Increased gallstone formation after sleeve gastrectomy and the preventive role of ursodeoxycholic acid

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Abstract

Background and study aims : **To investigate the incidence of gallstone formation, and the use of Ursodeoxycholic Acid (UDCA), weight loss and serum lipid profile changes following obesity surgery.**

Patients and methods : **Patients who underwent bariatric surgery due to obesity were retrospectively reviewed and divided into 2 groups for their prophylactic UDCA use. Patients who had a previous gallbladder pathology and ones who did not have a preoperative ultrasonography (US) were excluded. The patients who have returned to our clinic for a control ultrasound between 6 and 18 months following the surgery were included in this study, but only if they did not have any gall bladder pathology demonstrated with an US prior to surgery. Body mass index (BMI) and lipid profile measurements were also recorded.**

Results : **Of the 108 patients who had undergone obesity surgery, it is reported that 42 (38.9%) were given UDCA as a preventative medication, and 66 (61.1%) were not prescribed any preventative medications. During the ultrasound controls in the postoperative period between 6 and 18 months after surgery, gallbladder stones were seen in 42 patients (38.9%) and biliary sludge development was detected in 5 patients (4.6%). A total of 47 patients (43.5%) developed gallbladder pathology. Fewer patients who took UDCA developed gallstones when compared with the patients who did not take UDCA (10% vs 33%). Also, there is a correlation between BMI loss rate and the frequency of gallstone development. Though the decrease in triglyceride (TG) levels was higher in patients with gallstone development, this decrease was not statistically significant.**

Conclusions : **Stone or sludge development in the gallbladder due to rapid weight loss after obesity surgery is quite common. However, we observed that the gallstone development decreased significantly with the prophylactic use of UDCA in patients who had undergone obesity surgery.** (Acta gastroenterol. belg., **2020**, 83, **33-38**).

Key words : gallstone; bariatric surgery, weight loss, ursode-oxycholic acid

Introduction

Sleeve Gastrectomy (SG) is performed by removing a part of the stomach through the big curvature without disturbing the innervation or food passage or interfering with the biliary system. After SG, fewer complication rates were reported when compared to Roux-en-Y Gastric Bypass (RYGB). It was also found that SG provides more weight loss than the adjustable gastric band (AGB). Therefore, the use of SG for the treatment of morbid obesity has increased rapidly (1).

It has been shown that gallstones develop frequently in patients who experience rapid weight loss following dietary restrictions and bariatric surgery (2-6). However, data on the development of gallstones after SG is limited. To the best of our knowledge, there has been limited research into the incidence of post-SG gallstone formation (symptomatic and non-symptomatic). It has been reported that the risk of developing gallstones is high within 2 years after weight loss surgery, especially in the first 10 months (7). Additionally, complications such as cholecystitis, cholangitis, pancreatitis and cholecystoenteric fistula may develop after the formation of gallstones (8,9). Some centers perform a cholecystectomy at the same time as the bariatric surgery as a preventative measure. Yet not all patients develop gallstones after bariatric surgery. Therefore, the risks and complications of the cholecystectomy procedure should be considered based on the presence of risk factors (10,11). Ursodeoxycholic acid (UDCA) is one of the secondary bile acids, which are the metabolic byproducts of intestinal bacteria. When given as a medication, UDCA reduces cholesterol absorption and is used to dissolve (cholesterol) gallstones. Furthermore, UDCA prevents gallstone formation. Therefore, it is widely used as an alternative to prophylactic cholecystectomy. It has been reported that UDCA reduces the incidence of gallstone formation by inhibiting biliary cholesterol crystallization which results from rapid weight loss or very low-calorie diets (12).

The aim of this study is to evaluate the incidence of gallstone formation following rapid weight loss induced by bariatric surgery and to compare the efficacy of UDCA given for prophylaxis. Additionally, the effect of UDCA use on BMI and serum lipids was assessed.

