ORIGINAL ARTICLE

Changes in gallbladder motility and gallstone formation following laparoscopic gastric banding for morbid obesity

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Morbid obesity is associated with cholesterol gallstone formation, a risk compounded by rapid weight loss. Laparoscopic gastric banding allows for a measured rate of weight loss, but the subsequent risk for developing gallstones is unknown.

METHOD: Twenty-six normal-weight volunteers (body mass index [BMI} less than 30) were compared with 14 morbidly obese patients (BMI greater than 40). Gallbladder volumes were measured ultrasonographically, after fasting and following stimulation with intravenous cholecystokinin-octapeptide (CCK-8)

RESULTS: Preoperatively, fasting gallbladder volume and residual volume after CCK stimulation were both two times greater in the obese group (P<0.02 versus controls). Per cent gallbladder emptying was not different. Gallbladder refilling was four times higher in the obese patients (P<0.01). By six weeks postoperatively, the obese patients lost 1.4±0.1% body weight per week. Gallbladder emptying decreased 18.4% (80.3±3.9% to 65.5±6.9%; P<0.05); residual volume rose one-third (not significant), and refilling fell 60.5% (0.43±0.09 to 0.26±0.04 mL/min; P=0.07). Three patients with weight losses of greater than 1.7% per week developed gallstones; gallbladder emptying fell outside the 95 percentile. By six months, weight loss slowed to 0.5±0.1% per week; gallbladder motility improved modestly. No further stones developed.

CONCLUSION: Rapid weight loss following laparoscopic gastric banding impairs gallbladder emptying and when pronounced, gallstones form by six weeks postoperatively. The accompanying reduction in gallbladder emptying, increased gallbladder residual volume and decreased refilling promote gallbladder stasis and hence stone formation.

Key Words: *Bariatric surgery; Gallbladder motility; Gallstone disease; Morbid obesity*

Motilité altérée de la vésicule biliaire et formation de calculs après un cerclage laparoscopique de l'estomac pour obésité morbide

CONTEXTE : L'obésité morbide est associée à la formation de lithiase biliaire à cholestérol, phénomène accru par la perte de poids rapide. Le cerclage laparoscopique de l'estomac permet de régler la vitesse de la perte pondérale, mais on ne connaît pas les risques de formation de calculs qui y sont associés.

MÉTHODE : Nous avons comparé 26 sujets de poids normal (indice de masse corporelle [IMC] <30) à 14 patients atteints d'obésité morbide (IMC>40). Le volume de la vésicule biliaire a été mesuré par échographie, à jeun et après stimulation à l'octapeptide de la cholécystokinine (CCK-8) par voie intraveineuse.

RÉSULTATS : Avant l'opération, le volume de la vésicule biliaire à jeun et le volume résiduel après la stimulation au CCK étaient deux fois plus grands chez les patients obèses que chez les sujets témoins (P<0,02). Le pourcentage de vidange de la vésicule était le même dans les deux groupes. Par contre, le remplissage était quatre fois plus important chez les obèses (P<0,01). Six semaines après l'opération, la perte de poids corporelle s'était faite au rythme de 1,4±0,1 % par semaine. La vidange de la vésicule avait diminué de 18,4 % (de 80,3±3,9 % à 65,5±6,9 %; P<0,05); le volume résiduel avait augmenté du tiers (non significatif) et le remplissage avait diminué de 60,5 % (de 0,43±0,09 à 0,26±0,04 ml/min; P=0,07). Des calculs se sont formés chez trois patients dont la perte de poids avait été supérieure à 1,7 % par semaine; la vidange de la vésicule était sortie du 95e rang centile. Au bout de six mois, la perte de poids avait ralenti (0,5±0,1 % par semaine); la motilité de la vésicule s'était quelque peu améliorée. Il n'y a pas eu d'autres formations de calculs.

