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Effect of Laparoscopic Sleeve Gastrectomy on Metabolic Parameters – Data from A Two-Year Prospective Survey

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Abstract

Purpose: Laparoscopic sleeve gastrectomy has proven effectiveness regarding weight reduction, but metabolic consequences, especially in the long-term, have not yet been adequately clarified. The aim of the present study is to examine metabolic changes after laparoscopic sleeve gastrectomy in a two-year prospective survey.

Methods: Eighty-one patients were examined before laparoscopic sleeve gastrectomy and 3, 6, 12, 18, and 24 months postoperatively. Different markers of metabolic diseases including blood lipids and liver enzymes, inflammation markers and markers of glucose metabolism were assessed.

Results: Body weight was significantly reduced from 144.4 ± 23.0 kg before surgery to 101.3 ± 20.0 kg 24 months postoperatively. Excess weight loss after 24 months was 58 ± 20 % in our study population. Besides body weight changes, significant improvements were found for triglycerides ($p < 0.001$), low density lipoprotein cholesterol ($p < 0.01$), and high density lipoprotein cholesterol ($p < 0.001$). Moreover, C-reactive protein and leukocytes, as well as the liver enzymes improved in the 2-years-course (all $p < 0.001$). These changes resulted in a sharp reduction of the prevalence of the metabolic syndrome from 69 to 26 % ($p < 0.001$). Furthermore, the number of patients with hypertension and diabetes – assessed by fasting glucose and glycated hemoglobin –, were reduced to less than half.

Conclusions: Laparoscopic sleeve gastrectomy improves lipid profile and liver enzyme status, and reduces signs of inflammation in obese patients within 2 years. These changes suggest a significant risk reduction of metabolic diseases in obese patients undergoing laparoscopic sleeve gastrectomy.

Abbreviations: CRP: C-reactive protein; GGT: Gamma Glutamyl Transferase; GPT: Glutamate Pyruvate Transaminase; GOT: Glutamate Oxaloacetate Transaminase; FLI: Fatty Liver Index; FRS: Framingham Risk Score; LSG: Laparoscopic Sleeve Gastrectomy; RYGB: Roux-en Y Gastric Bypass

Keywords: Laparoscopic sleeve gastrectomy, Bariatric surgery, Blood lipids, Inflammation, Metabolic diseases, Liver enzymes

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Introduction

Obesity is associated with a number of comorbidities among which metabolic diseases play an outstanding role. Three major pathways have been identified that trigger obesity-associated metabolic diseases: dyslipidemia, insulin resistance and low-grade inflammation. These may lead to nonalcoholic fatty liver disease, cardiovascular diseases and type 2 diabetes [1]. To estimate the risk of metabolic diseases associated with obesity, surrogate markers have been established such as triglycerides and cholesterol indicating dyslipidemia, C-reactive protein (CRP) and leukocytes indicating inflammation, and liver enzymes associated with nonalcoholic fatty liver disease if other liver diseases have been excluded.

The aim of any obesity therapy is, besides body weight reduction, improvement or even avoidance of metabolic disorders. Different methods of bariatric surgery, which has become a major treatment option of severe obese patients, have already proven their success in improvement of lipid profile, inflammation status and liver damage [2, 3]. The relatively new bariatric procedure laparoscopic sleeve gastrectomy (LSG) leads to promising initial results regarding the effect on weight loss within the first postoperative years [4]. Furthermore, a randomized trial, comparing different strategies of obesity therapy has recently been published. It shows that LSG is more effective regarding glycemic control at 3 years postoperatively compared to intensive medical therapy, while Roux-en-Y gastric bypass still seems to be the most effective treatment option [5]. It remains to be seen which other metabolic effects can be achieved by LSG, in particular, when stable weight has been reached. Therefore, we assessed over a two-year period the postoperative changes of metabolic parameters and thus of metabolic risk in severely obese patients undergoing LSG.

