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ORIGINAL CONTRIBUTIONS

Ursodeoxycholic Acid for 6 Months After Bariatric Surgery Is Impacting Gallstone Associated Morbidity in Patients with Preoperative Asymptomatic Gallstones

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Abstract

Background Obesity is a predisponing factor for gallstone formation with a prevalence > 10% in patients undergoing gastric bypass procedure. Although there is a strong recommendation for concomitant cholecystectomy in patients with symptomatic gallstones, the evidence level for patients with asymptomatic gallstones is weak. According to recent literature, up to 21% of asymptomatic gallstones become symptomatic after bariatric surgery. Secondary prophylaxis with ursodeoxycholic acid (UDCA), which is altering the composition and excretion of the bile acid pool, was the objective of this study.

Methods Retrospective analysis of the patient records of all patients undergoing laparoscopic Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy (SGx) at our center between January 2007 and October 2017.

Results We enrolled a total of 704 patients with routine preoperative ultrasound. In 61 patients, asymptomatic gallstones were detected and these patients were treated with UDCA for 6 months after bariatric surgery. One patient developed a single episode of symptoms 3 months after SGx, which did not require surgery. One patient developed chronic cholecystitis and underwent cholecystectomy 6 months after SGx. All other patients ($n = 59$; 96.8%) remained asymptomatic under UDCA therapy.

Conclusion UDCA for 6 months after bariatric surgery seems to reduce the incidence of gallstone-associated morbidity when compared to the current literature. Thus, our results call the concept of prophylactic concomitant cholecystectomy in patients with asymptomatic gallstones into question while at the same time paving the way for a future clinical trial.

Keywords Cholelithiasis · Ursodeoxycholic acid · Asymptomatic gallstones · Weight loss · Concomitant cholecystectomy

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Abbreviations

BMI	Body mass index
EWL	Excess weight loss
RYGB	Roux-en-Y gastric bypass
SGx	Sleeve gastrectomy
UDCA	Ursodeoxycholic acid
US	Ultrasonography

Introduction

Morbid obesity represents an important risk factor for the formation of gallstones and the onset of gallbladder disease. In particular, obesity is strongly associated with the risk of developing cholesterol gallstones. Furthermore, also the rapid weight loss induced by bariatric procedures represents an important risk factor in the onset of gallbladder disease. In fact, a rapid decrease in body weight is related to gallstone formation

[1, 2]. Taken together, the incidence of gallstones in morbidly obese patients is actually higher than in the normal population, and it is also higher during the period of rapid weight loss after bariatric procedures [3]. In detail, rapid weight loss of more than 50% of the excess weight was identified as the unique predictive factor of symptomatic gallbladder disease after laparoscopic Roux-en-Y gastric bypass (RYGB) in a recent multivariate analysis [4].

Although there is an increased risk of developing gallbladder disease after bariatric surgery compared to the normal population, the value of prophylactic concomitant cholecystectomy during bariatric procedures is still controversially discussed [5]. The rate of adverse postoperative events after concomitant cholecystectomy during RYGB has been reported to be significantly increased compared to patients undergoing RYGB alone. These data provide evidence to avoid prophylactic concomitant cholecystectomy [6]. Taken together, there are no univocal guidelines on the management of asymptomatic cholelithiasis due to a weak evidence level [7].

Along the same lines, the prophylactic administration of ursodeoxycholic acid (UDCA) is also controversially discussed. Of note, UDCA administration for 6 months after bariatric surgery was demonstrated to reduce the incidence of gallstone formation and cholecystectomy rate in a recent meta-analysis [8]. This cited analysis focussed on patients without pre-existing gallstones in order to verify the impact of UDCA on postoperative gallstone formation. However, there is currently no evidence on the impact of prophylactic UDCA in patients with pre-existing asymptomatic gallstones. A recent report suggests that patients with pre-existing gallstones have a lesser propensity to develop symptoms compared to patients with gallstones that developed after bariatric surgery [9], thus calling the concept of prophylactic concomitant cholecystectomy into question. Here, our aim was to retrospectively analyze the impact of prophylactic UDCA administration for 6 months after bariatric surgery on gallstone-associated morbidity in patients with preoperative asymptomatic gallstones.

Patients and Methods

We retrospectively analyzed the records of all patients who underwent either laparoscopic sleeve gastrectomy (SGx) or laparoscopic Roux-en-Y gastric bypass (RYGB) at our institution between January 2007 and October 2017. Minimum clinical follow-up was 6 months. Patients undergoing re-procedures and patients with previous cholecystectomy were excluded from analysis.

We followed the indications for bariatric surgery and the specific procedure according to the German guidelines for obesity surgery [10]. All patients underwent abdominal ultrasonography (US) during preoperative evaluation.