CONCLUSION : La perte de poids rapide après le cerclage laparoscopique de l'estomac altère la vidange de la vésicule biliaire et, lorsque le phénomène est marqué, cela donne lieu à la formation de calculs dans les six semaines suivant l'opération. La diminution de la vidange de la vésicule, l'augmentation du volume résiduel et la diminution du remplissage favorisent la stase biliaire, d'où formation de calculs.

Gallstones are common. The prevalence in developed countries ranges between 6% and 16% in adults, and is especially high in women during their reproductive years. This frequency increases to 30% in morbidly obese women (1). Although treatment for mild obesity is mainly dietary, major surgery plays a role in those who are morbidly obese. Both dieting and surgery, however, are associated with a heightened risk of developing gallstones. Those losing considerable weight are at an even greater risk of stone formation, when compared with similarly obese persons on a weight maintenance diet (2). Rapid weight loss generates an 18-fold increase in gallstone development (3), whereas less rapid weight loss appears relatively safe. Weight loss of up to 1.5 kg per week, or up to 1% to 1.5% of the total body weight per week is not associated with

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any increase in stone formation (4).

The livers of obese patients secrete abnormal bile, containing an excess of cholesterol relative to its solubilizing capacity. In the presence of a nucleating factor, the excess cholesterol then precipitates from this supersaturated bile. Gallbladder stasis also contributes to cholesterol gallstone formation, allowing the time necessary for the microcrystals of cholesterol to precipitate, be retained, aggregate and subsequently grow into macroscopic stones. After an overnight fast, obese people have larger gallbladder volumes compared with those of normal sized individuals (5,6). Body mass index (BMI), however, is not the sole determinant of gallstone formation. Large people in general, regardless of their BMI, also have large fasting gallbladder volumes, but do not necessarily develop gallstones (7), perhaps because of a more normal cholesterol solubility of bile.

Reports to date have been divergent in terms of the gallbladder motility exhibited by obese individuals compared with that of 'normal' lean subjects. Some have shown impaired gallbladder motility in obese persons (5,8-11), whereas others have reported no difference (12,13). Certainly, impaired gallbladder emptying has been implicated when obese patients consume a very low calorie diet (5,12,14) or after surgery has induced weight reduction (3). Studies in human and animal models suggest that gallbladder emptying is impaired even before the gallstones become evident (15-18). The use of agents to pharmacologically stimulate the gallbladder to empty more frequently can prevent this eventuality (19).

The effect of weight loss after the laparoscopic insertion of an adjustable gastric band on gallbladder motility has not been determined. This form of surgery has multiple advantages: performed laparoscopically, it results in an early discharge from hospital (one to three days); allows the initiation of oral fluids soon after recovery from anaesthesia; and it maintains the normal integrity of the gastrointestinal tract. The weight loss is gradual over time (20). Therefore, it should represent a lesser risk for gallstone formation.

The aims of the present study were to: determine if gallbladder size and emptying were abnormal in obese people; determine the frequency of gallstone formation after gastric reduction surgery for obesity; and define the effects of weight reduction following gastric banding on gallbladder motor function.

METHODS

Study group

Controls: Twenty-six (14 men, 12 women) healthy volunteers with a BMI of less than 30 kg/m^2 were recruited based on the absence of any previous clinical history of biliary symptoms or surgery, and their not receiving any medication (eg, calcium channel blockers, antispasmodic medications, progesterone) or having a clinical condition (eg, diabetes mellitus) that could affect gallbladder motility. This control group provided measurements for average sized, healthy adults with a normal weight.

Obese patients: Fourteen (one man, 13 women) morbidly obese patients with a BMI of greater than 40, or a BMI greater than 35 plus the presence of a comorbid factor(s) (ie, diabetes, cardiac conditions, hypertension and/or orthopedic problems), were assessed and found to be fit for elective laparoscopic surgery, using gastric banding to reduce food ingestion. Type II diabetes was present in three patients. None consumed any medication known to affect gallbladder motility, including female sex hormones.

