

# Obesity and Gallstones

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The formation of gallstones (cholelithiasis) has been identified as one of the risks associated with obesity. In this chapter, we:

- briefly describe the conditions and manner of gallstone formation,
- review the prevalence, incidence, or relative risk in various population samples,
- review some personal and dietary factors, known or suspected to affect gallstone formation and especially relevant to obesity,
- review some methods for prevention and treatment.

## GALLSTONE FORMATION

There are two common types of gallstone in the USA and Europe. The most common, and the only type associated with obesity, is the cholesterol gallstone which consists mainly of accretions of cholesterol crystals around a nucleus. The other gallstone type, the pigment stone, is less frequently seen, contains larger amounts of calcium, and is usually associated with chronic hemolytic states and bacterial infections rather than with obesity (1).

Cholesterol gallstone formation is a process that requires the convergence of several conditions. First, in order for gallstones to form, the bile must be supersaturated with cholesterol. The degree of cholesterol saturation of bile is affected by many factors including the rate of cholesterol synthesis by

the liver, the amount and composition of bile salts, the amount of phospholipids, and the rate of bile acid synthesis (2).

While bile supersaturation is a necessary condition for gallstone formation, it is not sufficient, as studies have identified many individuals with supersaturated bile and no sign of gallstones. An environment conducive to stone formation must also be present. This can take the form of conditions or contents in the gallbladder which promote nucleation and cholesterol crystallization, and provide binding materials to help form the stone-like accretions. Conditions which can make nucleation more or less likely have been identified and categorized as pronucleating (e.g. presence of mucin and other glucoproteins) or antinucleating factors (e.g. apolipoproteins A-I and A-II).

The lithogenicity of the gallbladder environment is also increased when the time that gallbladder contents are allowed to remain in stasis is lengthened. Thus, failure to have regular or complete gallbladder contractions to expel the gallbladder contents allows a longer time for nucleation and accretion to occur and can thereby contribute to the formation and growth of stones.

This outline of the conditions facilitating formation of stones will provide a framework for our subsequent discussion of the personal, environmental and behavioral factors affecting gallstone formation in obesity. However, we first look at some of the epidemiological evidence linking gallstones and obesity.

## EPIDEMIOLOGY

Gallbladder disease occurs frequently and is widespread. It is estimated that about 12% of adults in the USA have gallstones. Over 500 000 cholecystectomies occur annually in the USA (3,4).

A note about the research methods used to arrive at such figures is warranted. The prevalence of gallstones in various populations has been estimated using at least three different methods: surveys counting subject reports of cholecystectomies and symptoms; surveys using ultrasound screenings of population samples; and tabulations of autopsy results. In considering these data the following methodological observations should be kept in mind:

- About two-thirds of gallstones are asymptomatic and will not be detected unless radiology or ultrasonography is employed, and even with modern ultrasound instruments there is a small false-negative rate (about 4%) in severely obese subjects (5,6).
- Gallstones may be passed or evacuated without intervention, or may resolve spontaneously (7). Most cases remain asymptomatic and only a small proportion eventually require medical attention (5).
- Autopsy data provide only crude estimates of prevalence as autopsies are not performed on random or representative samples of the population.
- Estimates based on hospitalization and other forms of clinical diagnosis data are suspect even if the survey is based on a representative sample of hospitalized cases because there may be unequal rates of diagnosis (ascertainment bias) or unequal access to medical facilities.

Thus, the adequacy of each survey method will depend on the uses to which the data are put. If the purpose is to estimate medical needs then surveys of self-reported cholecystectomies and symptoms may be adequate. On the other hand, if the interest is in risk factors and etiology, then ultrasound screening will provide better data.

A classic report of gallbladder disease epidemiology in the USA comes from the Framingham Study (3). A random sample of people (2336 men, 2873 women) aged 30 to 62 living in the town of Framingham, Massachusetts, was enrolled in a longitudinal study beginning in 1949. In this sample, over a

10-year period, there were 97 definite and 20 doubtful cases of gallbladder disease among the men and 330 definite and 96 doubtful cases among the women. Two hundred and one of these cases (31 men, 170 women) were found upon initial examination (prevalence: men 13/1000, women 59/1000), and 226 (66 men, 160 women) developed the disease during the 10-year follow-up. Women had a relative risk 2 or more times that of men.