Material and Methods

Patients and surgical procedure

Eighty-one obese patients (18-65 years) of an ongoing prospective study, who underwent LSG between May 2009 until June 2012 in the Department of General, Visceral and Transplant Surgery of the University Hospital of Tuebingen, Germany, were included in the analysis. All study participants were consecutively enrolled and signed an informed consent form. This was established for the multicenter research project "Obesity and the gastrointestinal tract" (No.FKZ 01GI0843), which was approved by the ethical committees of the Medical Faculty and the University Hospital of Tuebingen. LSG was performed according to the surgical technique that has been previously described in detail [6]. It includes a 34-FR tube, which is build by stapling the greater curvature starting at 7-8 cm prepyloric and using a 60-mm Endo-GIA (Ethicon Endo-Surgery - a company of the Johnson & Johnson Medical GmbH, Norderstedt, Germany). The staple line is overstitched by simple sutures, not to prevent insufficiency but rather to prevent staple line bleeding. All patients met the criteria of the national S3 guideline for surgery of obesity, which postulates a body mass index $\geq$ 40 kg/m^2 without comorbidities or a body mass index between 35 and 40 kg/m^2 with comorbidities, given that conservative weight loss therapies failed [7]. All sleeve gastrectomies were completed successfully laparoscopically with no conversion to open surgery. According to the inclusion criteria of the trial, the study participants were between 18 and 65 years old. Subjects were excluded if they lost < 10 % of their initial body weight six months after start of intervention or if they did not participate in at least three consultations during the study period.

Six examinations were conducted, 1 before surgery and 5 after surgery at 3, 6, 12, 18 and 24 months post-interventional. Data was collected at baseline in *n*=81 subjects, after 3 months in *n*=79 subjects, after 6 months in *n*=78 subjects, after 12 months in *n*=68 subjects, after 18 months in *n*=48 subjects and after 24 months in *n*=47 subjects. In total, 401 out of 486 (83 %) study visits were attended by the patients.

At every study visit body weight, body height, waist circumference and blood pressure were measured, body mass index was calculated and blood samples were taken to measure the blood lipids total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol and triglycerides, the inflammation markers CRP and leukocyte count, and the liver enzymes glutamate pyruvate transaminase (GPT) and gamma glutamyl transferase (GGT). Metabolic syndrome was assessed. The Fatty Liver Index (FLI), which indicates a hepatic steatosis – provided that FLI is ≥ 60 – was calculated prior to surgery, and 12 and 24 months postoperatively as described previously [8]. Furthermore, the 10-year risks of severe cardiovascular disease events were evaluated at these follow-up visits using the 10-year hard coronary heart disease Framingham Risk Score (FRS) [9]. All data were recorded in approved case report forms.

Baseline characteristics

The mean age of the study participants was 46 years, and most of the patients were women (79 %). Mean initial body mass index was 51.1 ± 7.1 kg/m^2. Table 1 summarizes the anthropometric characteristics of the subjects prior to surgery.

Table 1: Absolute values of anthropometric data and vital signs

	Pre-OP (n=81)	**3months (n=79)**	**6months (n=78)**	**12months (n=68)**	**18months (n=48)**	**24months (n=47)**
Body weight [kg]	144,4 ± 23,0	120,3 ± 19,5***	109,4 ± 18,2***	100,7 ± 18,2***	100,6 ± 18,3***	101,3 ± 20,0***
BMI [kg/m^2]	51,1 ± 7,1	43,0 ± 6,4***	38,9 ± 6,2***	35,7 ± 5,9***	35,5 ± 5,4***	36,0 ± 6,4***
EWL [%]	-	34,0 ± 10,7	48,7 ± 14,4***	61,0 ± 18,2***	61,3 ± 15,8***	58,4 ± 20,3***
WC [cm]	140,9 ± 14,5	124,6 ± 13,2***	116,7 ± 12,5***	110,7 ± 14,0***	113,3 ± 12,7***	112,6 ± 13,7***
Pulse [beats/min]	75,9 ± 10,7	70,1 ± 10,0***	66,2 ± 9,8***	63,2 ± 9,1***	64,7 ± 8,6***	67,5 ± 9,7***
SBP [mmHg]	137,7 ± 16,4	130,1 ± 15,6**	125,6 ± 13,0***	125,9 ± 14,4***	126,7 ± 12,2***	127,0 ± 14,6***
DBP [mmHg]	83,6 ± 12,0	78,4 ± 10,3**	78,4 ± 11,2**	81,0 ± 8,9	84,0 ± 9,5	83,3 ± 12,7
Results are expressed as mean ± standard deviation						
Abbreviations: *BMI* Body mass index, *EWL* Excess weight loss, *WC* Waist circumferrence, *SBP* Systolic blood pressure, *DBP* Diastolic blood pressure						
Statistics: *p<0.05, **p<0.01, ***p<0.001 = significant compared to preoperative values						