A Swedish adjustable gastric band (Obtech Medical AG, St-Antons-Gasse, Switzerland) was inserted laparoscopically, to create a proximal gastric pouch with a volume of approximately 20 to 30 mL. Using the pars flaccida technique for placement of the gastric band, a proximal gastric pouch was fashioned with a volume of approximately 20 to 30 mL. The insertion of the laparoscope allowed visualization of the liver and upper abdomen. Retraction of the liver upwards exposed the gastroesophageal junction and the spleen. A grasper introduced via the working ports retracted the stomach downwards to expose the angle of His at the gastroesophageal junction. Minimal dissection was done at the angle of His to open the peritoneum and identify the left crus and then the right crus through the lesser omentum. All dissection was done without division of tissue and hence there was little chance of endangering the vagi. A reticulated grasper was inserted between the crura and the esophagus and the adjustable gastric band was attached to it so as to place it in the pars flacida position. The band was secured by multiple sutures.

All patients had an initial gallbladder ultrasound within one month of their surgical procedure. Subsequent studies were preformed at six weeks and at six months following surgery, respectively. No major complications followed the surgery. All patients commenced oral intake on the first postoperative day and were discharged within three to seven days.

Study protocol

Gallbladder volumes were measured after an overnight fast. Cholecystokinin-octapeptide (CCK-8) (KinevacTM, Bracco Diagnostics/Diagnostiques Canada Inc, Mississauga, Ontario) was then infused intravenously at 20ng/kg/h over 45 min to induce gallbladder emptying. Gallbladder volumes were measured at three intervals: before initiating the infusion (ie, after an overnight fast) and then at 15 min intervals; during the CCK-8 infusion (conditions that stimulate gallbladder emptying); and for a further 45 min after stopping the CCK (conditions when gallbladder refilling commences). The duration of the last two measures, therefore, was 90 min.

Ultrasound measurement of gallbladder volume

This was carried out using a real time ultrasound device (Diasonic DRF1, Diasonics Inc, USA) with either a linear 3.5 MHz or a 5 MHz transducer, for both controls and obese patients, depending on the patient's build. Longitudinal and transverse scans of the gallbladder were obtained following deep inspiration, using abdominal markers to standardize the gallbladder views. Any measure for these two dimensions used the largest diameter of the gallbladder. The gallbladder volume was calculated using the ellipsoid method (21).

Per cent gallbladder emptying was calculated as:

(Fasting volume – residual volume at 45 min) / (fasting volume) $\times$ 100.

The residual gallbladder volume was taken at the nadir of emptying. This smallest volume occurred by 45 min into the CCK-8 infusion.

The gallbladder refilling rate was calculated as:

(Gallbladder volume at 90 min – gallbladder volume at 75 min/15 min).

The rationale for choosing to calculate the refilling time after 75 min was to allow more than five biological half-lives of CCK-8 (22), so that virtually no residual CCK-8 should remain in the cir-

TABLE 1
Demographics and gallbladder measurements of both male and female volunteers

	Men (n=14)	Women (n=12)
Age	35 (23-57)	41 (25-59)
Body mass index	26.4±0.7	23.7±0.6
Gallbladder volume (mL)	22.3±2.1	20.1±2.4
Gallbladder emptying (%)	76.2±4.3	77.8±2.4
Gallbladder residual volume (%)	4.9±0.9	4.2±0.5
Gallbladder refilling (mL/min)	0.10±0.04	0.10±0.05

Data are presented as mean ± SEM, except for age (years) which is presented as median (range). No statistical differences were noted between the two groups

culation. Two of the present authors (BOA-J and PD) independently assessed the ultrasound results; any differences were resolved by consensus. Repeat ultrasound studies to verify the findings were performed on those who developed gallstones. The range of accuracy of the ellipsoid method of ultrasound volume measurement is quite accurate (23); intraobserver and interobserver variation is usually within 10%. With large gallbladders, the variation is almost always less than 10%. When the gallbladder is small, the frequently variation is greater than 10%, but the absolute difference is small. The accuracy would, therefore, appear sufficiently precise to sustain the close significance in the relatively small number of patients who developed cholelithiasis.