Patients who were diagnosed with symptomatic cholecystolithiasis underwent concomitant laparoscopic cholecystectomy. Patients with asymptomatic gallstones did not undergo concomitant cholecystectomy but were treated with UDCA for 6 months after the bariatric procedure. During longitudinal clinical follow-up, changes in body weight, body mass index (BMI), and excess weight loss (EWL) as well as the presence of new-onset symptoms related to previously asymptomatic gallstones were recorded at each study visit. EWL was calculated on preoperative weight and assuming a normal BMI of 25 kg/m^2. Statistical analysis was performed using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, USA). Variables normally distributed are expressed as mean, while variables not normally distributed as the median. The X^2 test was used to compare categorical variables and the t test to compare continuous variables. The study was authorized by the local Ethics Committee (685/2017BO2).

Results

During the study period, a total of 838 obese patients underwent either of the two bariatric procedures. In detail, 593 patients underwent SGx and 245 patients RYGB. Next, 134 patients were excluded due to previous cholecystectomy. Out of 704 patients remaining, 62 patients revealed gallstones during preoperative routine ultrasound. One patient with preexisting gallstones underwent concomitant cholecystectomy due to clinical symptoms and intraoperative finding of acute cholecystitis, while the other patients ($n = 61$) were defined as asymptomatic cholecystolithiasis (Fig. 1). These patients were treated with UDCA for 6 months after surgery and longitudinally monitored for symptoms related to cholecystolithiasis during the study period.

Symptoms under UDCA Treatment

Out of the 61 patients with preoperatively asymptomatic gallstones, 39 (63.9%) underwent SGx and 22 (36.1%) RYGB. Fourteen patients (23%) were male and 47 (77%) female. The median age was 44 years (range 22–74) and the mean preoperative weight and BMI were 144.8 ± 28.3 kg and 50.7 ± 7.8 kg/m^2, respectively (Table 1). The median clinical follow-up was 26 months (range: 6–93). During the first 6 months of clinical follow-up under UDCA treatment, only one male patient developed biliary colic and was successfully treated with analgesic and anti-spasmodic medication. In absence of clinical and sonographic signs for cholecystitis, the patient did not undergo cholecystectomy. Another female patient had to undergo cholecystectomy due to chronic