Both initial prevalence and incidence of new gallstones during the 10-year period increased with increasing age and obesity. For obesity, as relative weight (a ratio of subject's weight to median weight for all individuals of same sex and height) increased from  $< 0.9$  to  $> 1.2$ , relative risk increased from 0.55 to 1.25 in men, and from 0.85 to 1.77 in women.

While the Framingham Study was important because of its size and representative sample, it relied on self-report for its data and could not be used to estimate prevalence for asymptomatic gallstones. Jorgensen (8,9) reported on a study which used ultrasound screening on a cross-sectional, stratified random sample of 3608 Danish men and women, age 30, 40, 50 and 60, between 1982 and 1984. Rates ranged from a low of 1.8% in 30-year-old men, to 22.4% in 60-year-old women. The study also showed increasing prevalence of gallstones with increased body mass index (BMI,  $\text{kg}/\text{m}^2$ ) in women but only a trend in men. In BMI categories  $< 20$ , 20–25, 25–29, 30 + , the mean prevalence was 5.5, 6.3, 5.3, 9.0% in men, and 7.5, 10.6, 13.0, 28.4% in women, pooling across age categories. These figures suggest that differences in BMI in the 20–30 range may be more important for women, while prevalence for men is less affected until BMI exceeds 30.

The Danish data show clearly that prevalence increases with both age and obesity. However, because persons tend to gain weight as they age, at least until around age 50, it is necessary to adjust the prevalence of gallstones for the age of the subjects if we want an estimate of the degree of association with BMI apart from its association with age.

One study that made such adjustments used data from 90 302 women in the Nurses Health Study (10). Aged 34 to 59 at baseline in 1980, an 8-year follow-up period identified 2122 cases of cholecystectomy, and in a 6-year period, 488 cases of newly diagnosed symptomatic but unremoved gallstones. The incidence of cholecystectomy or diagnosed gallstones was clearly related to BMI, rising in a monotonic fashion from 0.28 per 100 person/years at BMI

< 24, to around 1/100 person/years with BMI in the range of 30–35, and more than 2/100 for a BMI of 45 and greater. Multivariate adjustment for known or suspected confounding factors such as age attenuated only slightly the association of obesity and gallstone risk, indicating that most of the association is with BMI rather than age. Unfortunately, the sample is limited to women and data for a comparable sample of men are not available.

Acalovschi *et al.* (11) studied the rate of gallstone formation in a sample of 157 obese women hospital patients in Romania. The mean sample BMI ( $\pm$  SD) was  $31.4 \pm 3.6$  kg/m<sup>2</sup>. Morbidly obese women (BMI > 40) and subjects with an abnormal initial ultrasound were excluded from the longitudinal study. These women were followed over a period of 2 to 6 years. Mean age at follow-up was 50.1 years. The cumulative incidence of gallstones, symptomatic and asymptomatic, was 2.6 cases per 100 women per year. Most of the cases were asymptomatic. Age, family history, early onset obesity and hyperlipoproteinemia type IV were associated with increased risk of gallstone formation.

A study of 2228 Japanese men, age 49 to 55, retiring from the Self-Defense Forces who had a retirement health examination including an ultrasound scan, failed to find an association of BMI with gallstones, although there was an association of BMI with having previously undergone cholecystectomy. The authors suggest that the power of the study may have been inadequate, but, in addition, the BMI of most of the men in the sample was low: 75% of the sample had a BMI below 25.4, and the BMI range is also limited. The authors observe that the overall prevalence rate of gallstone disease (gallstones or cholecystectomy) in their sample was 3.3%, much lower than among 50-year-old European men, which they cite as 24.5% in Norway, 6.7% in Denmark and 7.5% in Britain (12).