This study received approval from the Clinical Research Ethics Committee of Flinders Medical Centre, Flinders University of South Australia.

Statistical analysis

The statistics program SPSS (10 Edition SPSS Inc, USA) was used to perform an analysis of variance (ANOVA). The Bonferroni correction or the nonparametric Mann-Whitney analysis were used where appropriate. A P<0.05 was accepted as significant.

RESULTS

Normal versus obese

Table 1 summarizes the age and BMI of both male and female volunteers. There was no difference between the two sexes in any of the parameters measured in the study. Combining both men and women was therefore appropriate, although an obvious difference in the distribution of the sexes existed between the healthy and the obese groups (P=0.005 by Fisher's exact test).

Table 2 provides the age, sex and BMI of both the volunteers and the obese patients. There was no difference in age between the controls (volunteers) and the obese group. No effort was made to match the sex distribution in the obese group because women predominantly sought this type of surgery. Gallbladder volumes after an overnight fast were markedly increased in the obese patients before surgery. Their gallbladders were twice as large as those of the volunteers. Following the CCK-8 infusion, their gallbladder residual volumes were double those of the normal weight controls. The per cent gallbladder emptying with CCK-8, however, did not differ between the two groups. Because of their larger fasting gallbladder volume, the absolute volume of bile emptied was greater in the obese patients (34.7±5.4 mL, compared with that of the volunteers [16.7±1.5 mL, P<0.05]). Besides the larger gallbladder volume with fasting and the increased residual volume after the CCK-8 infusion, the gallbladder refilling rate was four times greater in the obese compared with that of the volunteers (P<0.01).

TABLE 2
Demographics and gallbladder measurements in volunteers and obese patients before surgery

	Volunteers (n=26)	Obese patients (n=14)	P value
Age	35 (23-59)	34 (25-57)	
Sex (male:female)	14:12	1:13	
Body mass index	25.1 (21.8-29.5)	45.3 (36-61.5)	<0.01
Gallbladder volume (mL)	21.3±1.5	43.0±6.6	<0.02
Gallbladder emptying (%)	76.91±2.5	80.3±3.9	NS
Gallbladder residual volume (%)	4.6±0.5	8.3±2.7	<0.02
Gallbladder refilling (mL/min)	0.10±0.02	0.43±0.09	<0.01

Data are presented as mean ± SEM, except for age (years) and body mass index which are presented as median (range). NS Not significant

Obese patients six weeks after surgery

Of the 14 patients enrolled at the beginning of this study, three developed gallstones, while three others elected not to continue in the study. The BMI decreased in the remaining 11 patients from 44.5±3.2 to 40.4±2.8 (or 1.4±0.1% body weight per week), from that recorded preoperatively compared with six weeks following surgery, respectively. In these obese patients, the fasting gallbladder volume decreased 25%, from 43.0±6.6 mL before surgery to 29.1±6.1 mL at the sixth postoperative week, respectively (Figure 1A). They also experienced a significant reduction in gallbladder emptying, from 80.3±3.9% to 65.5±6.9% (P< 0.05) (Figure 1B). Their emptying remained less than that of the volunteer control (P<0.05). This decrease in gallbladder emptying allowed the gallbladder residual volume to increase by one-third, from 8.3±4.5 mL to 11.2±4.5 mL, between the preoperative and six weeks postoperative measurements, respectively. Although this increase in residual volume did not reach significance (Figure 1C), all values remained higher than those in the control group (P<0.05). Gallbladder refilling decreased 39.5%, from 0.43±0.09 mL/min to 0.26±0.04 mL/min between the preoperative and six weeks postoperative measurements respectively, at a significance of P=0.07 (Figure 1D). Refilling remained well above the volunteer group (P<0.05).

