Cholelithiasis after Weight Loss Surgery: Challenge and Prophylaxis

Ahmed Talha *MD, MRCS;*[1] ***Ayman Farouk,*** *MD,*[1] ***Ihab Hasouna,*** *MD.*[2]

1) Department of Surgery, Medical Research Institute, Alexandria University, Egypt.
2) Department of Internal Medicine, Faculty of Medicine, Alexandria University, Egypt.

Background: *Rapid loss of weight after bariatric surgery is associated with a high incidence of gallstone formation. This study was carried out to detect the efficacy of six months regimen of prophylactic Ursodeoxycholic acid in the prevention of gallstones and to identify the predictive factors for gallstone formation after weight loss surgery.*

Methods: *A randomized controlled trial was carried out involving 108 patients with a preoperative diagnosis of morbid obesity were subjected to either laparoscopic sleeve gastrectomy (LSG) or greater curve plication (LGCP) with follow-up for a minimum one year; they were divided into two groups; (group A; receiving Ursodeoxycholic acid) and (group B; receiving placebo). Data were collected about: Patient clinical history, baseline characteristics and postoperative follow-up.*

Results: *The demographic parameters were comparable in the two groups. The incidence of cholelithiasis after surgery was 14.3% (13 cases). The mean %EWL was significantly higher in those who develop gallstones than others (P= 0.045). Also, there was a significant increased cholelithiasis post-LSG than LGCP (P=0.036). There was a significant decrease in the incidence of gallstone formation from 22% in placebo to 6.5% in treated group with Ursodeoxycholic acid (P = 0.041).*

Conclusions: *The percentage of excess weight loss was the only predictive postoperative factor for gallstone formation. A six months use of Ursodeoxycholic acid is an effective prophylaxis for gallstone formation after weight loss procedures although a larger study is required to reach a definitive conclusion.*

Key Words: *Obesity; gallstone; bariatric surgery; ursodeoxycholic acid.*

Introduction:

Worldwide prevalence of obesity is increasing, and the incidence of obesity in the US has increased from 22.9% between 1988 and 1994, to 34% in 2006.[1–3]

Obesity is associated with increased risk for hypertension, diabetes, pulmonary disease, hyperlipidemia, cardiomyopathy, malignancy, arthritis, infertility, sleep apnea, gallstone formation and psychosocial impairments. Given the fact that with weight loss improves many of these comorbidities,[4] much effort has gone into the development of effective treatment modalities focused on sustained weight loss. Dietary regimen, behavioral modification, and exercise have been largely unsuccessful in achieving and maintaining long-term results in morbidly obese patients. Therefore, more aggressive treatment is typically required for obese subjects at risk for medical complications of obesity. Surgery has become an attractive alternative because it represents a long-term solution.[5]

Bariatric surgery is the most effective modality for long-term weight loss and for resolving the associated comorbidities.[6] The

primary mechanisms through which bariatric surgery achieves its outcomes are believed to be the mechanical restriction of food intake, reduction in the absorption of ingested foods, or a combination of both.[7] However, controversies exist regarding the ideal weight loss metabolic procedure that allowed continuous search for new techniques.

Many operative modalities have been devised, among those most commonly performed nowadays; adjustable gastric banding (AGB); Roux-en-Y gastric bypass (RYGB); biliopancreatic diversion with duodenal switch (BPD); and sleeve gastrectomy (SG) and greater curve plication (GCP) preferably through minimally invasive approach.[5–8]

Between 35–38% of patients with morbid obesity develop gallstones as they lose weight after bariatric surgery.[5,9–11] A routine synchronous cholecystectomy during bariatric surgery is recommended by some centers.[9,12] Therefore, a preventive therapy for gallstone formation is recommended in several studies. Ursodeoxycholic acid (500 mg/d) is highly effective in preventing gallstone formation in patients undergoing dietary-induced weight reduction.[13]

This study was carried out to detect the efficacy of six months regimen of prophylactic Ursodeoxycholic acid in the prevention of gallstones and to identify the predictive factors for gallstone formation after weight loss surgery.