Clinical and biological assessment

Blood was collected by venipuncture between 07.30 and 09.00 a.m. after an overnight fast. All parameters were detected in plasma samples, which were immediately sent to local laboratory for analysis. Total cholesterol, high density lipoprotein cholesterol and low density lipoprotein cholesterol were measured enzymatically. To detect triglycerides, an enzymatic color test using glycerol kinase was performed. GPT and GGT were measured photometrically, CRP by immunoturbidimetry and leukocytes were detected by using flow cytometry. Increased or decreased values were defined as concentrations above or under the following reference ranges: total cholesterol 130-190 mg/dl, high density lipoprotein cholesterol > 45 mg/dl, low density lipoprotein cholesterol ≤ 160 mg/dl, triglycerides ≤ 200 mg/dl, CRP ≤ 0.50 mg/dl, leukocytes 4.0-9.5 tsd/µl, GPT ≤ 34 U/l, GGT ≤ 40 U/l.

Definitions of obesity-related diseases

Metabolic syndrome was defined (according to the National Cholesterol Education Program criteria) as the presence of three or more of the following criteria: blood pressure of ≥ 130/85 mmHg, waist circumference > 102 cm in men and > 88 cm in women, high density lipoprotein cholesterol < 40 mg/dl in men and < 50 mg/dl in women, triglycerides ≥ 150 mg/dl and fasting plasma glucose of ≥ 110 mg/dl [10].

The definition criteria of arterial hypertension followed the World Health Organisation recommendations [11]. It is defined as systolic blood pressure of ≥ 140 mmHg, diastolic blood pressure of ≥ 90 mmHg, or both.

Remission of type 2 diabetes was defined as a fasting plasma glucose level of less than 100 mg/dl and a glycated hemoglobin level of less than 6.5 % without active pharmacologic therapy [12].

Statistical Analyses

Data analysis was performed using the statistical software SPSS, version 20.0 (IBM®SPSS®, Chicago, IL). Continuous variables are expressed as means ± standard deviation and categorical variables as numbers and percentages. Time courses were compared to baseline values by using linear mixed models for repeated measures. This statistical instrument has been recommended for analyses of data from repeated measurements, including missing data [13]. The analysis of the present study, using linear mixed models, considers missing values without performing listwise deletion and therefore losing too much data. Frequencies were compared using cross tables, according to the method of McNemar for time courses. *P* values < 0.001 were interpreted as statistically highly significant, *p* values between 0.001 and < 0.01 as very significant and *p* values between 0.01 and <0.05 as significant.

Results

Eighty-one patients (79 % women; 21 % men) were included in the analysis. They had a mean age of 45.8 ± 11.2 years and a mean overweight (initial body weight - (24.9 kg/m^2 x size [m]^2) of 74.3 ± 20.9 kg prior to surgery. Early complications occurred in 5 (6 %) patients, including staple line leaks in 3 (4 %) patients and wound healing dehiscence in 2 (2 %) patients. There was no mortality during follow-up. Anthropometric data, including body weight, body mass index, excess weight loss and waist circumference, was constantly improved during the first year after LSG and remained stable during the second postoperative year (Table 1). Additionally, pulse and systolic blood pressure could be reduced significantly (Table 1), which was not caused by antihypertensive drugs - the frequency of this medication use was reduced significantly over two years after LSG (Table 2).

