Some risk factors of gallstone formation after laparoscopic sleeve gastrectomy and the role of ezetimibe versus ursodeoxycholic acid in its prevention

Alaa Elgamal[a], Ahmad Tarek Fawzy[b]

[a]Assistant Professor of Internal Medicine, Mansoura Faculty of Medicine, Mansoura University, Mansoura, [b]Professor of Surgery, Menofia Faculty of Medicine, Menofia University, Menofia, Egypt

Correspondence to Dr. Alaa Eldin ElGamal, MD, Head of Internal Medicine Department, AlRashid Hospital, Po Box 8999., Salmyia 22060, Kuwait
Tel: 0096590989025;
e-mail: alaaelgamal456@yahoo.com

Received 3 April 2014
Accepted 29 April 2014

The Egyptian Society of Internal Medicine
2014, 26:75–79

Aims
Obese patients are at increased risk for gallstones during rapid weight loss and after laparoscopic sleeve gastrectomy. The aims of this study were to evaluate the prophylactic effect of ursodeoxycholic acid and ezetimibe for prevention of gallstone formation after sleeve gastrectomy and to identify some risk factors.

Settings and design
This was a prospective randomized study conducted at Al Rashid Hospital, Kuwait.

Patients and methods
A total of 215 obese patients were included. Preoperative assessment was performed, including history, examination, obesity evaluation (body weight, BMI, waist circumference), full laboratory work, gastroscopy, and abdominal ultrasonography. After laparoscopic sleeve gastrectomy, patients were divided randomly into: group 1 (control), group 2 (ursodeoxycholic acid), and group 3 (ezetimibe). Patients were scheduled for 3-, 6-, and 12-month visits for assessment of % excess weight loss and abdominal ultrasonography.

Results
A significant reduction in gallstone formation was found in the ezetimibe group (5.5%) compared with the control group (17.6%). A statistically significant increase in % excess weight loss was observed in patients with gallstones (38.5%) versus patients without gallstones (28.2%). Percentage of gallstone formation during first 6 months postoperatively was double that during the next 6 months in both the control and treatment groups.

Conclusion
Risk of gallstone formation during the first 6 months after laparoscopic sleeve gastrectomy was double that during the second 6 months. Ezetimibe is effective in reducing relative risk by 70% and ursodeoxycholic acid by 50% versus control; hence, we recommend usage of one of these medications for 1 year postoperatively. Furthermore, we recommend more work on combining both medications together.

Keywords:
gallstone disease, laparoscopic sleeve gastrectomy, obesity, risk factors

Egypt J Intern Med 26:75–79

1110-7782

Introduction

Obese persons are at risk for cholesterol gallstones because of high saturation of cholesterol in their bile. About 75% of gallstones are of cholesterol type. The risk increases during rapid weight loss using low-calorie diets and after bariatric surgery. The mechanism for gallstone formation during rapid weight loss is not completely understood; several mechanisms have been suggested including increased bile cholesterol saturation and gallbladder stasis, increased secretion of mucin and calcium, and increased prostaglandins [1–4].

To reduce the risk for gallstone formation, policies of prophylactic cholecystectomy are proposed [5]. However, this is not widely accepted.

The risk of developing gallstones during weight reduction is well accepted [6,7]. Between 10 and 25% of persons who lose weight through very low-calorie dieting develop gallstones [8,9]. In addition, 35–38% of patients develop gallstones as they lose weight after bariatric surgery [10–12]. A routine cholecystectomy during bariatric surgery is recommended by some centers [13], but it may be a difficult procedure with an incidence of complications [14,15]. Ursodeoxycholic acid enhances the conversion of cholesterol to bile acids [16]. It also enhances cholesterol transport as liquid crystals [17]. Furthermore, it has an inhibitory action on the prostaglandins and biliary glycoprotein, which is the possible explanation for its action on decreasing the saturation index [18].

Ezetimibe is a cholesterol-lowering agent that inhibits intestinal cholesterol absorption [1]. A long-term study is needed to observe whether ezetimibe can reduce gallstone prevalence [19]. Unexpectedly, it was found that ezetimibe treatment can induce a complete resistance to cholesterol gallstone formation [20,21].

