et al. 2015).

The benefit of imaging studies in NAFLD is still limited. Ultrasound, which is generally used in the workup of liver diseases, cannot differentiate between simple hepatic steatosis and the presence of Inflammation like NASH. Also, the sensitivity in detecting NAFLD using ultrasound is reduced in the obese (Bril, Ortiz-Lopez, et al. 2015).

Newer imaging modalities like elastography have limited informative value in case of obesity, which is usually associated with NAFLD (Castera, Forns, et al. 2008). Other imaging modalities like MRI and CT-scan are not always applicable, because of the large body habitus in the obese, so that many patients may not fit in the scanners and may even exceed the recommended table weight load-limit (Fursevich, LiMarzi, et al. 2016). All this makes liver biopsy during bariatric

surgery a good screening method that can be routinely and safely performed during bariatric surgery. Nevertheless, some authors still stand against routine liver biopsy. According to Laurin et al., Liver biopsy in bariatric surgery has no consequences, since a reliable therapy is not available and the complications accompanying a liver biopsy like bleeding should not be underestimated (Laurin 2002). However, in our cohort, complications like bleeding, liver damage, bile leakage were not perioperatively encountered and we were able to identify 11 Patients with asymptomatic liver cirrhosis, who were put under strict surveillance. The safety of the liver biopsy was also reported by other Authors (Dolce, Russo et al. 2009, Collins, Beban, et al. 2019).

Due to the unreliable results of using non-invasive methods in screening for NAFLD, a concrete methodology for following up patients with a positive diagnosis for NASH should be implemented. Patients who undergo bariatric surgery are expected to lose weight so that some non-invasive methods like ultrasound, elastography, MRI might become adequate (Castera, Forns, et al. 2008, Bril, Ortiz-Lopez, et al. 2015), However till now all imaging modalities were of limited value for monitoring treatment over time (Bril, Ortiz-Lopez et al. 2015). This leads to the question, if a second biopsy is needed in order to follow up on the disease after bariatric surgery and whether the risk outweighs the benefits of such a procedure. This again emphasizes the importance of developing a reliable non-invasive method for diagnosing and monitoring NAFLD.

As previously stated, in our center no complications were encountered after liver biopsy. Thanks to these biopsies, we identified 11 Patients with asymptomatic liver cirrhosis, that otherwise would not be recognized.

5.6 Type of Operation and NAFLD

We included in our cohort only patients undergoing RYGB and SG. 139 Patients had a RYGB (48.2%) the rest n=148 (51.8%) received SG. Since macroscopic evaluation and identification of liver disease is intraoperatively not possible (Teixeira, Bellodi-Privato, et al. 2009).

Interestingly, Patients with NASH had more sleeve gastrectomies (66%) compared to RYGB 34%. This was also reported in a retrospective analysis of 53 patients who underwent a second biopsy after bariatric surgery, 34 patients (64.1%) had initially a sleeve gastrectomy (von Schonfels, Beckmann, et al.

2018). This may be due to the association of NASH with cardiovascular disease, where antiplatelet medication or anticoagulation is part of the therapy. These patients undergo usually sleeve gastrectomy because the bioavailability of these medications after RYGB is not known. Another reason is that, in presence of macroscopic features of liver cirrhosis, a sleeve gastrectomy is done to avoid worsening of liver fibrosis, as previously stated.

5.7 Effect of bariatric surgery at follow up

The follow-up was available for 234 patients (81.2%). The mean follow up time was 24.9 months (± 13.6) and was carried out at our Institution or by external medical providers following the S3-German Guidelines (Runkel, Colombo-Benkmann, et al. 2011). During this time 2 patients died, one patient died of advanced osteosarcoma and the other patient died of myocardial infarction.

At follow-up, the median BMI was 36.2 (± 7) kg/m². 61% of the patients showed an excess weight loss above 50%. The BMI of our patients at follow up was similar to the results of other studies (Golzarand, Toolabi, et al. 2017, Peterli, Wolnerhanssen, et al. 2018). In a meta-analysis of 80 studies for long term follow up after bariatric surgery, patients undergoing RYGB lost -13.75 kg/m² vs. 11.32 kg/m² for patients who underwent sleeve gastrectomy at long term follow up(Golzarand, Toolabi et al. 2017). In our cohort, the mean BMI loss was higher 15.4 kg/m² at follow up with no significant difference between both operations.