International comparisons are difficult to make because samples tend to be non-representative and methods of determining prevalence may differ. Thus the Japanese sample consisted of males retiring from the military, one US sample was female nurses, and the Romanian sample was selected from hospitalized women. Furthermore, there may be special subpopulations within a nation whose gene pool or risk factors may differ substantially from the majority population, which can greatly change the prevalence. For example, in the USA 70% of

Pima Indian women over age 25 have been reported to have gallstones (4), and Mexican Americans are known to have elevated gallstone rates compared to persons of Caucasian descent (13).

Tables 28.1 and 28.2 summarize a large amount of epidemiological data.

Because obesity combines with variables such as sex, age and ethnicity in non-additive and non-linear ways to alter greatly the prevalence and incidence of gallstones, few general summary statements can be made: women have higher rates than men; rates increase with age; rates are greatest at highest levels of BMI.

## FACTORS RELATED TO INCREASED GALLSTONE FORMATION IN THE OBESSE

Why gallstones form in some persons and not in others, and in particular, why the obese are predisposed to the development of gallstones is an object of continued study. In this section we discuss some of the individual and environmental factors related to increased gallstone risk and the manner in which these factors may affect the mechanisms of gallstone formation.

### Diet and Diet Composition

It has been suggested that high total caloric intake (after BMI is taken into account), meal spacing, fasting, caloric restriction and many other dietary variables can affect gallstone formation (14). We mention here some of the findings on diet composition most relevant to obesity.

#### *Dietary Cholesterol*

Surprisingly, there is little evidence that cholesterol intake or serum total cholesterol is related to risk for formation of cholesterol gallstones. It has been suggested that since obese people have higher bile saturation indices than the non-obese, perhaps because of increased hepatic secretion of cholesterol into the bile, that dietary cholesterol may make little additional difference for these individuals (3,14).

**Table 28.1** Gallstone prevalence in men

Study <sup>a</sup>	Number of subjects	Age range (years)						
		20	30	40	50	60	70	80
<b>North American studies</b>								
Michigan (1959) <sup>b</sup>	1233			← 11.1% →				
<b>Hispanic Americans (1989)</b>								
Mexican Americans	634	← 2.6% →	← 9.7% →	← 15.5% →				
Cuban Americans	134	← 0.0% →	← 5.1% →	← 14.3% →				
Puerto Ricans	200	← 2.0% →	← 3.3% →	← 11.1% →				
<b>European studies</b>								
Austria (1984)	67				← 16% →			
Denmark (1987)	1843		1.8%	1.5%	6.7%	12.9%		
Italy (1988)	1239	← 2.3% →	← 2.0% →	← 6.7% →	← 14.7% →	← 14.4% →		
Italy (1987)	878	← 1.1% →	← 4.4% →	← 9.2% →	← 11.0% →			
Norway (1987)	637	← 4.9% →	← 12.9% →	← 18.2% →	← 24.5% →	← 37.0% →		
Wales <sup>b</sup> (1976)	849				< 6.0% >	← 5.0% →	← 8.0% →	

<sup>a</sup>Reference details for studies may be found in Diehl (4).

<sup>b</sup>Prevalence determined by oral cholecystography.

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**Table 28.2** Gallstone prevalence in women

Study <sup>a</sup>	Number of subjects	Age range (years)							
		20	30	40	50	60	70	80	
North American studies									
Nova Scotia (1980) <sup>b</sup>	133	← 14.6% →	← 33.3% →	← 14.3% →					
Hispanic Americans (1989)									
Mexican Americans	654	← 13.8% →	← 26.4% →	← 44.1% →					
Cuban Americans	189	← 10.8% →	← 19.2% →	← 21.7% →					
Puerto Ricans	382	← 9.0% →	← 21.2% →	← 12.1% →					
European studies									
Austria (1984)	86				← 32.5% →				
Denmark (1987)	1765			6.1%	14.4%	22.4%			
Sweden (1985)	424		4.8%	17.4%	21.8%				
Sweden (1988)	109								
Italy (1984)	1081	← 2.5% →	← 5.9% →	← 10.9% →	← 17.8% →	← 25.0% →			
Italy (1987)	1033	← 2.9% →	← 9.5% →	← 16.1% →	← 27.0% →				
Norway (1987)	734	← 6.0% →	← 15.3% →	← 24.8% →	← 29.2% →	← 41.3% →			
Wales (1976) <sup>b</sup>	278			< 12.0% >	← 14.1% →	← 10.1% →		50.5%	

<sup>a</sup>Reference details for studies may be found in Diehl (4).