The three patients who developed stones all had a weight loss of greater than 1.7% (1.73, 2.01 and 2.33%, respectively, for each) of their total body weight per week over the six weeks. None were diabetic. Indeed, two out of the three patients were above the 95 percentile (mean ±2SD) of weight loss for this group (Figure 2). These three also exhibited a lower gallbladder emptying, well outside the 95 percentile when compared with the rest of the group (Figure 2). Two of these three patients also were consistently out of the 95 percentile range for the obese group, in terms of gallbladder volume, residual volume and refilling rate (data not shown).

Obese patients six months following surgery

One of the 11 patients elected not to continue with the study. One of the three patients who developed stones experienced an attack of acute cholecystitis that required surgery. Nine

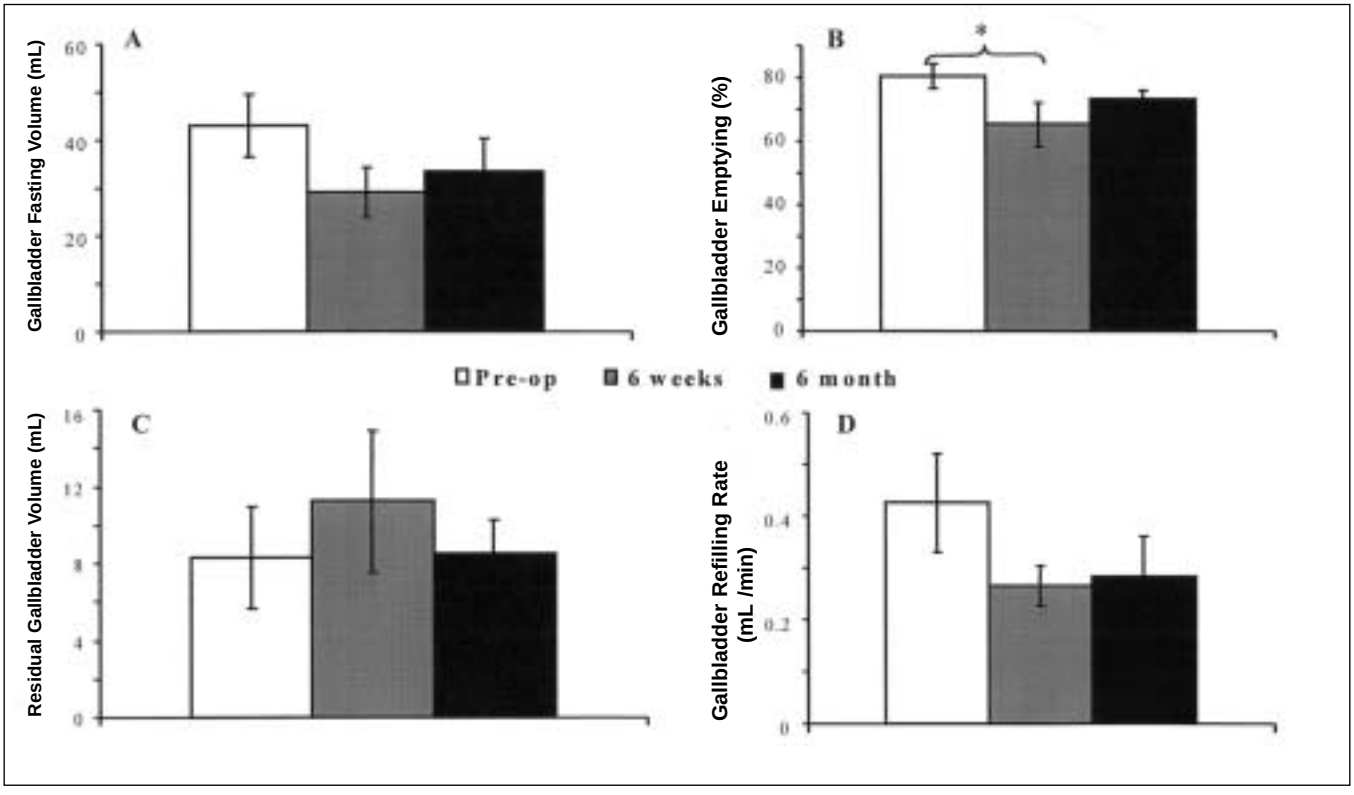

Figure 1) **means P<0.05. Gallbladder measurements for the obese patients at three time periods: preoperatively, six weeks postoperatively and six months postoperatively (n = 14, 11, and 9 respectively).* **A)** *Gallbladder fasting volume;* **B)** *Gallbladder emptying with cholecystokinin;* **C)** *Gallbladder residual volume; and* **D)** *Gallbladder refilling rate. Group data are presented as mean ± SEM.*