We observed changes in all lipid parameters except for total cholesterol. Mean level of total cholesterol changed from 200.5 ± 32.0 mg/dl prior to surgery to 188.2 ± 35.4 mg/dl 3 months after surgery, to 195.9 ± 42.1 mg/dl 6 months after surgery, to 194.3 ± 35.2 mg/dl 12 months after bariatric intervention, to 195.5 ± 33.4 mg/dl 18 months after surgery and to 186.9 ± 40.7 mg/dl 24 months postoperatively (*p* > 0.05). Among the changes, the improvements in mean levels of high density lipoprotein cholesterol and triglycerides were already

statistically significant after one year (Figures 1a and 1b). The improvements remained stable during the second year after LSG.

During the whole study period, mean low density lipoprotein levels were within the normal range of the general population. No changes were observed during the first 18 months after surgery, but 24 months postoperatively mean level of low density lipoprotein cholesterol decreased significantly compared to preoperative value (Figure 1c). These improvements in lipid profile were likely a result of LSG and not because of increased lipid lowering medications (Table 2).

Table 2: Incidence [n, %] of comorbidities and medication use

	Pre-OP (n=81)	**3months (n=79)**	**6months (n=78)**	**12months (n=68)**	**18months (n=48)**	**24months (n=47)**
Comorbidities						
Metabolic Syndrome[1]	56 (69)	43 (54)	26 (33)***	14 (21)***	13 (27)***	12 (26)***
Hypertension[2]	53 (65)	40 (51)**	34 (44)***	20 (29)***	15 (31)***	13 (28)***
CVD[3]	10 (12)	10 (13)	10 (13)	8 (12)	5 (10)	6 (13)
Type 2 Diabetes[4]	28 (35)	19 (24)*	13 (17)***	9 (13)***	5 (10)***	7 (15)**
Medication use						
Lipid lowering drugs	7 (9)	6 (8)	6 (8)	6 (9)	4 (8)	3 (6)
Antihypertensive drugs	46 (57)	22 (28)*	22 (28)**	15 (22)***	11 (23)**	10 (21)***
CVD medication	13 (16)	5 (6)	4 (5)	5 (7)	3 (6)	6 (13)
Diabetes medication	15 (19)	12 (15)**	10 (13)**	8 (12)***	5 (10)**	6 (13)**
Frequencies are expressed as n (%). Abbreviations: *CVD* Cardiovascular Diseases.						
[1]according to the NCEP criteria; [2]systolic blood pressure ≥ 140 mmHg, diastolic ≥ 90 mmHg, according to the World Health Organisation definition; [3]according to the patients records and history; [4]remission was defined as a fasting plasma glucose < 100 mg/dl and a glycated hemoglobin < 6.5 % without active pharmacologic therapy.						
Statistics: *p<0.05, **p<0.01, ***p<0.001 = significant compared to preoperative incidences.						

Before surgery, metabolic syndrome was consistent in 69 % of the patients (Table 2). After 24 months, only 26 % of the patients had a metabolic syndrome ($p < 0.001$). Accordingly, cases of arterial hypertension (Table 2) and mean waist circumference (Table 1) were reduced significantly after LSG during the first 24 months after surgery ($p < 0.001$). Furthermore, the prevalence of diabetes defined as fasting plasma glucose level of ≥ 100 mg/dl and/or a glycated hemoglobin level of ≥ 6.5 % decreased from 35 % before LSG to 17 % after 6 months ($p < 0.001$, n=78), and to 10-15 % after 12-24 months (all $p < 0.01$, n=47-68, Table 2).