<sup>b</sup>Prevalence determined by oral cholecystography.

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### **Dietary Fat**

Of interest here are effects of low dietary fat content. Two separate effects need to be distinguished: ingestion of fats in the long-term regular diet versus fat content of diet during a weight loss program. With respect to the former, populations consuming a diet of regular foods with low fat content (animal fat in particular) are suspected to be at lower risk for gallstone formation and vegetarians have been found to have low gallstone rates (15). The situation with respect to fat ingestion during caloric restriction for weight loss appears to be quite different. Several studies which used very low calorie liquid diets (VLCD) with very low fat content to produce rapid weight loss showed strikingly elevated rates of gallstone formation.

For example, Liddle *et al.* (7) observed gallstone formation in 13 of 51 obese patients following 8 weeks on a 520 kcal (2177 kJ) diet during which patients lost a mean of 16.6 kg. In another study, Yang *et al.* (16) enrolled 457 adults in a hospital-based weight reduction program consisting of a 520 kcal diet (55 g protein, 79 g carbohydrates, 1 g fat). After 16 weeks 248 patients remained in the program and received a second ultrasound scan. Eleven of 58 men and 16 of 190 women developed gallstones during the interval. Univariate analysis comparing subjects who developed gallstones with those who did not identified three variables on which they differed significantly. These included larger initial BMI, greater BMI decrease during the intervention, and higher initial triglyceride levels. Subjects who showed greatest BMI change were most likely to develop gallstones, suggesting that rate of weight loss may be a factor in producing these elevated rates of gallstone formation.

However, both of the above studies used diets which were extremely low in fat content ( $< 2$  g/day). Ingestion of fat promotes the release of cholecystokinin (CCK), a hormone secreted by the mucosa of the upper gastrointestinal tract which stimulates gallbladder contractions. The contractions expel the gallbladder contents thereby helping to prevent the accumulation of crystals and binding material which contribute to the growth of gallstone accretions. Suggestions that gallbladder stasis secondary to extremely low intake of dietary fat might be responsible for increased gallstone formation rates during rapid weight loss were put forward by Klawansky and Chalmers (17).

Stone *et al.* (18) showed that gallbladder functioning in individuals with elevated BMI was not impaired compared to normal weight individuals. A liquid meal containing less than 1 g of fat resulted in impaired emptying in both normal weight and obese subjects, whereas the addition of 10 or 20 g of fat to a liquid meal restored gallbladder emptying to maximal stimulus levels in both normal and obese individuals.

The effect of low fat content was initially difficult to separate from that of caloric restriction and rate of weight loss since all these variables were confounded. However, other, more recent studies have tended to clarify the important variables.

Gebhard *et al.* (19) attempted to separate the effects of rapid weight loss from those of very low fat content. They randomized obese men and women into a 520 kcal, less than 2 g fat/day diet group, and a 900 kcal (3769 kJ), 30 g fat/day diet group. The latter included one 10 g fat meal to stimulate gallbladder contraction. Over the 24 weeks of the study the subjects were gradually introduced to regular foods and by the end of the program subjects were on a 1200–1500 kcal/day (5025–6281 kJ/day) intake. Both groups lost similar amounts of weight (about 22% of initial weight) by the end of the 24-week period. Four subjects on the 2 g fat/day diet developed gallstones by the 12th week, whereas no one in the other group did ( $P = 0.021$ ). The authors suggest that gallstone risk during rapid weight loss may be reduced by stimulating gallbladder emptying with adequate dietary fat.