Study design:

This was randomized controled trial study, where all patients from age 18 to 60 years, with a preoperative diagnosis of morbid obesity based on the guidelines issued by International Federation for Surgery of Obesity (IFSO)[14] underwent either laparoscopic sleeve gastrectomy (LSG) or laparoscopic greater curve plication (LGCP) at the Department of Surgery, Medical Research Institute Hospital, Alexandria University and continued their follow-up for a minimum of one year. 108 patients were divided into two groups; (group A; receiving Ursodeoxycholic acid; 500 mg/d for six months in the immediate postoperative period) and (group B; receiving placebo), were offered the opportunity to participate in this trial. Informed consent was obtained from all participants and approval was obtained from the ethics committee of our institutions.

The exclusion criteria included the following: American Society of Anesthesiologists (ASA) class IV and V, patients with contraindication for laparoscopy, prior cholecystectomy, presence of gallstones, use of other investigational drugs, pregnancy or refusal.

Randomization method:

Eligible patients were randomized into two groups; (group A; receiving Ursodeoxycholic acid) and (group B; receiving placebo) using sealed opaque envelopes containing computer-generated random numbers. The randomization was performed one week before surgery during the preoperative assessment. Data were collected about: Patient clinical history, baseline characteristics and postoperative follow-up evaluating the percentage of excess weight loss (% EWL) and gallstone formation.

Study Protocol:

All patients underwent the following basic preoperative investigations, including the following: (1) blood tests: complete blood count, coagulation profile, renal and liver function tests and hormonal profile including TSH and cortisone levels; (2) radiologic imaging: chest radiograph and ultrasonography of abdomen and pelvis; (3) electrocardiogram; (4) echocardiogram; and (5) respiratory function tests.

Eligible patients had undergone either LSG or LGCP. Ambulation was encouraged, and chest physiotherapy was started in the immediate postoperative period. An upper gastrointestinal contrast study using water-soluble contrast (Gastrograffin) was done on the first postoperative day. Clear liquids were started on confirmation of staple-line integrity. The patient was discharged once oral intake of 1,500–2,000 ml/24 h was established. Prokinetics, and proton pump inhibitors were continued for ten days. All

medications were given orally in crushed or liquid form. The drain was removed on the second postoperative day. A liquid diet was given for two weeks, a pureed/soft diet for six weeks, and normal diet thereafter. Dietary counseling was provided, and a normal consistency, low-calorie, high protein diet is advised at two months from surgery. Patients were followed up at 1, 3, 6, and 12 postoperative months and then annually. Abdominal Ultrasonography investigation of the gallbladder was performed in all patients at six and twelve postoperative months.

Statistical analysis:

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 20 software (SPSS, Inc., Chicago, IL, USA). Significance was set at a P-value <0.05. Qualitative data were described using number and percent. Quantitative data were described using mean and standard deviation for normally distributed data. Comparison between different groups regarding categorical variables was tested using Chi-square test while for two groups comparison t-test was used for parametric data.

Results:

From March 2010 to October 2013, 134 patients were submitted to bariatric surgery and 108 patients were eligible. 91 patients completed follow-up gallbladder sonography and were randomly classified into two groups; 45 to placebo and 46 to 500 mg/d Ursodeoxycholic acid. Twenty six patients refused to participate in the study or did not meet the inclusion criteria. (Figure I) 66 patients (72.5%) patients underwent LSG and 25 patients (27.5%) underwent LGCP **Table (1)**.

There were 36 men (39.6%) and 55 women (60.4%). There were no significant differences with respect to age, sex, or preoperative BMI between those who developed gallstones or not. **Table (1)** However, the group who formed gallstones have significantly higher mean % EWL in the first postoperative year (P = 0.045). **Table (1)** Regarding the type of operation there was a significant difference between those who developed gallstones or not (P = 0.036) as in LSG 10.9% versus 3.3% in LGCP; patients showed a noticeably more rapid weight loss, with significant incident development of gallstone formation **Table (1)**.