Not less important is the resolution of obesity-related comorbidities. At baseline was the prevalence of type 2 diabetes mellitus 37.5%, hypertension 65.6%, hyperlipidemia 62.3%, obstructive sleep apnea 37.6% and GERD 15.6% and dropped postoperatively to 11.4%, 36.7%, 33%, 14.9% and 4.2% respectively. This was similar to the results of the swiss SM-BOSS trial, a randomized clinical trial to assess the effect of SG and RYGB on weight loss in morbid obesity (Peterli, Wolnerhanssen, et al. 2018).

Liver function was assessed at baseline and follow-up using serologic studies. The levels of AST (25.9 ±18 U/L), ALT (33.4 ±20 U/L), GGT (68.8 ±80 U/L) improved significantly at follow up (22.5 ±24 U/L), (25.8 ±27 U/L), and (29 ±30 U/L) respectively. This was similar in other studies (Kalinowski, Paluszkiewicz, et al. 2017, Motamedi, Khalaj, et al. 2019). Although the prevalence of NAFLD in our cohort was as high as 75.6% the mean levels for AST and ALT were in the

normal range. This range as well as the applied values for the upper limit of normal ALT (approximately 40 IU/L) were established in the 1980s. These were primarily for screening for viral hepatitis A and B. This could be the explanation of normal AST and ALT levels despite the presence of NAFLD. That is why some studies have lowered the threshold of ALT to improve the sensitivity and negative predictive value of ALT in patients with HCV and NAFLD (Kariv, Leshno, et al. 2006, Ooi, Burton, et al. 2017).

The lipid profile was also controlled at follow up. LDL, HDL, triglyceride, and total cholesterol levels improved significantly at follow-up. LDL dropped from 105 ± 32 mg/dl to 93.9 ± 33 mg/dl *(p-value <0.001)*, HDL increased from 43.8 ± 12 mg/dl to 59.3 ± 18 mg/dl *(p-value <0.001)*, triglyceride dropped from 209 ± 108 mg/dl to 149.8 ± 99 mg/dl *(p-value <0.001)* and total cholesterol dropped from 189 ± 38 mg/dl to 180. 5 ± 36.2 mg/dl *(p-value <0.001).* This was reflected by a drastic decrease in the incidence of Hyperlipidemia from n=179 (62.3%) to n=69 (33%). Some authors reported complete remission of hyperlipidemia at 1 year in 96.3% of the patient after bariatric surgery (Climent, Benaiges, et al. 2017). The improvement in the lipid profile of the patients provides a long-term protective cardiovascular effect. Sjöström et al. reported a reduction in the number of cardiovascular events (HR 0.47) and cardiovascular deaths (HR 0.67) in obese adults after bariatric surgery (Sjostrom, Lindroos, et al. 2004).

Regarding micronutrient status in our cohort. Vitamin levels like folic acid, Vitamin B12, and Vitamin D were assessed at the follow-up. The levels of folic acid and vitamin D improved at follow-up significantly *p-value <0.001*. Vitamin B12-level was normal before and after surgery and showed no statistical difference at follow up. The good micronutrient status in our patients may indicate good compliance of our patients to medication and shows the importance of regular follow up visits after bariatric surgery to ensure adequate intake of medication. This was also reported by Johnson et al. in a retrospective analysis of micronutrients after bariatric surgery. In their cohort, vitamin B12 and folate deficiency were uncommon. He also reported improved levels of Vitamin D after surgery (Johnson, Ikramuddin, et al. 2019).

5.8 Effect of NAFLD at baseline and on the late outcome after bariatric surgery.

The association of NAFLD with the anthropometric and biochemical measurements as well as with obesity-related comorbidities was assessed at baseline and follow-up.

At follow up higher BMI levels tended to be in the NASH group compared with other groups, yet it did not reach statistical significance *(p-value 0.056)*. the BMI loss (15,8 kg/m²) was similar to other bariatric surgery publications (Golzarand, Toolabi, et al. 2017, Peterli, Wolnerhanssen, et al. 2018).