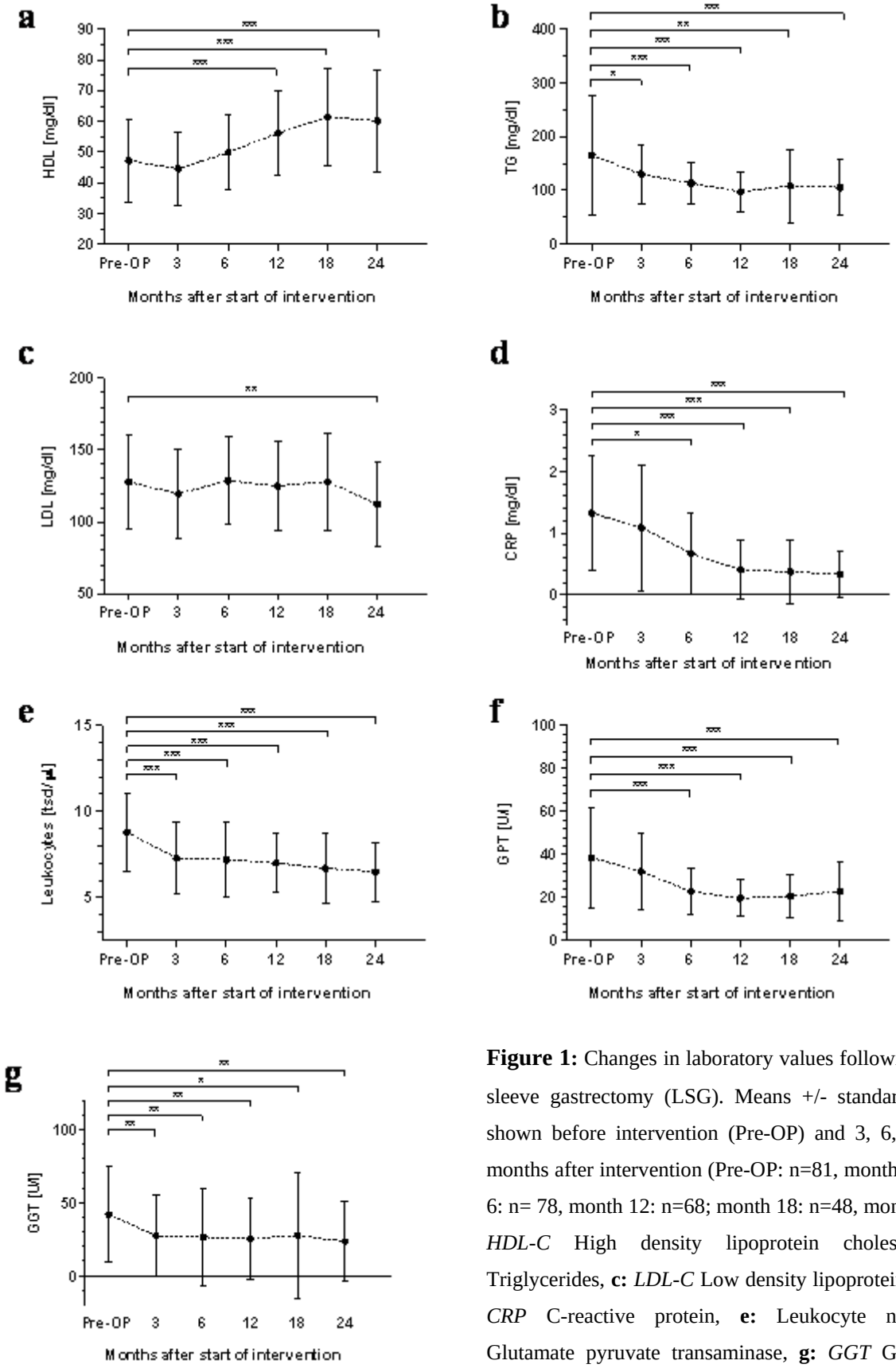

Figure 1: Changes in laboratory values following laparoscopic sleeve gastrectomy (LSG). Means +/- standard deviation are shown before intervention (Pre-OP) and 3, 6, 12, 18 and 24 months after intervention (Pre-OP: n=81, month 3: n=79, month 6: n= 78, month 12: n=68; month 18: n=48, month 24: n=47). **a:** *HDL-C* High density lipoprotein cholesterol, **b:** *TG* Triglycerides, **c:** *LDL-C* Low density lipoprotein cholesterol, **d:** *CRP* C-reactive protein, **e:** Leukocyte number, **f:** *GPT* Glutamate pyruvate transaminase, **g:** *GGT* Gamma glutamyl transferase

Statistics: *p<0.05, **p<0.01, ***p<0.001 = significant compared to preoperative values

The inflammation markers CRP and blood leukocyte numbers as well as the liver enzymes GPT and GGT improved significantly during the first 24 months after LSG compared to preoperative values (Figures 1d-1g). The mean FLI decreased from 99.2 ± 1.9 from baseline to 72.3 ± 26.8 at month 12 and to 70.6 ± 27.6 at month 24 (all $p < 0.001$). Before LSG, 100 % of the patients had a FLI of ≥ 60. During the first postoperative year, the number of patients with a FLI ≥ 60 decreased to 69 %. The number remained stable during the second postoperative year (69 % at 24 months).

The mean FRS was 3.7 ± 4.1 % before LSG. It was reduced to 1.9 ± 2.5 % at 12 months after LSG ($p < 0.01$) and to 2.2 ± 2.6 % at 24 months postoperatively ($p < 0.05$).

Discussion

Previous studies demonstrated that LSG, which is still considered a relatively new bariatric method, is highly effective regarding weight reduction [4, 14]. The present study confirms this by showing an excess weight loss of 58 ± 20 % within 24 months after surgery and a corresponding reduction of body weight from 144.4 ± 23.0 kg prior to surgery to 101.3 ± 20.0 kg. There are only a few data available on the effectiveness of LSG regarding markers of metabolic risk. Compared to other major bariatric methods, changes of lipid profile, inflammation markers and liver enzymes after LSG have only been rarely studied and most of the previously published studies had a limited follow-up of at maximum 12 months [3, 15–19].