Ultrasonography investigation of the gallbladder was performed in all patients. During follow up, 13 of them (14.3%) developed gallstones postoperatively in a range of 6 - 12 months and 78 (85.7%) did not develop gallstones **Table (1)**. Of those developed gallstones 5 cases (38.5%) were symptomatizing and the other 8 cases (61.5%) discovered by routine ultrasonography during follow up. So the incidence of symptomatizing cholelithiasis after surgery in this series was 5.5 % **Table (2)**.

There were no significant differences with respect to age, sex, preoperative BMI, %EWL or the type of surgery between those receiving medication and placebo in any of the patient groups.**Table (3)**.

No patient was withdrawn from the study because of a serious adverse drug reaction. No severe side effects from medication were observed. Mild and moderate side effects such as nausea and constipation were equivalent in both groups

Gallstone formation was significantly less frequent (P = 0.041) with Ursodeoxycholic acid than with placebo at 12 months: 6.5% versus 22%, respectively. **Table (2)**. 5 cholecystectomies were performed (mean 14.9 ± 4.3) months after surgery in patients with symptomatic cholelithiasis: 1 patient in the Ursodeoxycholic acid group and 4 patients in the placebo group, 2% versus 8.9 %, respectively. (P =0.11) **Table (2)**.

Discussion:

Obesity and rapid weight loss are well known risk factors for cholelithiasis as approximately one third of patients may develop gallstones after bariatric surgery. Furthermore, 10% to 15% of all patients will require cholecystectomy for complaints related to gallstones.[9–13] Some centers routinely perform cholecystectomies with bariatric procedures to prevent

complications of cholelithiasis, prophylactic cholecystectomy is not preferred as the operation may increase the overall operative time and length of hospital stay. In addition, a cholecystectomy after losing weight may be technically easier than during maximum obesity.[11–13] Also, Angrisani et al[15] reported that laparoscopic cholecystectomy in obese patients was technically more difficult, and required a significantly longer operating time. In the present study, we excluded patients who had previous cholecystectomy or requiring concomitant cholecystectomy to avoid the debate about this difficulty and the prolonged operative time.

The risk of developing gallstones in obese patients is increased that could be due to a higher cholesterol saturation of gallbladder bile, diminished gallbladder motility with subsequent stasis and increased levels of gallbladder mucin promoting precipitation of cholesterol crystals[16] During rapid weight loss produced by weight loss surgery with very low caloric diet, the incidence of gallstone formation increased,[17] but the underlying mechanism is not fully understood, and some pathogenic mechanisms have been proposed including: increased cholesterol saturation index of bile as a result of cholesterol mobilization from adipose tissues and excretion in bile, increased gallbladder secretion of mucin and calcium, and increased presence of prostaglandins and arachidonic acid.[16,18–21]

The present study revealed five out of thirteen cases who developed gallstones were symptomatic with the overall symptomatic gallstone incidence after surgery 5.5 % which is lower than the findings as Tucker et al.[22] reported incidence of 6%, Portenier et al[23] 8.1%, Papasavas et al[24] 6.9%, Villegas et al[25] 7.3% while Abo-Ryia et al[26] reported 8%. This may be because we had two groups one was taking Ursodeoxycholic acid with a lower incidence of gallstone formation, thus, decreasing the overall number of gallstone incidence.