Hypertension, OSAS, and GERD improved significantly at follow up. The improvement was independent of the presence of NASH in the histology. Interestingly, the prevalence of type 2 diabetes mellitus at follow-up was not associated with liver histology, however, the preoperative mean HbA1c was higher in patients with NASH 6.7% compared to Borderline 6.3% *(p-value 0.05)* and no NASH 6.0% *(p-value 0.001).* At follow up there was no difference between groups *(p-value 0.4)* with a total mean of HbA1c 5.5%. Our results differ from Cazzo et al., who reported that T2DM was associated with NASH after bariatric surgery (Cazzo, Jimenez et al. 2018).

Hyperlipidemia in NAFLD is atherogenic in nature and is characterized by hypertriglyceridemia, high LDL, and low HDL (Chatrath, Vuppalanchi, et al. 2012). these features are found in our patients at baseline. Treating patients with NAFLD and Hyperlipidemia is a challenge since the pharmacological effects of many drugs in patients with NAFLD with elevated liver profiles are still debatable. Although some authors suggest that NASH is associated with higher levels of non-HDL cholesterol (Wang, Wang, et al. 2018), in our cohort in the incidence of Hyperlipidemia was not different between NAFLD subgroups preoperatively (*p-value = .075).* However, at follow up Hyperlipidemia was associated to NASH compared to No NASH (*p-value = 0.002*) and to borderline NASH *(p-value = 0.04).* This could be because even with the resolution of NASH in bariatric patients, high non-HDL-Cholesterol may persist as suggested by Corey et al. (Corey, Vuppalanchi, et al. 2015), which implicates that pharmacological therapy on top of bariatric surgery may be needed in patients with biopsy-proven NASH, to avoid possible cardiovascular complications of hyperlipidemia in the future.

5.9 Effect of type of surgery on the NASH.

RYGB and SG are the most commonly performed surgeries to treat obesity worldwide (Angrisani, Santonicola, et al. 2017). RYGB and SG have been compared in terms of weight loss and their metabolic parameters. Both procedures have demonstrated to result in significant weight loss and impressive comorbidity resolution in the short postoperative term (Vidal, Ramon, et al. 2013, Lim, Taller, et al. 2014, Peterli, Wolnerhanssen et al. 2017, Sharples and Mahawar 2020), This was the case in our cohort as well.

According to the literature, RYGB leads to better long-term weight loss than SG at 5 years after surgery, this was the result of a meta-analysis focussing only on RCTs comparing 5-year outcomes between RYGB and SG (Sharples and Mahawar 2020), as well as many other publications (Jammu and Sharma 2016, Perrone, Bianciardi, et al. 2017, Ahmed, King et al. 2018). In our cohort, when taking only patients with NASH into consideration, EWL was similar for RYGB and SG at follow up. However, Patients with SG had initially significantly higher BMI compared with RYGB.

In terms of comorbidity control after RYGB and SG in NASH, better lipidemic control was noted in the RYGB group. LDL and TC levels were significantly lower after RYGB. This was similar to the results of Sharples and Mahawer et al(Sharples and Mahawar 2020). However, liver function was better in SG than RYGB at follow up. ALT, AST, and GGT were significantly lower in the SG group. In the Cochrane Review reporting the influence of bariatric surgery on NASH, significant or nonsignificant improvement or no change in liver function tests was reported after RYGB in 9 studies with variable results regarding AST, ALT, ALP, and GGT (Chavez-Tapia, Tellez-Avila, et al. 2010). In a study, randomizing patients with NAFLD to SG or RYGB, better liver function was observed for the SG at follow up (Kalinowski, Paluszkiewicz, et al. 2017), which is the case in our cohort as well. In a study by Billeter et al, SG led to greater improvement in LFTs than RYGB (Billeter, Senft, et al. 2016). However, to show the real impact of bariatric surgery on the liver in NAFLD Patients, a second biopsy is needed.