The recommended dose for gallstone prophylaxis for ursodeoxycholic acid appears to be 600 mg or 4–5 mg/kg [19,21]. This is approximately half of the therapeutic dose for dissolution of cholesterol stones.

Shiffman *et al.* [22] showed that ursodeoxycholic acid (600 mg/day) is effective in preventing gallstone formation in patients undergoing dietary-induced weight reduction. The prophylactic administration of ursodeoxycholic acid has been shown to be effective in gastric bypass procedure [23,24] as well as in vertical banded gastroplasty [25,26].

Aim

The aim of this study was to define the incidence of gallstone formation and timing of its occurrence in obese patients after laparoscopic sleeve gastrectomy in addition to highlight the risk factors for the development of gallstones after bariatric surgery, including age, sex, diabetes mellitus, dyslipidemia, preoperative BMI, and excess weight loss percentage (EWL%) of the original weight. Furthermore, we evaluated the prophylactic effect of ursodeoxycholic acid and ezetimibe treatment for its prevention.

Patients and methods

All patients submitted to laparoscopic sleeve gastrectomy performed between 2009 and 2011 at Al Rashid Hospital were enrolled in the study. A total of 215 patients completed the study, whereas 48 patients were excluded for having history of cholecystectomy, gallstone disease, or they refused to share in the study.

All patients were subjected to follow-up abdominal ultrasonography (US) obtained preoperatively and at 3, 6, and 12 months after surgery or until gallstone formation [27].

Eligible patients were between 20 and 60 years of age and had a BMI of at least 40 kg/m^2 or BMI of at least 35 kg/m^2 with comorbidities according to the guidelines of the National Institutes of Health Consensus Development Conference Statement [28].

Exclusion criteria were history of cholecystectomy, presence of gallstones, pregnancy, or inadequate use of contraceptive methods.

All patients were subjected to preoperative clinical examination with obesity evaluation and laboratory evaluation performed before surgery, including fasting blood sugar, lipid profile, ECG, chest radiography, abdominal US, gastroscopy, hormonal level (thyroid function test and serum cortisol), vitamin assays of B1 and B12, and ferritin, and other basic preoperative work was performed. Laparoscopic sleeve gastrectomy was performed by one operator and two assistants for all the cases.

We divided patients randomly into three groups: group 1, the control group; group 2, using ursodeoxycholic acid at a dose of 4–5 mg/kg/day in divided oral doses; and group 3, using ezetimibe at a dose of 10 mg/day orally. All treatments initiated 10 days after surgery and continued for 12 months or until gallstone development.

Patients agreed to take the trial medication for 12 months or until gallstones developed. Medication compliance was monitored at every visit. There were no serious or significant adverse effects experienced during the study. EWL was recorded and abdominal US was performed blindly by two radiologists for all patients at every visit (at 3, 6, and 12 months). Informed consent was obtained from each patient before initiation of the study, and hospital ethical committee approval was obtained for the protocol of the study.

Statistical analysis

All data were analyzed by a personal computer using the software program; median, SD, range, and mean values were calculated. Univariate analyses were performed using the Wilcoxon–Mann–Whitney *U*-test for continuous variables and using the χ^2-test, and statistically significant levels are those below 0.05.

Results

Table 1 shows basal clinical and laboratory characteristics. Sixty-eight patients without medication were compared with 146 patients on medications (75 on ursodeoxycholic acid and 72 on ezetimibe). There were no significant differences between the two groups with respect to age, BMI, waist circumference, blood pressure, fasting blood sugar, and lipid profile.

Table 2 reveals the number and percentage of gallstone formation in the three groups. It shows that 12 (17.6%) of 68 patients developed gallstones in group 1 and six (8%) of 75 patients developed gallstones in group 2, whereas only four (5.5%) of 72 patients developed gallstones in group 3. Table 2 shows no significant difference in gallstone formation between the control and ursodeoxycholic acid groups, whereas a statistically significant reduction in gallstone formation was observed in the ezetimibe group compared with the control group.