Weight loss after antiobesity surgery is maximal during the first postoperative year, decreasing over time. The peak of symptomatic gallstone disease at 2 years after surgery.[27,28]

The higher occurrence of cholelithiasis following weight reduction surgery was in the phase of greater weight loss that encouraged surgeons to use Ursodeoxycholic acid as prophylaxis in the first 6 postoperative months.[9,29]

This drug is a bile acid that prevents biliary lithiasis by decreasing cholesterol and mucin concentration, increasing bile acid concentration, decreasing bile saturation, and enhancing gallbladder emptying.[9,29,30]

Two controlled trials[31,32] have shown the effectiveness of six months of Ursodeoxycholic acid treatment in lowering the incidence of gallstone formation. Cholelithiasis was found in 22-32% of controls versus in 2- 3% of treated patients at 6-12 months. Similarly, we found a significant decrease in the incidence of cholelithiasis after bariatric surgery from 22 % in placebo versus 6.5% in patients receiving Ursodeoxycholic acid for six months in the immediate postoperative period.

Age, obesity, female gender and parity are known risk factors for gallstones formation of are known, in the general population which is most likely due to the female sex hormones.[33] We tried to identify the risk factors for cholelithiasis after weight loss surgery by comparing the patients who developed gallstones during rapid weight loss with those who did not. In our study, Age, gender and mean preoperative BMI were not significant between both groups so, not considered as predictors for gallstone formation which is similar to that reported by others.[26,27,34] However the mean percent of excess weight loss in the first postoperative year was significantly higher in the group that formed gallstone which is in accordance to the findings of Schmidt et al.[35] Ming Li et al.[34] Wudel et al.[30] Yang et al.[28] and Abo-Ryia et al[26] In another study, only weight loss of more than 25% was associated with an increased risk of gallstone disease after antiobesity surgery.[35]

It is accepted that gallstone formation after bariatric surgery is related to weight loss.[9]