patients completed the six month study. From six weeks to six months, their BMIs further decreased from 41.9±3.5 to 37.4±2.6 (or 0.5±0.1% body weight per week). Gallbladder measurements changed modestly towards those found before surgery. The gallbladder volume increased from 29.1±6.1 mL at six weeks to 33.5±6.7 mL at six months while emptying increased from 65.9±6.9% to 74.3±2.9% (not significant). The residual volume decreased from 11.2±4.5 mL at six weeks to 8.5±1.8 mL. Gallbladder refilling rate remained virtually unchanged between six weeks and six months (Figures 1A, 1B, 1C and 1D), but remained significantly above that of the volunteers (P<0.05).

Of the three patients who developed gallstones at six weeks, one required a cholecystectomy. Another still had stones at six months but had no symptoms. In the third patient, the gallstones disappeared and were not evident even on repeat ultrasonography. This latter patient exhibited an improved gallbladder emptying from 56.4% to 67.1%, while weight loss of 2.3% per week at six weeks fell to 0.3% per week by six months. This patient was also the only one of the three whose gallbladder volume, residual volume and refilling rate fell within the 95 percentile of the group at six weeks when gallstones were first detected.

DISCUSSION

Obese patients, as shown here, exhibited a significant increase in their gallbladder volume with the same per cent emptying response to CCK-8 as the controls, but yielded a significant increase in the gallbladder residual volume and refilling rate. The present study further demonstrates that very obese women who rapidly lose weight after laparoscopic gastric banding are at high risk for developing gallstones. Following such surgery, 27% (three of the 11 patients) acquired gallstones at six weeks. Their rate of weight loss was 1.7% of the total body weight per week for the six weeks following surgery. No further stones developed thereafter. Instead, one of the stones disappeared. All three patients exhibited a greater per cent weight loss per week and much reduced gallbladder emptying (outside the 95 percentile), compared with that of the obese patients without gallstone formation. Two out of the three patients differed from the others in terms of larger gallbladder fasting and residual volumes, and lower gallbladder refilling rates. The third patient was not different, and by six months, the gallstones had disappeared on ultrasound. At six months, all patients showed a trend towards their preoperative measurements.

The current study did not demonstrate any differences between the male and female volunteers in their gallbladder motility in terms of emptying, refilling or gallbladder volume. A sex difference in the incidence of gallstones exists between men and women (24-26), but this is not linked to any proposed difference in gallbladder motility caused by the female sex hormones (27,28). Men generally have greater fasting gallbladder volumes than women (29). It thus seemed reasonable to combine the sexes, because women predominated in these morbidly obese patients seeking bariatric surgery.

Gallbladder volume after an overnight fast and following a standard infusion of CCK-8 was different in the obese compared with that of the normal controls, as has been demonstrated previously (5,7). Increased gallbladder volume with poor mixing and a long residence time favours the develop-