Table 1 Basal clinical and laboratory characteristics of the study groups

	Group 1 (control) (*N* = 68)	Medication group (group 2+3) (*N* = 75+72 = 147)	*T*-value	*P*-value
Sex [*n* (%)]				
Female	52 (76.4)	126 (85.7)		
Male	16 (23)	21 (14.2)		
Age (years)	34.75 ± 8.39	35.12 ± 6.12	0.929	0.179
BMI (kg/m^2)	47.3 ± 1.2	46.2 ± 6.12	0.192	0.181
Waist circumference (cm)	115.62 ± 7.7	114.25 ± 2.05	0.635	0.263
BP (mmHg)				
Systolic	133.62 ± 14.61	141.5 ± 14.41	0.413	0.338
Diastolic	84.37 ± 10.15	85.25 ± 9.99	0.893	0.186
FBS (mmol/l)	6.98 ± 1.29	7.92 ± 0.85	0.087	0.465
Total cholesterol (mmol/l)	5.57 ± 1.38	5.96 ± 1.2	0.665	0.253
LDL (mmol/l)	4.41 ± 0.86	4.36 ± 0.61	0.917	0.180
HDL (mmol/l)	0.92 ± 0.2	0.97 ± 0.36	0.76	0.224
Triglycerides (mmol/l)	2.72 ± 0.54	3.02 ± 1.25	0.34	0.367

BP, blood pressure; FBS, fasting blood sugar; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; Significance, $P < 0.05$.

Table 2 Percentage of gallstone formation in the treatment groups versus control

	Total (*n*)	Number with gallstones (%)	χ^2	*P*-value
Group 2	75	6 (8)	2.166	0.141
Group 1	68	12 (17.6)		
Group 3	72	4 (5.5)	7.759	0.005
Group 1	68	12 (17.6)		

Significance, $P < 0.05$.

Table 3 shows some risk factors for gallstone formation. We found a significant association of gallstone formation with EWL after 1 year; it was 38.5% versus 28.2% in patients with gallstones versus patients without gallstones. With respect to other risk factors, we did not find any significant variation in patients with gallstones versus patients without gallstones.

Table 4 shows the comparison of EWL during the study duration at intervals of 3, 6 months, and 1 year in patients with gallstone formation in the treatment groups, showing no significant difference in the degree of weight loss during the duration of the study in both group 2 and group 3.

Table 5 shows the timing of gallstone formation during the first 6 months versus next 6 months; it was 4.7 versus 2.04% in the treatment group, whereas in the control group it was 11.76 versus 5.88%.

Discussion

Because of increasing incidence of obesity and its complications, the demand for bariatric surgery is increasing [29]. Morbid obesity has a high incidence of gallstone formation. Postoperatively, gallstone formation is correlated with rapid weight loss in a high incidence [22]. In the last few years, laparoscopic sleeve gastrectomy is rising to be one of the most effective surgeries; especially, it reverses some metabolic abnormalities such as diabetes mellitus, hypertension, and dyslipidemia. A five-fold increased risk for gallstone disease was found after antiobesity surgery compared with that in the general population [5].

Festi *et al*. [30] reported that 54% of patients developed gallstones during low-fat diet. Relatively high-fat intake could prevent gallstone formation, probably by maintaining an adequate gallbladder emptying.

Controversy exists whether the gallbladder should be removed when performing gastric restrictive procedures. Amaral and Thompson [10] recommended a routine cholecystectomy at the time of bariatric surgery. Other surgeons only recommend removal of the gallbladder in the presence of gallbladder disease [31,32]. Pure restrictive surgery such as laparoscopic sleeve gastrectomy should result in less gallstone formation because the food continues to follow the normal gastrointestinal transit maintaining the enteric–endocrine reflex.

A trial of ursodeoxycholic acid during weight loss after vertical banded gastroplasty suggests that it is fully effective in prevention of gallstone formation, whereas 24% of patients on control developed gallstones [27].

Ezetimibe reduces plasma cholesterol concentrations by inhibiting the Niemann-Pick C1-like 1 protein, an intestinal sterol influx transporter that facilitates the uptake of cholesterol for intestinal absorption inducing a resistance to cholesterol gallstone formation due to 60% reduction in biliary cholesterol saturation index [33].