Materials and methods

A total of 169 patients with morbid obesity who underwent SG between March 2016 and March 2018 were evaluated retrospectively. 108 patients who had undergone preoperative control abdominal US examinations during which no pathologies such as stone or sludge in the gallbladder were found were involved in this study. In the study, abdominal US examinations

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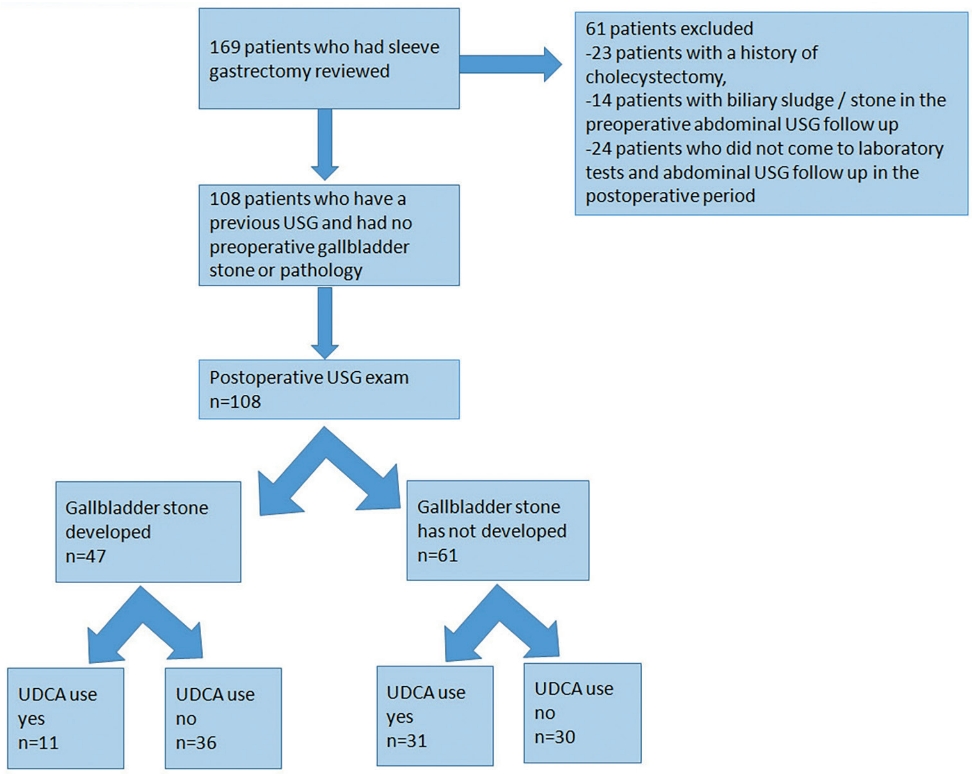

Fig. 1. — COHORT diagram for the inclusion of the patients. UDCA : Ursodeoxycholic acid.

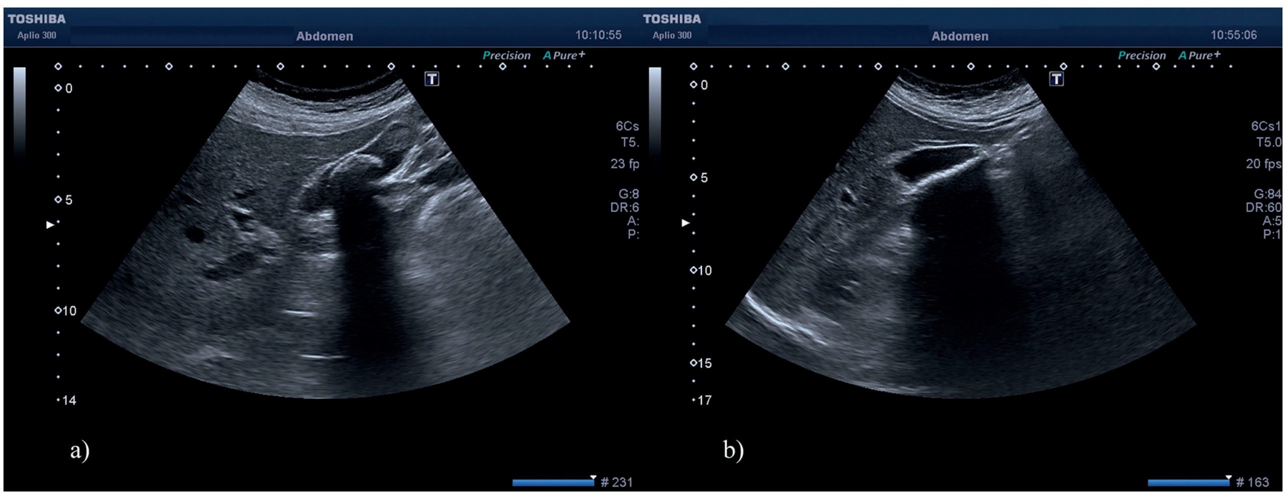

Fig. 2. — Ultrasound is the most common diagnostic tool for gallstones; it easily determines the number and size of stones. Ultrasound images showing single large (a) and multiple small stones (b) in the gallbladder.