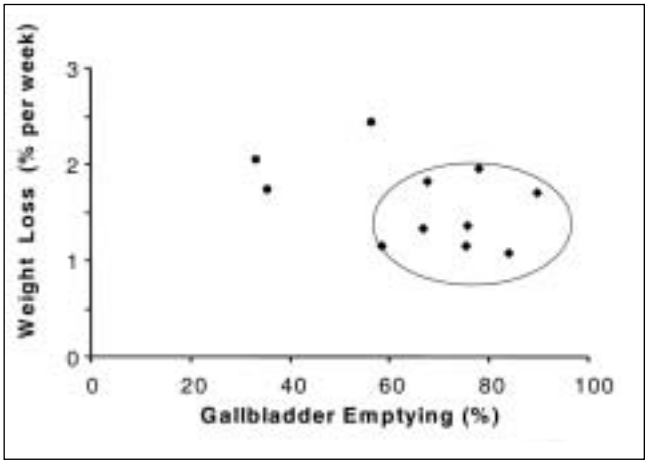

Figure 2) *Gallbladder emptying in relation to the percentage of weight loss per week at six weeks following surgery. The circle represents the mean ±2SD for 95 percentile of the group that did not develop gallstones. Symbols: The diamond shaped markers inside the circle represent the eight patients who did not develop gallstones. The remaining round markers represent the three patients who developed gallstones at six weeks*

ment of biliary sludge and hence stone formation (30). Further, after an overnight fast, quite saturated bile from the liver is likely to enter a gallbladder with a large volume. Even after a meal has partially emptied the gallbladder, a relatively large residual volume of bile remains. Gallbladder filling is contingent on the rate of hepatic bile secretion, the relative resistance to entry through the cystic duct and within the gallbladder (intra-vesicular pressure), and the metering effect of sphincter of Oddi tone. The hepatic secretion rate, in turn, predominantly reflects the portal venous return of bile salts; this is presumably higher in obese people because they empty a larger absolute volume of gallbladder bile and have large bile salt pools. The high refilling rate of the gallbladder may reflect a high rate of hepatic bile secretion – these large individuals empty a large bolus of bile salts into the small intestine that recycles via the enterohepatic circulation – and a relatively low intravesicular pressure (P) (from LaPlace's law [$P \alpha 2T/r$], the large gallbladder residual volume with its elevated radius [r] should be associated with a low intravesicular pressure for the same wall tension [T]). A third component, the sphincter of Oddi tone, if elevated, could enhance gallbladder filling, but there is no reason to suspect this.

The bariatric surgery performed to restrict intake resulted in a dramatic weight loss in all patients after six weeks. There was also a significant reduction in gallbladder emptying. The patients who developed gallstones were affected the most; their emptying fell outside of the 95th percentile of the group. All three patients who developed gallstones had a greater weight loss than that recommended for safe weight reduction (4). Two of these patients were out of the 95th percentile for the group. This rapid weight loss led to a depressed gallbladder emptying and a greater gallbladder residual volume. Further, the drop in the refilling rate likely reduced the turnover of gallbladder bile, aggravating stasis. The lowered emptying might have depressed the enterohepatic recycling of bile salts, reducing their flux through the liver and perhaps contributing to a relative higher cholesterol content in bile. The result was gallstone formation in these patients following surgery; particularly associated with brisk weight loss. After six months, all gallbladder parameters began to normalize, with gallstones disappearing in one of the patients who had exhibited a significant improvement in all parameters, especially gallbladder emptying. These apparently beneficial changes occurred despite these patients still being obese, likely reflecting the more modest rate of weight reduction.

The advantages of laparascopic gastric banding include a shortened hospitalization and a quicker return to normal oral intake and activity after surgery. The preservation of the normal anatomy of the gastrointestinal tract and of the enterohepatic circulation of bile salts should lessen the predisposition towards gallstone formation. Bile salts secretion is the driving force for bile formation, and with phospholipids, is essential for cholesterol solubilization. Generally, the liver of an obese person secretes cholesterol excessively (31). Rapid weight loss further aggravates this cholesterol hypersecretion, likely through its mobilization from fat. Reduced intake, especially in the weeks following restrictive bariatric surgery, results in less frequent and less effective stimulation of the gallbladder to empty. These conditions cause bile to become more supersaturated with cholesterol because of depressed enterohepatic cycling of bile salts, which lowers their hepatic secretion, and also because of the excessive cholesterol being secreted. Further, bile resides for longer periods in the gallbladder, allowing the necessary time for nucleation and the precipitation of cholesterol microcrystals, crystal aggregation and stone growth. The laparoscopic procedure aims to provide earlier feeding and gradual weight loss compared with the gastric bypass operation, but did not prevent stone formation in those patients with excessive rates of weight reduction. Although the numbers in this study are not large, the incidence of gallstones (three out of 11 patients, or 27%) is somewhat less than that after gastric bypass surgery for obesity (36% to 50%) (2,32), but is similar to that from dietary therapy (2,5).