Table 3 Some risk factors for gallstone formation

	Patients with gallstones (*N* = 22)	Patients without gallstones (*N* = 193)	*T*-value	*P*-value
Age (years)	28.79 ± 8.22	32.12 ± 9.28	0.54	0.294
Female sex (%)	86.36 (19/22)	82.38 (159/193)	0.32	0.374
EWL degree (kg) and percentage after 1 year	49.59 ± 6.35 (38.5%)	37.04 ± 7.38 (28.28%)	1.67	0.048
Waist circumference (cm)	116 ± 4.56	117.37 ± 2.87	0.37	0.333
BMI	45.87 ± 2.1	46.2 ± 1.52	0.38	0.352
FBS (mmol/l)	6.58 ± 1.14	6.98 ± 1.29	0.43	0.333
Total cholesterol (mmol/l)	6.10 ± 0.80	5.97 ± 0.78	0.77	0.221
Triglycerides (mmol/l)	2.71 ± 0.88	2.72 ± 0.54	0.93	0.176
Family history (%)	36.3 (8/22)	31.6 (60/193)	—	—

EWL, excess weight loss; FBS, fasting blood sugar; Significance, $P < 0.05$.

Table 4 Excess weight loss in patients with gallstone formation in the treatment groups

	Group 2	Group 3	*T*-value	*P*-value
Initial weight (kg)	126 ± 14.24	138.5 ± 122.12	0.183	0.427
Weight loss at 3 months	17.83 ± 2.78	20.75 ± 3.86	0.124	0.450
Weight loss at 6 months	23.83 ± 3.43	32.75 ± 0.95	1.416	0.338
Weight loss at 12 months	40 ± 1.67	41.5 ± 3.10	0.212	0.416

Significance, $P < 0.05$.

Table 5 Timing of gallstone formation in the treatment group versus the control group

	First 6 months	Next 6 months
Treatment group (*n* = 147)	7/147 (4.7%)	3/147 (2.04%)
Control group (*n* = 68)	8/68 (11.76%)	4/68 (5.88%)

In our study, the incidence of gallstone formation postoperatively in the control group was 17.6 versus 6.8% in the treatment group. There are a lot of diverse results as in the study by Li *et al.* [34] who showed that the overall incidence of gallstone formation was 7.8% in a group without prophylactic drugs. Miller *et al.* [27] showed 22% gallstone formation in control versus 3% in the ursodeoxycholic acid group during the first 12 months.

Kielani *et al.* [35] proposed that the incidence of gallstone formation is highest during the first 6 months after surgery showing 33.8% in the first 6 months versus 21.6% in the next 6 months postoperatively. In our study, the percentage of patients with gallstones in the treatment group was 4.7% during the first 6 months versus 2.04% in the next 6 months. However, in the control group, it was 11.76 versus 5.88% in the first 6 months versus next 6 months, which supports the hypothesis that gallstone formation is highest during the first 6 months following surgeries due to rapid weight loss during that period.

Some studies settled that the duration of use of prophylactic medications is between 2 and 6 months [36]; however, Sugerman *et al.* [26] suggested the duration of 12 months, whereas Dietel and Petrov [11] showed the peak incidence of gallstone formation at 16 months after surgery.

In our study, ezetimibe use appears to be more effective in prevention of gallstone formation than ursodeoxycholic acid in comparison with the control group. The explanation of this difference is not clear; however, it may be because both drugs have different mechanisms. On this basis, we recommend the use of both drugs in the same patients to get better effects.

In this study, we found that the most relevant risk factor associated with gallstone formation is the degree of weight loss. It was 38.5% in those with gallstones versus 28.2% in those without gallstones. There was no clear association between some other risk factors and gallstone formation in our study. In a study conducted by Li *et al.* [34], postoperative weight loss of more than 25% of original weight was associated with symptomatic gallstone formation.