were performed by only one researcher. Abdominal US examinations are performed by using 3.5 MHz convex ultrasound probe with Toshiba Aplio 300 device (Toshiba Medical Systems Corporation, USA). The protocol of the study was approved by the ethics committee of our hospital. All patients who had a preoperative US prior to the surgery and returned to the hospital for follow up US between 6 and 18 months were included in the study. Patients who had no ultrasound examination before or after the operation, those who had a history of gallstones or sludge in the gallbladder, and who had a history of cholecystectomy were excluded. COHORT diagram is presented in Figure 1. Patients who underwent bariatric surgery between March 2016 and July 2017 were not given UDCA prophylactically. Patients who underwent bariatric surgery after July 2017 were given prophylactically a daily dose of 2x250 mg UDCA due to the high rate of gallstone formation. Both groups were included in the study.

Preoperative body weight, height, body mass index (BMI), serum triglyceride, total cholesterol, HDL and LDL levels of all patients included in the study were recorded. After the operation, the same measurements were repeated, and the symptoms associated with gallstones were inquired. We compared the preoperative values of the patients with weight and serum lipid profiles and their measurements taken 12 months after the operation.. In the postoperative period, patients were invited for a follow up US at 6, 12 and 18 months after the operation. If the patient has more than one exam between 6 and 18 months after the operation, all recent images were evaluated. However, there were patients who did not return. Those were excluded from the study.

Patients with gallstone and/or biliary sludge development were identified (Figure 2). The effect of UDCA use was also evaluated. We analyzed the relationship between age, sex, preoperative serum lipid profile, BMI and stone development. Also, the relationship between postoperative BMI loss rate, the change in serum lipid profile, and stone development were also compared between the groups.

Statistical Examinations

While evaluating the findings obtained in the study, IBM SPSS Statistics 22 (IBM, SPSS, Turkey) was used for statistical analysis. While evaluating the study data, the suitability of the parameters to the normal distribution was evaluated with the Shapiro Wilks test, and it is detected that parameters are seen available to normal distribution. While evaluating the study data, in addition to descriptive statistical methods (mean, standard deviation, frequency), in comparison of the quantitative data, the Student t test was used to compare the parameters between the two groups. The Continuity (Yates) Correction was used to compare qualitative data. Significance was evaluated at the level of $p<0.05$.

Results

All patients undergoing surgery were between 19 and 66 years old. One hundred sixty nine patients who underwent SG during the study period were evaluated. 61 patients were excluded from the study: 23 patients with a history of cholecystectomy; 14 patients with biliary sludge / stone in the preoperative abdominal ultrasound; and 24 patients who did not come to laboratory tests and abdominal ultrasonographic control in the postoperative period. Therefore, the study was carried out on a total of 108 patients with ages ranging from 19 to 66 years. Age average is 39.62±10.62 years. In 47 (43.5%) cases, gallstone or mud was formed. 42 cases (38.9%) used UDCA while 66 (61.1%) did not receive UDCA treatment.

Demographic data, baseline characteristics and lipid profile values of both groups, developed gallstones (Group A) or no gallstones (Group B) are shown in Table 1. There were no significant differences in gender, mean age, initial BMI or initial weight in patients with gallstones. Preoperative lipid profile values were similar in both groups.

Table 1. — **Comparison of demographic information and preoperative findings of patients who developed gallstones (Group A) and no gallstones (Group B) according to Ursodeoxycolic acid (UDCA) use**

	Developed Gallstones Group A (n=47)		No Gallstones Group B (n=61)		p
	UDCA use		UDCA use		
	Yes	No	Yes	No	
Age	39.96±10.3	40.38±10	38.72±10.6	39.41±11	0.882
Female, n (%)	18(38%)	25(53%)	17(28%)	25(41%)	0.696
Initial BMI, kg/m2	45.87±5.4	48.64±5	44.18±4.2	45.03±4.7	0.166
Initial Weight, kg	129.84±19.1	126.65±18.5	120.32±13.2	116.53±12.9	0.030
Total Cholesterol**	179.12±30.1	167.34±29.1	169.41±31.2	164.51±30	0.389
Triglyceride**	100.18±21.5	96.74±24.9	100.18±23.4	102.95±27.4	0.432
HDL**	44.34±6.1	47.21±7	46.41±7.5	47.18±8.1	0.378
LDL**	102.37±28.4	106.29±30.5	100.43±29.1	102.45±29.8	0.532