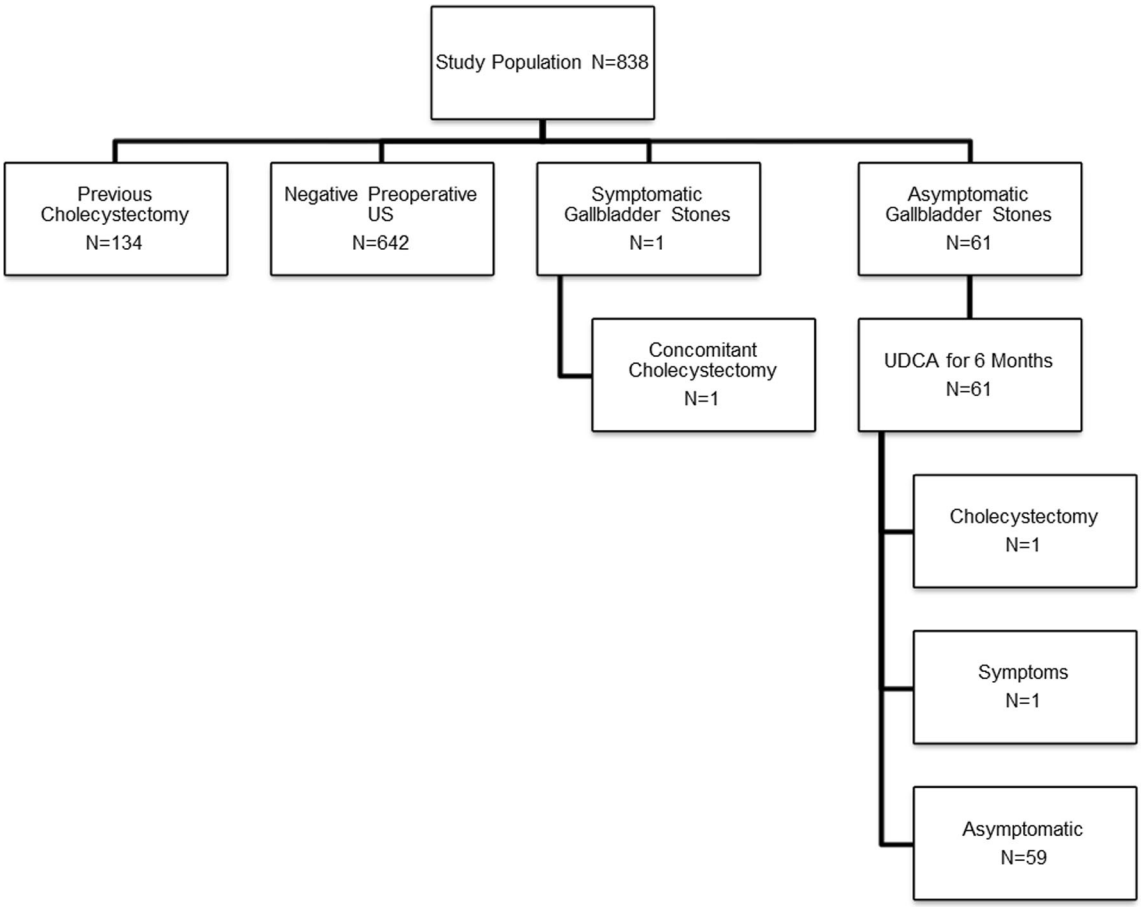

Fig. 1 Study flow

cholecystitis 6 months after surgery. The remaining 59 patients (96.7%) stayed asymptomatic under treatment with UDCA. Both patients with new-onset of symptoms were in the SGx group; the EWL of the two symptomatic patients within the first 6 months after surgery were 77% for the male and 43% for the female patient.

Symptoms after UDCA Withdrawal

A total of 56 preoperatively asymptomatic patients also continued clinical follow-up between months 7 and 12 after surgery, when UDCA treatment was already suspended. Here, the patient who underwent cholecystectomy 6 months after surgery was excluded; another 4 patients were lost to clinical follow-up. By postoperative month 7, all patients had already significantly lower weight and BMI compared to the individual baseline at the time of surgery. Of note, EWL during the secondary 6-month period (months 7 to 12) was significantly less pronounced when compared to the first 6 months after surgery. During months 7 to 12, another two female patients, one in the SGx cohort and another one in the RYGB cohort, became symptomatic, both did not require cholecystectomy (Table 2).

Table 1 Comparison of demographics between patients with negative preoperative ultrasound and patients with asymptomatic gallstones

	Negative preoperative ultrasound ($N = 642$)	Asymptomatic gallbladder stones ($N = 61$)	p value
Age (years) (median + range)	42 (18–69)	44 (22–74)	0.05
Sex (F/M)	458/184	47/14	0.38
Initial weight (kg) (mean ± SD)	144.7 ± 26.2	144.8 ± 28.3	0.98
Initial BMI (kg/m^2) (mean ± SD)	50.6 ± 7.2	50.7 ± 7.8	0.87
EWL (%) (after 12 months) (mean ± SD)	61 (5–176)	63 (20–114)	0.59

Table 2 Comparison of patient characteristics and new-onset symptoms of preoperatively asymptomatic gallstones under UDCA treatment (months 1–6) and after UDCA withdrawal (months 7–12)

	Asymptomatic gallbladder stones ($N = 61$)		
	Months 1–6 ($N = 61$), UDCA treatment	Months 7–12 ($N = 56$), no UDCA treatment	p value
Weight (kg) (mean ± SD) (at start of period)	144.8 ± 28.3	105.9 ± 20.8	< 0.05
BMI (kg/m^2) (mean ± SD) (at start of period)	50.7 ± 7.8	37.2 ± 6.7	< 0.05
Weight loss (kg) (median + range)	34 (11–91)	8 (− 31–26)	< 0.05
Loss of BMI (kg/m^2) (mean ± SD)	12.1 (3.9–25.2)	2.8 (− 8.6–10.2)	< 0.05
New-onset symptoms (6-month period)	2 (3.2%)	2 (3.6%)	0.66

Discussion

Although obese patients undergoing bariatric surgery procedure present with a high prevalence of gallstones [11], the recommendation level for the management of asymptomatic cases is weak [7, 10]. Current data on watchful waiting in obese patients with asymptomatic gallstones report that more than 20% of the patients become symptomatic after bariatric surgery [12]. Here, we analyzed the impact of pharmacological treatment with UDCA for 6 months after surgery on the rate of new-onset symptoms. Our data demonstrated that the vast majority of 96.7% of the patients remained asymptomatic under UDCA treatment despite significant weight loss, which is per se associated with a significantly increased risk of gallstone formation [13].

When starting our bariatric program in 2007, we set up the internal policy of treating all patients with asymptomatic gallstones with UDCA for 6 months. Therefore, we cannot provide an internal control group of untreated patients, but we identified corresponding studies reporting on watchful waiting after bariatric surgery in patients with pre-existing asymptomatic gallstones. Here, the rates of new-onset symptoms are ranging from 6 to 20.8% [9, 12, 14, 15]. Compared to the cited studies, our results (3.3% new-onset symptoms) are overall highly suggestive of a positive impact of UDCA on gallstone-associated morbidity in preoperative asymptomatic patients. The low prevalence of the particular clinical constellation of asymptomatic gallstones in morbid obesity might be an explanation why these patients have widely been underappreciated in clinical reports resulting in weak evidence level and discordant guidelines. Although we are aware of the limitations in comparing different study populations prohibiting to draw linear conclusions, we strongly believe that our results will add a critical aspect for discussing and refining future management strategies.