We suggest a combination of ursodeoxycholic acid and ezetimibe in prevention of gallstone formation after laparoscopic sleeve gastrectomy. The base of such combination was suggested by De Bari *et al.* [33], who stated that the cholelitholytic mechanism of ezetimibe is totally different from that of hydrophilic bile acids such as ursodeoxycholic acid; it has been proposed that a combined therapy of ezetimibe and ursodeoxycholic acid could be a faster means to promote the dissolution of cholesterol gallstones. This can be due to the two distinct mechanisms: the formation of unsaturated micelles by ezetimibe and a liquid crystalline mesophase by ursodeoxycholic acid [19].

Conclusion

Increased gallstone formation after laparoscopic sleeve gastrectomy is associated mainly with the degree of weight loss. Risk for gallstone formation after laparoscopic sleeve gastrectomy during the first 6 months doubles the risk during second 6 months

postoperatively. We found that ezetimibe is effective in reducing relative risk by 70% and ursodeoxycholic acid by 50%; hence, we recommend the use of one of these medications for 1 year postoperatively. Furthermore, we recommend more studies on combining both medications together to observe if we will have more favourable outcome compared to one medicine alone.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References

1 Portincasa P, Stolk MF, Van Erpecum KJ, Palasciano G, Van Berge-Henegouwen GP. Cholesterol gallstone formation in man and potential treatments of the gallbladder motility defect. Scand J Gastroenterol Suppl 1995; 212:63–78.

2 Festi D, Colecchia A, Larocca A, *et al.* Low caloric intake and gall-bladder motor function. Aliment Pharmacol Ther 2000; 14:51–53.

3 Shiffman ML, Shamburek RD, Schwartz CC, *et al.* Gallbladder mucin, arachidonic acid, and bile lipids in patients who develop gallstones during weight reduction. Gastroenterology 1993; 105:1200–1208.

4 Shiffman ML, Sugerman HJ, Kellum JH, *et al.* Gallstones in patients with morbid obesity. Relationship to body weight, weight loss and gallbladder bile cholesterol solubility. Int J Obes Relat Metab Disord 1993; 17:153–158.

5 Jones E, Marsk R, Rasmussent F, Freedman J. Incidence of postoperative gallstone disease after antiobesity surgery: population-based study from Sweden. Surg Obes Relat Dis 2010; 6:54–58.

6 Bennion LJ, Grundy SM. Risk factors for the development of cholelithiasis in man (second of two parts). N Engl J Med 1992; 307:798–800.

7 Kodama H, Kono S, Todoroki I, *et al.* Gallstone disease risk in relation to body mass index and waist-to-hip ratio in Japanese men. Int J Obes Relat Metab Disord 1999; 23:211–216.

8 Yang H, Peterson GM, Roth MP, *et al.* Risk factors for gallstone formation during rapid weight loss. Dig Dis Sci 1992; 37:912–918.

9 Zapata R, Severin C, Manriquez M, *et al.* Gallbladder motility and lithogenesis in obese patients during diet-induced weight loss. Dig Dis Sci 2000; 45:421–428.

10 Amaral JF, Thompson WR. Gallbladder disease in morbidly obese. Am J Surg 1985; 149:551–557.

11 Deitel M, Petrov I. Incidence of symptomatic gallstones after bariatric operations. Surg Gynecol Obstet 1987; 164:549–552.

12 Shiffman ML, Sugerman HJ, Kellum JM, *et al.* Changes in gallbladder bile composition following gallstone formation and weight reduction. Gastroenterology 1992; 103:214–221.

13 Schmidt JH, Hocking MP, Rout WR, *et al.* The case for prophylactic cholecystectomy concomitant with gastric restriction for morbid obesity. Am Surg 1988; 54:269–272.

14 Ammori BJ, Vezakis A, Davides D, *et al.* Laparoscopic cholecystectomy in morbidly obese patients. Surg Endosc 2001; 15:1336–1339.

15 Angrisani L, Lorenzo M, De Palma G, *et al.* Laparoscopic cholecystectomy in obese patients compared with non obese patients. Surg Laparosc Endosc 1995; 5:197–201.

16 Broomfield PH, Chopra R, Sheinbaum RC, *et al.* Effects of ursodeoxycholic acid and aspirin on the formation of lithogenic bile and gallstones during loss of weight. N Engl J Med 1988; 319:1567–1572.