5.10 NASH, an indication for bariatric surgery

Till today it remains uncertain if NASH should be considered as a primary indication for bariatric surgery. While on one hand, many studies report an improvement of the existing steatosis (Stratopoulos, Papakonstantinou, et al. 2005), other authors show the progression of liver fibrosis (Mathurin, Hollebecque, et al. 2009). A meta-analysis of 25 studies could not deliver a recommendation regarding the indication for bariatric surgery for NAFLD (Chavez-Tapia, Tellez-Avila, et al. 2010), since 21 Studies reported an improvement of NAFLD after bariatric surgery, and 4 studies reported worsening of liver fibrosis.

The close association between obesity and NAFLD leads to the presumption that weight loss improves insulin resistance and subsequently leads to an improvement of NAFLD (Chitturi, Abeygunasekera, et al. 2002, Marchesini, Bugianesi, et al. 2003). That is why, patients with NAFLD are recommended to undergo lifestyle modifications, increase their physical activity and consume a healthy diet to lose weight (Promrat, Kleiner, et al. 2010, Centis, Marzocchi, et al. 2013).

An important aspect of the pathogenesis of NAFLD is the worsening of fibrosis after bariatric surgery. As stated previously Mathurin et al. reported this phenomenon. However, an interesting point here is that worsening of liver fibrosis was only evident in patients who had already fibrosis preoperatively (Mathurin, Hollebecque, et al. 2009, Chavez-Tapia, Tellez-Avila, et al. 2010), which leads to the question, if bariatric surgery should be combined with other lines of therapy in this set of patients with known liver fibrosis in order to improve NAFLD and to prevent its progression.

Worsening of fibrosis could be caused by the persistence of hepatic inflammation after bariatric surgery(Klein, Mittendorfer, et al. 2006, Mathurin, Hollebecque, et al. 2009) Probably, in some cases the effect of weight loss should be supported through the administration of antioxidants like Vitamin E or antidiabetic medications Pioglitazone or Liraglutide to maximize the results (Day, 2012, Harrison et al., 2003, Aithal et al., 2008, Armstrong et al., 2015).

All in all, to date, a recommendation for bariatric surgery as an indication to treat NAFLD cannot be given. Its role is through larger clinical trials yet to be determined.

7.Conclusion

In the last few decades, bariatric surgery proven to be an effective way in treating obesity. The benefits of bariatric surgery extend beyond weight-loss, it improves all obesity-related disorders such as type 2 diabetes mellitus, hypertension, hyperlipidemia and obstructive sleep apnea. The present study highlights the benefits of bariatric surgery on weight loss and resolution of obesity-related disorders two years after the operation. Furthermore, it confirms the high incidence of NAFLD in patients undergoing bariatric surgery, underlining the correlation of obesity with NAFLD.

We compared patients with NASH to other NAFLD groups. The result was a comparable outcome, regarding weight-loss and resolution of obesity-related comorbidities like type 2 diabetes mellitus, arterial hypertension and OSAS at follow-up. However, presence of NASH at the primary operation was associated with persistence of hyperlipidemia at follow-up, despite proper weight-loss. We included only patients undergoing sleeve gastrectomy or Roux-Y gastric bypass. Both procedures resulted to have comparable effects regarding weight loss in NASH at follow up. We also showed that NASH patients undergoing sleeve gastrectomy had a significantly better liver function tests at follow-up.

6.Zusammenfassung

Adipositas per magna ist die größte medizinische Bedrohung des Jahrhunderts. In den letzten Jahrzenten ist die Anzahl an bariatrischen Operationen in Deutschland deutlich angestiegen. Aufgrund des engen Zusammenhangs zwischen Adiposität und der nicht alkoholischen Leberverfettung (NAFLD) sind Chirurgen häufig intraoperativ mit diesem Krankheitsbild konfrontiert. Allerdings wurde der Einfluss der NAFLD auf dem Erfolg der bariatrischen Operation nur noch eingeschränkt untersucht.

Das Ziel dieser Arbeit ist der Einfluss der Leberverfettung auf den Langzeiterfolg der bariatrischen Operationen (Schlauchmagen- Operationen und Roux-Y-Magenbypass), hinsichtlich Gewichtverlust und Verbesserung der Adipositas-assoziierten Komorbiditäten darzulegen. Diese retrospektive Studie bestand aus 288 Patienten, die in dem Zeitraum von 2012 bis 2014 am UKE operiert wurden und intraoperativ aufgrund makroskopischer Auffälligkeiten eine Leberbiopsie erhalten haben. Die Histologie wurde mit den langfristigen Ergebnissen der Operationen korreliert.