RYGB, duodenal switch and laparoscopic adjustable gastric banding appear to improve blood lipids and thus reduce risk for undesirable cardiovascular events [20–23]. The effects of LSG in this respect are less clear and to some extent conflicting [16, 17]. Our study shows that LSG improves glucose metabolism (fasting glucose and glycated hemoglobin) and systolic blood pressure. Mean resting pulse in our study was reduced by more than 8 beats per minute during 24 months after surgery. Elevated resting heart rate has turned out to be a risk factor for mortality independent of physical fitness and other major cardiovascular risk factors [24]. It is associated with an increased risk for mortality of 16% per 10 beats per minute increase in resting heart rate. Furthermore, lipid profile with respect to triglycerides, low density lipoprotein cholesterol and high density lipoprotein cholesterol was improved in our study population. Accordingly, the FRS could be reduced significantly in the postoperative period suggesting a decreased 10-year cardiovascular risk. Different results for lipid changes were found by Zhang et al. [16]. Mean levels of high density lipoprotein cholesterol and triglycerides also improved significantly after LSG, but beside total cholesterol, also low density lipoprotein cholesterol levels were preserved. This difference could be explained by the limited follow-up of one year in the study of Zhang et al., which might not include the delayed decrease of low density lipoprotein cholesterol, which has been shown in our study. Furthermore, controversial results are provided by the study of Hady et al. [17]. They found comparable results to the ones after RYGB. The study indicates improvements in all lipid parameters (total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol and triglycerides) within 12 months after LSG. Beside the limited follow-up compared to the present study, Hady et al. did not include medication use, which could also affect blood lipid levels. Our results, which include 2 years follow-up data from 47 patients who underwent LSG and which consider medication use, extend the existing information regarding the influence of LSG on lipid profile, e.g. by our finding of a delayed improvement of low density lipoprotein cholesterol only 24 months after surgical intervention. However, it has to be considered that low density lipoprotein levels are highly variable among patients in such a cohort limiting statistical power. Additionally, our results are somehow limited by the decreasing number of patients during follow-up and therefore do not allow final conclusions. However, our pilot data suggest that lipid parameters improve following LSG, which has to be confirmed in future large-scale trials. Thus, not only RYGB as shown earlier, but also LSG as suggested by our