17 Fromm H. Gallstone dissolution therapy: current status and future prospects. Gastroenterology 1986; 91:1560-1567.

18 Al Mofleh IA. Management of gallstones. Saudi J Gastroentrol 1996; 2:29–38.

19 Wang HH, Portincasa P, Mendez-Sanchez N, Uribe M, Wang DQ. Effect of ezetimibe on the prevention and dissolution of cholesterol gallstones. Gastroenterology 2008; 134:2101–2110.

20 Buhman KK, Accad M, Novak S, *et al.* Resistance to diet-induced hypercholesterolemia and gallstone formation in ACAT2-deficient mice. Nat Med 2000; 6:1341–1347.

21 Jia L, Ma Y, Liu G, Yu L. Dietary cholesterol reverses resistance to diet-induced weight gain in mice lacking Niemann-Pick C1-like 1. J Lipid Res 2010; 51:3024–3033.

22 Shiffman ML, Kaplan GD, Brinkman-Kaplan V, *et al.* Prophylaxis against gallstone formation with ursodeoxycholic acid in patients participating in a very-low-calorie diet program. Ann Intern Med 1995; 122:899–905.

23 Hood KA, Gleeson D, Ruppin DC, Dowling RH. Gall stone recurrence and its prevention: the British/Belgian Gall Stone Study Group's post-dissolution trial. Gut 1993; 34:1277–1288.

24 Wudel LJ Jr, Wright JK, Debelak JP, *et al.* Prevention of gallstone formation in morbidly obese patients undergoing rapid weight loss: results of a randomized controlled pilot study. J Surg Res 2002; 102:50–56.

25 Williams C, Gowan R, Perey BJ. A double-blind control-controlled trial of ursodeoxycholic acid in the prevention of gallstones during weight loss after vertical banded gastroplasty. Obes Surg 1993; 3:257–259.

26 Sugerman HJ, Brewer WH, Shiffman ML, *et al.* A multicenter, placebo-controlled, randomized, double-blind, prospective trial of prophylactic ursodiol for prevention of gallstone formation following gastric-bypass-induced weight loss. Am J Surg 1995; 169:91–96.

27 Miller K, Hell E, Lang B, Lengauer E. Gallstone formation prophylaxis after gastric restrictive procedures for weight loss. A randomized double-blind control-controlled trial. Ann Surg 2003; 238:697–702.

28 National Institutes of Health. Gastrointestinal surgery for severe obesity. NIH Consens Statement 1991; 9:1–20.

29 Brolin RE. Update: NIH Consensus Conference: gastrointestinal surgery for severe obesity. Nutrition 1996; 12:403–404.

30 Festi D, Colecchia A, Orsini M, *et al.* Gallbladder motility and gallstone formation in obese patients following very low-calorie diets. Use it (fat) to lose it (well). Int J Obes Relat Metab Disord 1998; 22:592–600.

31 Fakhry SM, Herbst CA, Buckwalter JA. Cholecystectomy in morbidly obese patients. Am Surg1987; 53:26–28.

32 Jones KB Jr. Simultaneous cholecystectomy: to be or not to be. Obes Surg 1995; 5:52–54.

33 de Bari O, Neuschwander-Teri BA, Liu M, Prtincasa P, Wang DQ. Ezetimibe: its novel effects on the prevention and the treatment of cholesterol gallstones and nonalcoholic fatty liver disease. J Lipids 2012; 2012:302847.

34 Li VK, Pulindo N, Fajnwaks P, Szomstein S, Rosenthal R, Martinez-Duartez P. Predictors of gallstone formation after bariatric surgery: a multivariate analysis of risk factors comparing gastric bypass, gastric banding, and sleeve gastrectomy. Surg Endosc 2009; 23:1640–1644.

35 Keilani ZM, El Djouzi S, Kuwada TS, Gersin K, Simms C, Stefanidis D. What are the incidence and timing of cholecystectomy after bariatric surgery? Poster presentation, program no. P503, SAGES Annual Meeting; San Diego, CA; 2012.

36 Spirt BA, Graves LW, Weinstock R, *et al.* Gallstone formation in obese women treated by a low-calorie diet. Int J Obes Relat Metab Disord 1995; 19:593–595.