Gastric banding restricts food intake and hence leads to weight loss. Factors such as meal frequency, total calories consumed and calories as fat all influence gallbladder emptying through the release of CCK. This in turn affects the enterohepatic cycling of bile salts and hence, biliary lipid composition. The standard dose of CCK-8 given to quantitated gallbladder empting in the present study provides a consistent stimulus, but would not necessarily reflect day-to-day changes in the food ingested. Likely the greatly reduced food intake in the first six weeks after surgery would have produced an even further decrease in gallbladder emptying. The apparent adaptation six months later presumably resulted from an improved dietary intake with more effective stimulation of the gallbladder, a decline in the rate of weight loss with less mobilization of cholesterol into bile and a relative improvement in cholesterol saturation. Indeed, the impaired gallbladder contractility evident in patients with cholesterol gallstones reflects the incorporation of this excess cholesterol into the plasma membranes of the gallbladder smooth muscle, altering their structure and function, and causing a defect in receptor-G protein coupling (33-35). During the severe weight loss six weeks after surgery, the greatly increased biliary cholesterol saturation would likely impair gallbladder motility to a greater extent than the lesser weight loss at six months. The present study was not designed to measure all these features.

CONCLUSIONS

We have demonstrated that morbidly obese patients have an enlarged fasting gallbladder volume, rather normal gallbladder emptying for its size, increased gallbladder residual volume and a high refilling rate. The weight loss that follows laparoscopic gastric banding surgery, particularly if excessively rapid, results in impaired gallbladder emptying, accompanied by an increase in gallbladder residual volume and a decrease in the refilling rate. Gallstones form as early as six weeks following surgery. Patients who developed gallstones had a greater decrease in their gallbladder emptying and a more pronounced weight loss compared with that of the reminder of the group. Early refeeding and a more gradual weight loss should ameliorate the gallbladder motility impairment and lessen stone formation. Given these findings, it seems reasonable to keep the rate of weight reduction at less than 1.5% of weight per week. The adjustable nature of gastric banding operations permits such fine tuning, better controlling weight loss and potentially eliminating the risk of gallstone formation following bariatric surgery.

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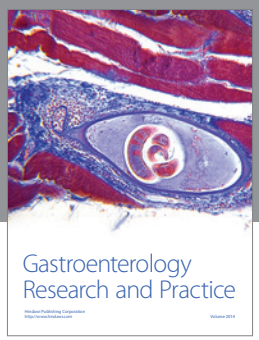

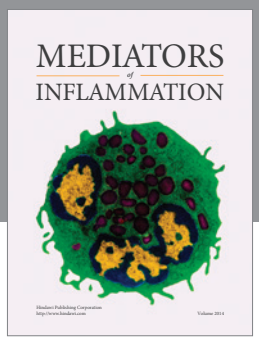

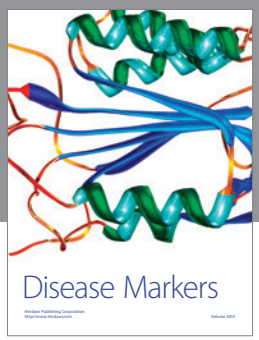

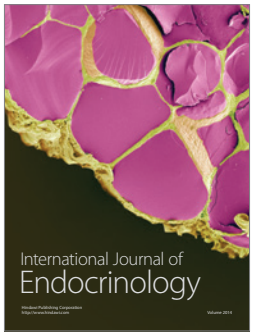

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