Festi *et al.* (20) also investigated effects of two diets of different fat content on gallbladder emptying and gallstone formation in obese subjects. First, ultrasound evaluation in 32 subjects established their gallstone-free status, then, for 3 months they consumed either 3.0 g of fat/day on a 2.24 MJ (535 kcal) or 12.2 g fat in a 2.415 MJ (577 kcal) diet. After the first 3 months the same low calorie diet (LCD) was fed to both groups: 4.194 MJ (1002 kcal) for 3 more months. Eleven subjects in each group completed the study with significant weight loss. Asymptomatic gallstones developed in 6 of 11 subjects in the low fat group versus none in the high fat group. High fat always induced greater gallbladder emptying. This study effectively separates effects of low fat from those of caloric restriction and seems to conclude along with others that the low fat content is primarily responsible for the high gallstone rates seen in previous studies.

However, the protective role of dietary fat during weight loss is not always sufficient to prevent the formation of stones. Vezina *et al.* (6) studied a series of 272 obese subjects who began a 13-week 900 kcal/day (3769 kJ/day) liquid diet program with normal gallbladder ultrasonograms. Two diet formulations were used, one with 16 g fat/day, the other with 30 g fat/day, including at least one meal with 10 g of fat. In the first series with the low fat content, 16 of 94 (17%) subjects developed stones. In the second series with the higher fat content, 20 of 178 (11.2%) developed stones. Since other studies had shown that 10 g of fat per meal results in maximal gallbladder emptying they concluded that cholelithiasis which occurs during rapid weight loss may not be solely attributable to low fat content and gallbladder stasis. Unfortunately, the study was not a randomized trial and there were differences in mean BMI between the two groups of subjects upon entry and differences in the amount of weight lost during the study, and both of these differences could account in part for the high incidence of gallstone formation seen in the high fat group. However, other studies by Hoy *et al.* (21) and Moran *et al.* (22), described below, also suggest that low fat content does not entirely explain the elevated rates seen in rapid weight loss.

### **Dietary Fiber**

Dietary fiber may induce bile acid synthesis, thereby reducing cholesterol saturation of bile. On this basis it has been suggested that fiber supplementation may have a beneficial effect in preventing gallstone development in obese patients on a calorically restricted diet (23).

The previously described study by Vezina *et al.* (6) varied fiber content (partially hydrogenized guar or cellulose) and amount in the diet. Among subjects consuming less than 1000 g of fiber, in 13 weeks 5 of 66 developed stones; among those consuming 1000–2000 g, in 13 weeks 8 of 88 developed stones. There was also no significant difference according to amount or type of fiber consumed.

Although there is some epidemiological evidence of a negative association of dietary fiber and gallstones, at this time evidence that fiber supplementation reduces the rate of gallstone formation in obese persons during rapid weight loss is lacking.

### **Weight Loss**

Survey data suggest an association of weight loss and increased risk for gallstones. For example, the Nurses Health Study reported a relative risk of 1.97 for women who had lost 10 kg or more during the prior 2 years compared with women who had remained within 3.9 kg of initial weight. (10). However, most of this increased risk was associated with a higher initial BMI before weight loss occurred.

Rapid weight loss has been clearly associated with increased rates of gallstone formation in well-controlled trials. Weinsier *et al.* (24) summarized the results of nine different studies in an analysis which showed an increasing curvilinear relationship between incidence of gallstone formation and rate of weight loss. Risk of gallstone formation increased dramatically when weight loss exceeded 1.5 kg per week. Although all of the studies considered in that analysis which showed high incidence rates used diets with less than 2 g fat per day, there have been no subsequent studies which examined comparable weight loss rates with greater amounts of fat. Furthermore, the effect of fat on gallbladder function is inconclusive in some studies and does not produce the expected emptying. Studies which have attempted to match weight loss and only vary fat content between groups tended to employ less severe caloric restriction. Then, also, there are periodic reports of weight loss studies with what should be adequate amounts of fat which nevertheless show a clearly increased rate of gallstone formation. One study, by Vezina *et al.* (6), has been described above. Another study, by Hoy *et al.* (21) provided both more energy (800–840 kcal/day or 3350–3518 kJ/day) and a higher fat content (15 or 25 g/day) than the studies of Yang (16) or Liddle (7), but still found that two cases of gallstones developed over the 10-week intervention. Another study of 36 patients which only restricted caloric intake by approximately 500 kcal/day (2094 kJ/day) and provided about 25% of calories (48 g/day) from fat nevertheless observed three new gallstones after 8 weeks (22). Thus, there are probably aspects of rapid weight loss other than extreme fat restriction which promote gallstone formation. Potential mechanisms are the increased hepatic cholesterol secretion and the reduction in bile acid secretion which are known to occur during caloric restriction and which may increase bile supersaturation (25).