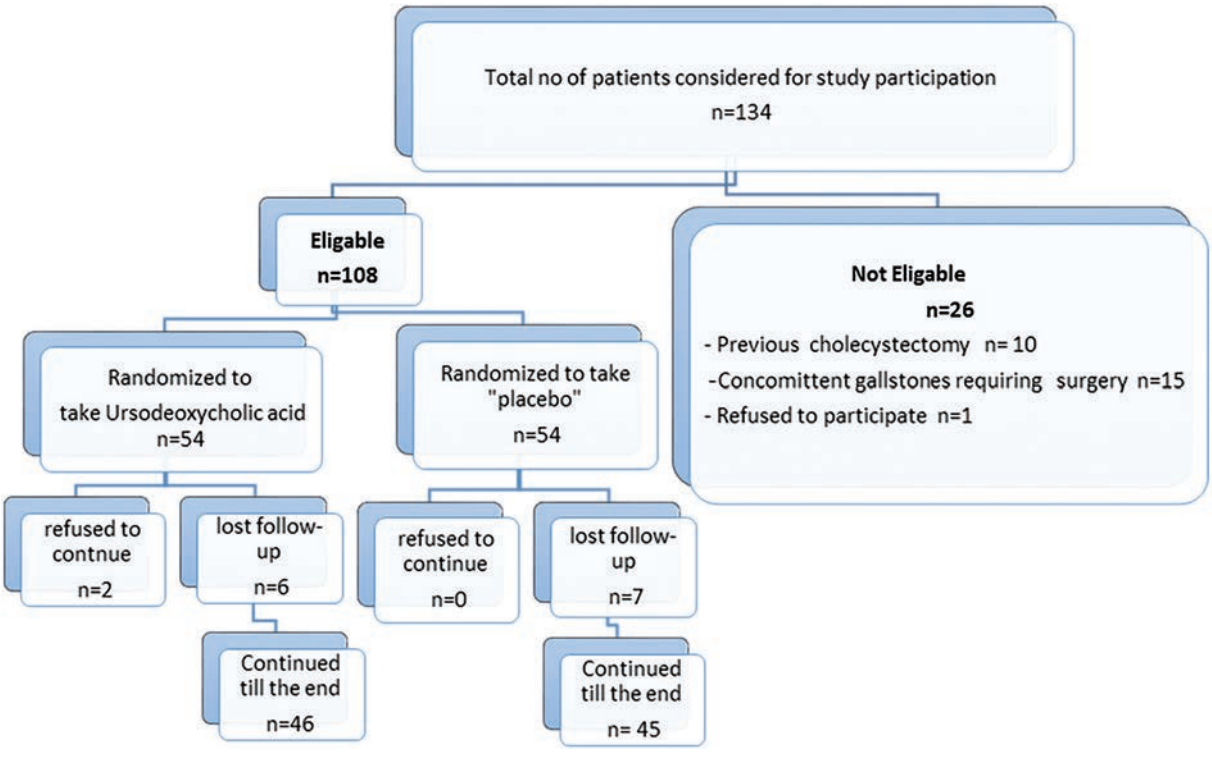

Figure (1): Trial flow sheet showing progress through the phases of the trial.

Table (1): Predictors of cholelithiasis in either group.

Variable	Gallstone	No gallstone	P-value
No (%)	13(14.3%)	78(85.7%)	0.001*
Mean age in years	31.2±8.11	30.8±7.65	0.852
Gender Male Female	5 (5.5%) 8 (8.8 %)	31 (34 %) 47 (51.6 %)	0.011* 0.003*
Mean preoperative BMI in kg/m²	48.2±11.25	49.1±12.1	0.521
Mean % EWL in the first year	26.2±8.3	23.1±9.22	0.045*
Type of operation LSG LGCP	 10 (10.9%) 3 (3.3 %) P= 0.036*	 56 (61.5 %) 22 (24.2%) P= 0.236	 0.012* 0.002*

BMI; body mass index, SD; standard deviation, %EWL; percentage of excess weight loss

Shiffman et al[36] showed that bile cholesterol normalized when the weight stabilized 24 months after gastric bypass. Miller et al[37] demonstrate in their prospective study on more than 1000 restrictive procedures that a weight stabilization phase is reached not before 24 months and in another study, a significantly reduced gallstone formation rate of 8% after 24 months compared with 30% in the placebo group.[9] According to Shiffman et al, at 6 months, gallstones had developed in 36% and gallbladder sludge in additional 13% of patients.[36] We reported 13 patients (14.3%) out of 91 had gallstones at one year and this short follow-up period could be an explanation of smaller percentage of gallstone formation in our patients.

The bariatric procedure used to achieve

Table 2: Distribution of patients free of gallstone at the time of surgery.

Gallstone formation after weight loss		Group "A" (n=46)		Group "B" (n=45)		P-value
		No	%	No	%	
Developed gallstones	Symptomatic	1	2.2	4	8.9	0.11
	Asymptomatic	2	4.3	6	13.3	0.365
	Total	3	6.5	10	22.0	0.041*
Did not develop gallstones		43	93.5	35	77.8	0.25
Total		46		45		

Table (3): Demographic data of both groups

Variable	Group "A" (n=46)	Group "B" (n=45)	P-value
Mean age in years	31.08±9.01	30.1±7.01	0.465
Gender Male Female	17 (37.0%) 29 (63.0%)	19 (42.2%) 26 (57.8%)	 0.365
Mean preoperative BMI in kg/m²	48.6±10.6	49.3±12.6	0.622
Mean % EWL in the first year	25.3±7.11	24.9±10.1	0.366
Type of operation LSG LGCP	 33 (71.7%) 13 (28.3%)	 33(73.3%) 12(26.7%)	 0.698 0.71

weight loss could influence the risk of developing symptomatic gallstone disease.[37] Patients who had undergone gastric bypass were at a greater risk than those who had undergone a restrictive procedure.[37] Previous studies have demonstrated similar rates of cholecystectomy after gastric bypass and gastric banding (8.1% and 6.8%, respectively)[38–40] In our study, we found a significant difference between both groups as the incidence of gallstone formation was higher in LSG than in LGCP while, Ming Li et al.[34] reported insignificant difference regarding the type of operation; Gastric Bypass, Gastric Banding, and Sleeve Gastrectomy.