Die Nachsorge von 226/288 Patienten ist erfolgt. Im Mittel betrug die Nachsorge 24.9 Monate. Die Leberbiopsien zeigten einer höhen Prävalenz der NAFLD 75.6%. 112 (38.9%) Patienten hatten keine NASH. 70 (24.3%) waren Borderline-NASH und bei 106 (36.8%) Patienten wurde eine NASH histologisch nachgewiesen.

Im Verlauf ist der BMI in unserer Kohorte von (52 ± 10.2) auf (36.6 ± 8) kg/m^2 gesunken. Die Gewicht-Abnahme (EWL) war allerding in allen NAFLD Gruppen vergleichbar. Die Prävalenz von Diabetes mellitus Typ 2 nahm von 35.7% auf 11.4% ab. Ebenso sank die Inzidenz der arteriellen Hypertonie von 65.6% auf 36.7%, der Hyperlipidämie von 62.3% auf 33% und der obstruktiven Schlafapnoe von 37.5% auf 14.9%. Nur die Hyperlipidämie war mit NASH assoziiert im Vergleich mit den Borderline NASH und NASH Gruppen bei der Nachsorge.

Insgesamt können die vorliegenden Daten die bekannte Effektivität der bariatrischen Chirurgie bestätigen. Zusätzlich zeigt unsere Kohorte, dass Patienten mit NASH einen vergleichbaren Langzeiterfolg nach bariatrischen Operationen haben. Die Persistenz der Hyperlipidämie nach bariatrischer Operation ist mit NASH vereinbart.

8. Abstract

Obesity is the most significant clinical association with non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatosis hepatitis (NASH). Patients undergoing bariatric surgery have a high incidence of NAFLD. However, there are few data regarding the late postoperative effect of NASH on weight-loss and resolution of comorbidities after Bariatric surgery. This study compares the long-term success of bariatric surgery in different NAFLD subgroups.

A single-center, retrospective analysis of a prospective database was conducted for patients, who had a liver biopsy during bariatric surgery between 2011 and 2014. Histology was compared to the long-term outcome.

The follow up was available for 226 out of 288 Patients. The median follow-up time was 24.9 (± 13.6) months. The baseline histology showed that 112 Patients (38.9%) had no NASH, 70 (24.3%) were borderline, 106 (36.8%) had NASH. At follow-up, BMI dropped from (52 ± 10.2) to (36.6 ± 8) kg/m^2. EWL was similar in all NAFLD groups at follow up. The incidence of type 2 diabetes mellitus dropped from 35.7% to 11.4%, hypertension from 65.6% to 36,7%, hyperlipidemia from 62.3% to 33%, and obstructive sleep apnea dropped from 37.5% to 14.9%. Only hyperlipidemia was associated with NASH compared to No NASH and Borderline NASH groups; *p-value (0.002)* and *(0.04)* respectively.

The beneficial effects of bariatric surgery are evident across all patients with NAFLD. Patients with NASH have comparable outcomes regarding, weight loss and resolution of obesity-related comorbidities. The persistence of hyperlipidemia is associated with NASH after bariatric surgery.

9. Abbreviations

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body mass index
EWL	Excess weight loss
HCC	Hepatocellular carcinoma
NAFLD	Non-alcoholic fatty liver disease
NAS	NAFLD activity score (Brunt score)
NASH	Non-alcoholic steatohepatitis
OSAS	Obstructive sleep apnoea
RYGB	Roux-Y Gastric Bypass
SG	Sleeve Gastrectomy

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11. List of Tables

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15 .Eidesstattliche Erklärung

Ich versichere ausdrücklich, dass ich die Arbeit selbständig und ohne fremde Hilfe verfasst, andere als die von mir angegebenen Quellen und Hilfsmittel nicht benutzt und die aus den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen einzeln nach Ausgabe (Auflage und Jahr des Erscheinens), Band und Seite des benutzten Werkes kenntlich gemacht habe.
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