Finally, it is possible that even modest rates of weight loss for long periods of time might increase risk by means of the mechanisms mentioned above. These effects would be difficult to detect for several reasons. The low incidence of gallstone events means that very large samples are required to reach statistical significance. Furthermore, cross-sectional studies find that lower BMIs are associated with lower gallstone risk, thus the increased risk, if any, during weight loss may be offset by a decreased risk as BMI falls.

### Weight Cycling

One study has reported an increased risk of cholecystectomy for women who intentionally lost weight and subsequently regained it (26). Compared to non-cyclers, and after adjusting for initial BMI, women who reported at least one episode of weight cycling during a 10-year period had relative risks of 1.31 (for moderate cycles of 10–19 lb (4.5–8.5 kg)) and 1.68 (for cycles of  $\geq 20$  lb (9 kg) loss or gain) of undergoing a cholecystectomy during a subsequent 6-year period. The rate of weight loss or regain during these cycles is not known and may be an important variable.

### Inactivity

Obesity tends to be accompanied by low levels of physical activity. A recent prospective study using the Nurses Health Study sample examined correlations of recreational physical activity reported by questionnaires and incidence of cholecystectomy. The authors report relative risk in the most active quintile to be about 0.7 that of the least active quintile, and that a significant effect remained even after adjusting for BMI and recent weight changes (27). Similar results have been found for men (28). The results tend to show decreases in risk with increasing activity over the entire activity range, suggesting that even modest levels of activity might have some protective effect.

### Fat Distribution

Surveys conducted as part of the San Antonio Heart Study investigated the occurrence of gall-

bladder disease in samples of Mexican American and non-Hispanic white participants whose fat distribution was also assessed by skinfold thickness measurements (13). The subscapular/triceps ratio was used as an index of central fat deposits. The usual associations were found between gallbladder disease status and age and BMI in men, but women showed, in addition, an association of increased gallstone risk with central fat deposits, the association being especially strong in the Mexican American group.

Gallstone pathogenesis may be correlated with certain regional fat distribution patterns, these patterns being possible indicators of metabolic disturbances such as impaired glucose tolerance and lipid metabolism. Hendel *et al.* (29) investigated whether intra-abdominal fat and metabolic disturbances are related to known gallstone pathogenic factors such as gallbladder volume, lithogenic index of bile or gall bladder ejection fraction. They found that fasting gallbladder volume, while not correlated with total fat mass or percentage fat mass in their sample of 57 obese men and women, correlated positively with intra-abdominal fat mass as measured by computed tomography (CT) scan ( $r = 0.51$ ), and also with impaired glucose tolerance ( $r = 0.36$ ). The data also showed a trend for impaired glucose tolerance to be associated with intra-abdominal fat mass. The lithogenicity index of bile, however, was more strongly correlated with total fat mass ( $r = 0.66$ ) than with intra-abdominal fat mass ( $r = 0.22$ ).

### Gastric Surgery

Many studies have reported gallstone occurrence in about 30% of cases following gastric restriction or bypass surgery (30,31). It is believed that this is most likely a consequence of the rapid weight loss which follows surgery rather than of any drastic alteration in gastrointestinal functioning. Because of the extremely high incidence, many of these surgery studies have looked at preventing or treating gallstones that form following the surgical procedure. Some of these studies are reviewed in the following section.