Our findings are in line with a number of data on the impact of UDCA on gallstone formation in patients without pre-existing gallstones. Here, UDCA administration was found to be associated with fewer cases of gallstone formation and fewer patients requiring cholecystectomy after bariatric surgery [8]. In more detail, three recent studies reporting on the incidence of gallstone formation within the first 6 months after bariatric surgery found a significant difference of 5–40% in untreated patients vs. 0–11% in patients treated with UDCA [16–18]. Furthermore, a meta-analysis revealed that treatment with UDCA is also linked to a lower rate of cholecystectomy ($p < 0.001$) [8]. Here, our results provide a critical novel aspect with first data on the impact of UDCA on pre-existing asymptomatic gallstones. Despite significant weight loss, only two of our patients (< 4%) became symptomatic within the first 6 months after bariatric surgery.

Our data are fueling the debate about the concept of concomitant cholecystectomy in asymptomatic patients. Although concomitant cholecystectomy has long been considered a routine step during bariatric procedures [19, 20], recent studies have put this concept into question [21, 22]. Of note, a retrospective analysis of > 70.000 patients undergoing bariatric surgery showed that there is a significant reduction of patients undergoing concomitant cholecystectomy from 26.3% in 2001 to only 3.7% in 2008. Furthermore, the authors demonstrated that concomitant cholecystectomy had higher rates of mortality, overall postoperative complications, re-interventions, less frequent routine discharge, and longer adjusted hospital stay. In conclusion, the authors recommend concomitant cholecystectomy only to be considered in patients with symptomatic gallbladder disease [6]. These findings are supported by another comprehensive register analysis in > 36.000 patients undergoing bariatric surgery demonstrating that laparoscopic RYGB with simultaneous cholecystectomy had a significantly higher complication rate and took more than 1 h longer than laparoscopic RYGB without cholecystectomy [23]. Of note, there is also emerging evidence that post-cholecystectomy patients have an increased risk of colorectal and stomach cancer [24]. Just recently, cholecystectomy has been shown to eliminate fecal commensal microbiota and the authors further identified several bile acid metabolism-related bacteria as contributors of colorectal cancer incidence [25]. These data provide emerging evidence that put the concept of prophylactic concomitant

cholecystectomy into question. Here, our results provide further evidence for favoring non-surgical management in asymptomatic patients. Interestingly, our rate of < 2% patients requiring cholecystectomy under UDCA treatment is notably lower than retrospective data on > 36.000 patients reporting cholecystectomy rates ranging from 6 to 10% according to the distinct bariatric procedure. Therefore, the authors recommend that biliary prophylaxis should be contemplated [22], which is in turn supportive of our data and internal policy.

From an economic point of view, the average price for 6 months of UDCA treatment (500 mg per day) comes to 150 €, which is usually fully covered by the health insurance in Germany. So there is no financial burden for the individual patient. On the other hand, 150 € for pharmaceutical treatment also seems to be cost-effective for the national health system when comparing to a prolonged hospital stay of 0.4 days for patients undergoing concomitant cholecystectomy [6] or 61 min of additional procedure time for simultaneous cholecystectomy as demonstrated by Wanjura et al. [23].

Interestingly, another two of our preoperatively asymptomatic patients became symptomatic after UDCA withdrawal, both without requiring cholecystectomy. Of note, concomitant weight loss during postoperative months 7 to 12 was significantly lower, thus raising the question if UDCA therapy should be continued for a total of 12 months after bariatric surgery. Here, studies exploring the impact of UDCA on gallstone formation after bariatric surgery mainly report on stable or only slightly increasing numbers of patients that developed new gallstones after UDCA withdrawal after 6 months [16–18]. Overall, these results suggest that an interval of 6 months of treatment with UDCA after surgery is successfully reducing the incidence of gallstone formation compared to untreated controls. On the other hand, these data do not provide a rationale for prolongation of UDCA treatment [8]. Taken together with our data, 6 months of treatment with UDCA seems to be a sufficient prophylactic interval during the period when postoperative weight loss is most pronounced. However, a randomized controlled trial is needed to finally answer this question.

In conclusion, we provide a critical novel aspect to the ongoing debate about cholelithiasis in patients undergoing bariatric surgery with critical new data on the impact of UDCA treatment on preoperatively asymptomatic gallstones. Here, we found that UDCA treatment has beneficial impact on the rate of new-onset symptoms when compared to the current literature. Although our study has the limitation that an internal untreated control group is missing, we strongly believe that our data call the concept of prophylactic concomitant cholecystectomy in patients with asymptomatic gallstones into question while at the same time paving the way for a future clinical trial.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institution and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained for all individual participants included in the study.

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