*Student t test, * p<0.05, **mg/dl.*

Table 2. — **Relation of Preoperative - Postoperative BMI (%) change, serum triglyceride, total cholesterol, HDL and LDL difference with stone development**

	Developed Gallstones (Group A) N=47	No Gallstones (Group B) N=61	p
	Mean±SD	Mean±SD	
BMI (%) change	36.00±6.5	31.11±9.3	0.003*
Triglyceride change	-14.30±15.7	-8.81±14.2	0.059
Total cholesterol change	-9.16±11	-9.71±11.6	0.485
HDL change	3.96±5	4.56±5.6	0.182
LDL change	-6.12±8.5	-6.75±9.2	0.267

*Student t test, * p<0.05*

Table 3. — **The evaluation of the relationship between prophylactic ursodeoxycholic acid (UDCA) use and post-operative stone development**

	UDCA use		p
	YES	NO	
	n (%)	n (%)	
Developed Gallstones	11 (%10.18)	36 (%33.33)	0.007*
No Gallstones	31 (%28.70)	30 (%27.77)	

*Continuity (yates) correction, * p<0.05*

The patients who developed gallstones lost more BMI and this was statistically significant (p=0.003).

Although the decrease in triglyceride levels of the patients who developed gallstones after surgery was higher than those without gallstone development, this difference was not statistically significant (p:0,059; p>0.05).

No significant correlation was detected between the change of Serum Total Cholesterol, HDL and LDL levels and gallstone formation (p>0.05).

The incidence of stone formation in patients using UDCA (10,18%) was significantly lower than those without treatment (10% vs 33%; p<0.05).

Discussion

Although the prevalence of cholelithiasis varies among countries, it ranges between 6% and 16% in adults. The incidence of it in morbidly obese women of reproductive age reaches up to 30% (7).

The risk of increased gallstone formation after rapid weight loss was first described in patients who underwent RYGB (13). Subsequently, this phenomenon was confirmed in several studies with individuals experiencing rapid weight loss following both RYGB and caloric restriction (2-6). In general, the incidence of gallstone formation after calorie restriction was reported to be between 10% and 26%; whereas after RYGB, gallstone formation rates were higher (between 30% and 53%) (4,5,14,15).

However, the data on gallstone formation after pure restrictive procedures such as SG and AGB is limited. Kiewiet et al. reported that the incidence of gallstone formation after AGB is 26,5% (6). In two randomized, placebo-controlled trials in which UDCA use was investigated in the prevention of gallbladder stones after vertical banded gastroplasty (VBG) and AGB, gallbladder stones developed in 24 to 30% of patients in the placebo arm and the UDCA using group was between 0% and 8% (16,17). In a study evaluating the incidence of symptomatic gallstones flowing SG was reported as 3.8% (18).

Some studies suggest that low-calorie diets and obesity increase the resistance to cholecystokinin. Reduced gallbladder mobility may induce gallstone development due to decreased cholecystokinin secretion, resulting from impaired gastroduodenal passage of nutrients or damage to the hepatic branches of the vagus nerve during surgery (19). Theoretically, the risk of developing gallbladder stones is expected to be greater than that of SG and other pure restrictive procedures, as more anatomical changes are achieved with RYGB. The risk of cholelithiasis is expected to be less with pure restrictive procedures such as SG and gastric banding. Because food continues normal gastrointestinal transit, enteric endocrine reflex remains intact (20). However, evidence supporting this theory is controversial. Melissas et al. and Braghetto et al. showed that gastric emptying time significantly increased after SG compared to normal subjects (21,22). This may lead to an increase in gallbladder motility by increasing the frequency of cholecystokinin secretion. Consequently, the crystallization of cholesterol in the gallbladder is inhibited hypothetically. After RYGB, in a study implemented on a rat model, an increase on gastric emptying durations is seen. However, some studies show there is no significant difference in gastric emptying times after RYGB in humans (23,24). Bastouly et al. reported that gallbladder emptying was significantly impaired after RYGB and the residual volume of gallbladder increased significantly. In the same study, it was reported that gallbladder motility has never been studied in patients with SG (19). With rapid weight loss after RYGB, increased gallbladder calcium and mucin concentration in addition to cholesterol supersaturation are expected to cause gallstones (25,26). However, these factors have not been adequately investigated for pure restrictive bariatric surgical procedures, including SG. In another study, Li et al. reported that there was no significant difference in symptomatic gallstones formation after SG and RYGB (18). Our study revealed that gallbladder stone formation occurred in 43.5% of the patients after SG, similar to the incidence in previous studies reported after RYGB . Therefore, the traditional idea that a more physiological surgical technique could result in less gallstone development may not be accurate.