Conclusion:

The percentage of excess weight loss was the only predictive postoperative factor for gallstone formation. A six months use of Ursodeoxycholic acid is an effective prophylaxis for gallstone formation after weight loss procedures although a larger study is required to reach a definitive conclusion.

Conflict of Interest: There is no conflict of interest or financial ties to include.

Reference:

1- Rennie KL, Jebb SA: Prevalence of obesity in Great Britain. *Obes Rev* 2005; 6: 11–12.

2- Flegal KM, Carroll MD, Ogden CL, et al: Prevalence and trends in obesity among US adults, 1999–2000. *JAMA* 2002; 288: 1723–1727.

3- Klein S, Wadden T, Sugerman HJ: AGA technical review on obesity. *Gastroenterology* 2002; 123: 882–932.

4- Pi-Sunyer FX: A review of long-term studies evaluating the efficacy in weight loss ameliorating disorders associated with obesity. *Clin Ther* 1996; 18: 1006–1035.

5- Balsiger BM, Murr MM, Poggio JL, Sarr MG: Bariatric surgery. Surgery for weight control in patients with morbid obesity. *Med Clin North Am* 2000; 84: 77–489.

6- Buchwald H, Avidor Y, Braunwald E, et al: Bariatric surgery: A systematic review and meta-analysis. *JAMA* 2004; 292(14):1724–1737.

7- De Maria EJ: Bariatric surgery for morbid obesity. *N Engl J Med* 2007; 356(21): 2176–2183.
8- Brody F: Minimally invasive surgery for morbid obesity. *Cleveland Clinic J Medicine* 2004; 71(4): 289–298.
9- Miller K, Hell E, Lang B, Lengauer E: Gallstone formation prophylaxis after gastric restrictive procedures for weight loss: A randomized double-blind placebo-controlled trial. *Ann Surg* 2003; 238: 697–702.
10- Shiffman ML, Sugerman HJ, Kellum JM, Moore EW: Changes in gallbladder bile composition following gallstone formation and weight reduction. *Gastroenterology* 1992; 103: 214–221.
11- Amaral JF, Thompson WR: Gallbladder disease in the morbidly obese. *Am J Surg* 1985; 149: 551–557.
12- Deitel M, Petrov I: Incidence of symptomatic gallstones after bariatric operations. *Surg Gynecol Obstet* 1987; 164: 549–552.
13- Wattchow DA, Hall JC, Whiting MJ, Bradley B, Iannos J, Watts JM: Prevalence and treatment of gallstones after gastric bypass surgery for morbid obesity. *Br Med J (Clin Res Ed)* 1983; 286: 763.
14- International Federation for the Surgery of Obesity: Statement on patient selection for bariatric surgery. *Obes Surg* 1997; 7: 41.
15- Angrisani L, Lorenzo M, De Palma G, et al: Laparoscopic cholecystectomy in obese patients compared with nonobese patients. *Surg Laparosc Endosc* 1995; 5: 197–201.
16- Festi D, Colecchia A, Larocca A, et al: Review: Low caloric intake and gall-bladder motor function. *Aliment Pharmacol Ther* 2000; 14(2): 51–53.
17- Everhart JE: Contributions of obesity and weight loss to gallstone disease. *Ann Intern Med* 1993; 119: 1029–1035.
18- 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.
19- 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.
20- Mason EE: Gallbladder management in obesity surgery. *Obesity Surgery* 2002; 12(2): 222–229.
21- Dittrick GW, Thompson JS, Campos D, et al: "Gallbladder Pathology in Morbid Obesity," *Obesity Surgery* 2005; 15(2): 238–242.
22- Tucker ON, Fajnwaks P, Szomstein S, et al: Is concomitant cholecystectomy necessary in obese patients undergoing laparoscopic gastric bypass surgery? *Surgical Endoscopy* 2008; 22(11): 2450–2454.
23- Portenier DD, Grant JP, Blackwood HS, et al: Expectant management of the asymptomatic gallbladder at Roux-en-y gastric bypass. *Surgery for Obesity and Related Diseases* 2007; 3(4): 476–479.
24- Papasavas PK, Gagné DJ, Ceppa FA, et al: Routine gallbladder screening not necessary in patients undergoing laparoscopic Roux-en-y gastric bypass. *Surgery for Obesity and Related Diseases* 2006; 2(1): 41–46.
25- Villegas L, Schneider B, Provost D, et al: Is routine cholecystectomy required during laparoscopic gastric bypass? *Obesity Surgery* 2004; 14(2): 206–211.
26- Abo-Ryia MH, Abd-Allah HS, El-Khadrawy OH, Moussa GI: Predictors of gallstone formation in morbidly obese patients after bariatric surgery: A retrospective observational study. *Surg Science* 2014; 5: 1–5.
27- Oliveira CIB, Chaim EA, Silva BB: Impact of rapid weight reduction on risk of cholelithiasis after bariatric surgery. *Obesity Surgery* 2003; 13(4): 625–628.
28- Yang H, Peterson GM, Roth MP, Schoenfield LJ, Marks JW: Risk factors for gallstones formation during rapid loss of weight. *Digestive Diseases and Sciences* 1992; 37(6): 912–918.
29- Uy MC, Talingdan-Te MC, Espinosa WZ, et al: Ursodeoxycholic acid in the prevention of gallstone formation after bariatric surgery: A meta-analysis. *Obesity Surgery* 2008; 18(12): 1532–1538.
30- Wudel LJ, 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. *Journal of Surgical Researc*h 2002; 102(1): 50–56.
31- Miller K, Hell E, Lang B, Lengauer E: Gallstone formation prophylaxis after gastric restrictive procedures for weight loss: A randomized double-blind placebo-controlled trial. *Ann Surg* 2003; 238: 697–702.
32- Sugerman HJ, Brewer WH, Shiffman ML, et al: A multicenter, placebo-controlled, randomized, double-blind, prospective trial of prophylactic ursodiol for the prevention of gallstone formation following