present data seems to reduce total cholesterol and low density lipoprotein levels [25–27].

Low-grade systemic inflammation is associated with obesity and is emerging as a cardiovascular risk factor [28]. It has been shown, to be well reflected by CRP in plasma [29]. The impact of weight loss, achieved by bariatric surgery, especially RYGB, on plasma levels of CRP has been examined in different studies. They indicate a significant improvement in CRP levels and thus in systemic inflammation and associated cardiovascular risk [26]. Reports on the reduction of leukocyte count in blood following bariatric intervention confirm these findings [30, 31]. There are only a few reports on this topic regarding LSG [18, 32, 33]. The results of these studies indicate LSG being successful regarding the reduction of chronic inflammation in obese patients; however, these studies had limited follow-up. There is no data on the long-term effects of LSG on inflammation, when patients reached stable weight. Our data on CRP and leukocytes suggest an improvement in chronic inflammation during the first year after LSG, which confirms the other reports on this topic. Moreover, it indicates an amelioration of CRP and leukocyte numbers during the second year postoperatively, although there were no changes in mean body weight. Finally, LSG reduced heart rate and systolic blood pressure in the patients within 24 months. These findings indicate that LSG leads to improvements in cardiovascular parameters not only during the major weight loss period within the first year, but also over the second year suggesting a sustaining effect when stable weight has been reached.

The accumulation of lipids in the liver often accompanies and parallels weight gain and obesity [34, 35]. Nonalcoholic fatty liver disease and steatohepatitis negatively affect liver function and were found to be associated with the development of insulin resistance [36, 37]. GPT and especially GGT have proven to be good predictors of nonalcoholic fatty liver disease and liver damage [19, 38, 39]. Different reports on changes in histological and/or biochemical changes of nonalcoholic fatty liver disease suggest a notable improvement of liver status after RYGB and laparoscopic adjustable gastric banding [38, 40]. However, reports on outcome after LSG are scarce. Wang et al. examined the effect of sleeve gastrectomy on high-fat-induced obese rats [41]. They could demonstrate that body weight control caused by sleeve gastrectomy can relieve high-fat-diet-induced steatohepatitis in rats. Karcz et al. investigated the influence of LSG on non alcoholic steatohepatitis [19]. They found a significant improvement in the hepatic transferases GPT and glutamate oxaloacetate transaminase (GOT), and liver histology in patients with nonalcoholic steatohepatitis after LSG. Our data on liver status are limited by the fact that we did not perform liver histology, because it is invasive and therefore not applicable because of ethical reasons. Instead, we examined transaminases as surrogate markers and calculated the FLI, which is a validated score and includes a combination of several parameters [8]. Present data of liver enzymes and FLI suggests that LSG supports improvement of the liver status in obese patients.

Conclusions

Our data suggest that LSG causes significant weight loss within 24 months postoperatively and also improves markers of metabolic diseases such as lipid parameters (low density lipoprotein cholesterol, high density lipoprotein cholesterol and triglycerides), inflammatory parameters (blood leukocytes and CRP), liver enzymes (GPT and GGT) and systolic blood pressure. Based on calculation of the FRS, the 10 years cardiovascular risk seems to be reduced following LSG. Thus, LSG not only reduces body weight significantly but could also lower the metabolic risk in severely obese patients.

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All authors declare that they have no conflict of interest.

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