Faster and more dramatic weight loss after bariatric procedures is thought to increase the incidence of gallstone formation. However, many studies have not shown a significant relationship between weight loss and traditional risk factors such as age, gender, and diabetes with the development of gallstones after bariatric surgery (27,28). Some features, such as ethnicity, genetics, advancing age and female gender cannot be modified, whereas others (e.g., diet, physical activity, rapid weight loss and obesity) are modifiable. On the other hand, the data from the studies appear to be contradictory. While Yang et al. showed the first BMI and the amount of BMI lost were determinative for gallstone formation, Hoy et al. reported that absolute weight loss for gallstones after calorie restriction is a risk factor (13,29). Wattchow et al. In the first six months after RYGB, a relationship between absolute weight loss and gallstone formation is reported (4). As a result of multivariate risk factor analysis on patients who underwent RYGB, AGB and SG, weight loss more than 25% was found to be a risk factor for gallstone formation (27). However, Shiffman et al. and De Oliveira et al. have not found a relationship between gallstone formation and weight loss (5,15). In our study, a significant relationship was found between BMI loss rate and gallstone development. The reasons behind this discrepancy between studies can be explained by different weight loss parameters and the timing of the different weight measurements. Also, weight loss rates or measuring the amount at a certain time point as body weight shows fluctuation after bariatric surgery may not give correct results. With frequent controls, it may be helpful to measure the maximum weight loss rate and amount. Besides, there was a more decrease in TG levels in patients who developed gallstones, which may be associated with a decrease in caloric intake after SG. Although not statistically significant, monitoring of TG levels may be a parameter that can be used to determine the gallstone development risk.

Although it is accepted, that gallstone development is common after bariatric procedures such as sleeve gastrectomy, there is no universally accepted method to prevent postoperative gallstones formation. To date, only two main prophylactic methods have been studied. These include the use of perioperative cholecystectomy and UDCA. In the past, routine prophylactic perioperative cholecystectomy was recommended after RYGB. However, since cholecystectomy is a more difficult and longer procedure in obese patients, it is no longer recommended due to high complication rates (30). On the other hand, studies have confirmed that UDCA use is safe and effective in the prevention of gallstones in very low-calorie diets, in fast weight loss following RYGB and after other restrictive procedures (16,31). This finding was also confirmed by a meta-analysis showing that gallstone formation was markedly reduced (8.8% in the placebo group compared with 27.7% in UDCA using group) (32). Despite strong evidence on the benefit of prophylactic UDCA, clinical use has not been universally widespread due to various difficulties. First of all, objective risk factors could not be established to identify high-risk patients who need prophylactic UDCA. Secondly, the gastrointestinal side effects of UDCA, such as nausea, vomiting, diarrhea and abdominal pain, are common. Such side effects after bariatric surgery may make it difficult for the patient to use the medication and harm the trust between the doctor and the patient who performs the surgery.

To determine the risk of developing gallstones in patients treated with SG, the main purpose of our study, we investigated several weight loss parameters. We also examined changes in serum lipid profile. We found a significant relationship between the BMI loss rate and gallstone formation. Besides, we found that the decrease in serum TG levels was more prominent in patients with gallstones. We have detected that the use of UDCA in patients who underwent SG as the second leg of the study significantly reduced gallstone formation. When evaluated with previous studies, it is seen that frequent ultrasonography control is necessary. Also, following bariatric surgery, weight loss parameters and serum lipid profile monitoring may provide useful information. Evaluation of the decrease in TG levels with the recording of the maximum weight loss rates may reveal the increased risk of gallstones formation. In the light of these data, it is seen that UDCA, which will be given prophylactically to selected patients at high risk, can prevent the development of gallstones.

In summary, although SG is a less invasive, pure restrictive bariatric procedure, the risk of developing gallstones is quite high in patients with SG, especially after a high rate of weight loss. We observed that the prophylactic use of UDCA significantly reduced gallstone formation after weight loss surgery. Furthermore, our data revealed a significant relationship between postoperative BMI loss rate and gallstone development. Even it was not statistically significant, the decrease in serum TG levels was higher in patients with gallstones. Based on these findings, we recommend more frequent follow-up examinations for patients with severe BMI loss and serum lipid change. Thus, the use of UDCA may be beneficial for high-risk patients.

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Conflict of interest

Authors declare no conflict of interest.

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