## PREVENTION AND TREATMENT OF GALLSTONES

Because ursodeoxycholic acid (UDCA) acts to decrease bile saturation it was investigated as an agent to preventing lithogenic changes in bile during weight loss. Aspirin was also studied as an agent which might inhibit nucleation and thereby reduce gallstone risk. Broomfield *et al.* (32) randomized 68 obese patients into placebo, UDCA (1200 mg/day) and aspirin (1300 mg/day) treatment groups. All participants consumed a low-calorie powdered food supplement (55 g protein, 79 g carbohydrate, 1 g fat) amounting to 520 kcal/day (2177 kJ/day). Mean weight loss in the groups was between 21 and 25 kg over a period of 16 weeks. Follow-up ultrasound scans at 4 weeks and 19 weeks showed that UDCA successfully prevented formation of gallstones. The aspirin medication resulted in a lower but non-significant difference from placebo.

To investigate further the possible preventive effects of aspirin, Kurata *et al.* (33) examined data from 4524 patients in a randomized, controlled trial where half the patients received 1 g of aspirin per day. Hospitalization rates for gallstone disease were approximately equivalent to national rates and the usual associations of age, triglycerides, obesity and female gender were found. No effect was seen for aspirin medication. The authors conclude that a larger dose might be effective but because of aspirin's gastrointestinal side effects, its eventual utility is questionable.

In another study, Marks *et al.* (34) looked at effects of ursodiol or ibuprofen on gallbladder contractions and bile among obese patients during weight loss treatment. After a VLCD of 529 kcal/day (2215 kJ/day) for 12 weeks, reduced contraction of the gallbladder, increased cholesterol saturation and increased nucleation and growth of cholesterol crystals were noted. However, no gallstones formed in any group. Ibuprofen treatment showed some promise in that it prevented an increase in saturation and reduction in gallbladder contraction and showed a trend opposing the increase in nucleation and growth of crystals.

A double-blind study of effectiveness of UDCA in preventing gallstone development after vertical band gastroplasty in 29 morbidly obese patients is reported by Worobetz *et al.* (35). Three months after surgery patients had lost a mean of 17% of pre-

operative weight. Six of 14 placebo patients versus none of 10 UDCA treated patients developed gallstones, suggesting that gallstone formation following gastroplasty can be prevented by UDCA therapy.

Sugerman *et al.* (31) investigated a 6-month regimen of prophylactic ursodiol to prevent development of gallstones after gastric bypass in patients with BMI of 40 or above before surgery. The study used three dose levels: placebo, and 300, 600 and 1200 mg daily. At 6 months, gallstone formation was noted in 32%, 13%, 2% and 6% respectively. The 600 and 1200 doses were significantly different from placebo. The authors conclude that a dose of 600 mg is an effective prophylactic in these patients.

In a multicenter, non-surgical study, Shiffman *et al.* (36) enrolled 1004 patients with BMI of 38 or greater into a 520 kcal/day (2177 kJ/day) liquid diet program. Subjects had ultrasound scans at the start and at 8 and 16 weeks. Again, subjects were randomized to placebo, 300, 600 or 1200 mg/day of ursodeoxycholic acid. Gallstones developed in 28%, 8%, 3% and 2% of subjects, respectively, and differences between groups remained even after long-term follow-up, showing that UDCA could be an effective prophylactic during well-defined, high-risk periods.

The use of UDCA for dissolution of existing gallstones has also been investigated, with mixed results. Administration of UDCA in a dose of 8–10 mg/kg/day leads to complete or partial gallstone dissolution in about 75% of cases. However, complications such as cystic duct obstruction and biliary pain may occur and only about 17% of cases achieved complete gallstone dissolution. (37).

Laparoscopic cholecystectomy is currently the preferred treatment for symptomatic gallbladder stones. Although it is more technically demanding in obese patients, the risks are comparable to those for non-obese patients and may be lower than with traditional surgical methods (38).

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