gastric-bypass-induced rapid weight loss. *Am J Surg* 1995; 169: 91–96; discussion 96–97.
33- Cirillo DJ, Wallace RB, Rodabough RJ, et al: Effect of estrogen therapy on gallbladder disease. *JAMA* 2005; 293: 330–339.
34- Ming VK, Pulido LN, Fajnwaks P, et al: Predictors of gallstone formation after bariatric surgery: A multi- variate analysis of risk factors comparing gastric bypass, gastric banding, and sleeve gastrectomy. *Surgical Endoscopy* 2009; 23(7): 1640–1644.
35- Li VK, Pulido 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(7): 1640–1644.
36- Shiffman ML, Sugerman HJ, Kellum JM, Brewer WH, Moore EW: Gallstone formation after rapid weight loss: A prospective study in patients undergoing gastric bypass surgery for treatment of morbid obesity. *Am J Gastroenterol* 1991; 86(8): 1000–1005.
37- Jonas E, Marsk R, Rasmussen F, Freedman J: Incidence of postoperative gallstone disease after antiobesity surgery: Population-based study from Sweden. *Surg Obes Relat Dis* 2010; 6: 54–58.
38- Miller K, Höller E, Hell E: Restrictive procedures in the treatment of morbid obesity – vertical banded gastroplasty vs. adjustable gastric banding. *Zentralbl Chir* 2002; 127: 1038–1043.
39- Portenier DD, Grant JP, Blackwood HS, Pryor A, McMahon RL, DeMaria E: Expectant management of the asymptomatic gallbladder at Roux-en-Y gastric bypass. *Surg Obes Relat Dis* 2007; 3: 476–479.
40- O'Brien PE, Dixon JB: A rational approach to cholelithiasis in bariatric surgery: Its application to the laparoscopically placed adjustable gastric band. *Arch Surg* 2003; 138: 908–912.