

# Excess Body Weight and Gallstone Disease

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## Keywords

Bariatric surgery · Cholecystectomy · Cholelithiasis · Diet · Obesity

## Abstract

**Background:** Approximately one fifth of adults are diagnosed with gallstones worldwide. Of these, around 25% develop gallstone disease (indicated by the presence of symptoms) and undergo cholecystectomy. **Summary:** The risk of gallstones is influenced by a combination of genetic and lifestyle factors, such as excess body weight. In fact, body mass has been demonstrated to be a major risk factor for symptomatic gallstones. Rapid weight loss can also initiate a pro-lithogenic state and further increase the likelihood of either gallstone formation or existing gallstones becoming symptomatic; however, sensible weight loss strategies can mitigate this risk. This review discusses the role of excess body weight and the risk of gallstone disease, as well as the options available for the prevention of symptomatic gallstones. **Key Messages:** Healthy weight loss diets combined with regular physical activity can promote successful weight loss and weight maintenance and reduce the risk of gallstones. Should rapid weight loss be required for health reasons or be expected, e.g., after bariatric surgery, prophylactic ursodeoxycholic acid during the period of weight reduction has been demonstrated to reduce the incidence of gallstones formation or symptomatic gallstone occurrence. The recent German guidelines on gallstones recommend simultaneous cholecystectomy during bariatric surgery but only for those with preexisting symptomatic stones.

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## Introduction

The global prevalence of gallstones has been reported to be up to 20% in adults [1]. The identification of gallstones per se does not necessitate treatment, as the majority of individuals with stones remain asymptomatic. However, approximately 25% develop symptoms and/or complications [2, 3] and are therefore diagnosed as having gallstone disease, for which (laparoscopic) cholecystectomy (gallbladder removal) is the gold standard treatment [1].

Gallstones are classified based on their localization (gallbladder or biliary tract) and composition, which is determined by physical-chemical alterations in bile, and differentiated by elevated cholesterol or bilirubin concentrations. Approximately 90% of gallstones are cholesterol stones and primarily composed of cholesterol [4]. The remaining 10% are made up of black and brown pigment stones which are mainly composed of calcium bilirubinate, calcium complexes, and mucin glycoproteins, or unconjugated bilirubin, respectively [4].

The risk of gallstones entails a combination of both nonmodifiable (genetic) and modifiable (environmental/lifestyle) factors. Genetic variants have been determined to account for approximately a quarter of the overall gallstone risk [5]. The most commonly reported genetic risk factor in humans identified in genome-wide association studies is the *ABCG8* p.D19H variant of the hepatocanalicular cholesterol transporter, a heterodimer of ATP-binding cassette transporters [6]. Modifiable risks entail a combination of factors such as body weight, parity, metabolic aberrations including obesity, hyperinsulinemia,

insulin resistance, and diabetes, or physical inactivity and energy-dense nutrition, including increased consumption of refined carbohydrates and saturated fats and a limited intake of fiber. In addition, certain medications, such as estrogens and progesterone, can predispose to lithogenic states [7]. This review focuses on the modifiable risk and prevention options for gallstones related to obesity in adults.

### Body Weight and Gallstones

Increased body weight is an established risk factor for gallstone formation, and indeed an increased BMI has been demonstrated to be causally linked to the risk of symptomatic stones, as illustrated in a mendelian randomization study in 77,679 individuals [8]. This report showed symptomatic gallstones in 5.2% (4,106 individuals) of cases in up to 34 years of follow-up, with the findings being more distinct in women. The distribution of body fat also affects the risk of gallstones, with prospective cohort studies showing an association between gallstone formation and central adiposity as compared to limb or lower-extremity adiposity [9]. The increased risk associated with abdominal adiposity can occur independently of BMI, as illustrated in 2 cohorts from the USA [10, 11]. Both obesity and abdominal obesity increase the risk not only of stone formation but also of requiring surgical treatment (cholecystectomy) because of the higher likelihood of presenting with symptomatic stones [10, 12, 13]. Abdominal adiposity is associated with insulin resistance which, given its stimulating effects on hepatic cholesterol secretion, is reported as a key factor in gallstone formation [14].

The influence of body weight on gallstones has also recently been suggested to occur independently of age. For example, a retrospective cross-sectional Asian study [15] observed participants younger than 50 years to have a higher risk of gallstones (OR = 5.4; 95% CI 2.3–12.7) if they were obese and showed features of the metabolic syndrome. Here, obesity was defined as a BMI >25 for Asians [16]. Features of the metabolic syndrome were defined according to a set of accepted unified criteria [see full details in 17]. Moreover, the prevalence of gallstones in individuals younger than 50 years with obesity and metabolic syndrome was identical to the prevalence of gallstones in elderly people who were metabolically healthy and not obese.

The pathophysiological mechanisms that increase the risk of gallstones with excess body fat are multifactorial. The primary risk is the occurrence of cholesterol gallstones, which result from the accumulation of cholesterol monohydrate crystals precipitating in gallbladder bile containing excess cholesterol as compared to bile salts

and phospholipids [18]. This excess cholesterol is secreted by hepatocytes as a direct result of increased body weight. Thus, increased body fat is lithogenic [19], and the higher the body weight, the greater the risk of cholesterol stones in the gallbladder [12]. It has been estimated that each extra kilogram of body fat yields the production of approximately 20 mg of additional cholesterol. This excess cholesterol contributes to the saturation of bile with cholesterol and, accordingly, cholesterol supersaturation of gallbladder bile has been documented in obese patients but not in nonobese controls [20]. Increased body weight is additionally associated with reduced gallbladder motility, another factor that contributes to stone production [21].

More recently, a Chinese study observed higher concentrations of (high-sensitivity) C reactive protein (CRP) to be an independent risk factor for new-onset cholesterol gallstones [22]. Specifically, a high-sensitivity CRP concentration >3 mg/L was associated with a 12% increased risk of stones. Currently, it remains unknown how elevated CRP increases the risk of gallstones; however, it has been suggested as being associated with obesity, where secretion of the proinflammatory cytokine interleukin-6 (an upstream stimulator of CRP production in the liver) is stimulated by adipose tissue and contributes to systemic inflammation in obesity [23, 24].

### Rapid Weight Loss and Weight Cycling

In general, weight loss reduces the risk of gallstones, with the exception of 2 specific settings: weight loss that is extremely rapid (i.e., >1.5 kg/week) and excessive weight reduction (i.e., >25% body weight) [25–27]. In both of these cases, the risk of gallstones occurring increases [28, 29]. Rapid weight loss can predispose to a lithogenic state and subsequently the formation of gallstones [27]. In addition, weight loss induced after bariatric surgery has been reported to initiate biliary sludge (composed of precipitated lipid particles such as aggregated crystals or microliths) and gallstones in 30% of cases during the 6-month period after receiving a gastric bypass or biliopancreatic diversion [30, 31]. A comparable incidence (30%) of gallstones after sleeve gastrectomy was reported at 6–12 months postsurgery in a prospective study [32]. These risks, however, have not been reported with laparoscopic gastric banding [33].

Weight cycling (i.e., weight that is lost and regained) is an independent risk factor for gallstones [34–36]. Weight fluctuations also increase the risk of requiring a cholecystectomy [35]. Syngal et al. [35] observed both moderate (4.5–8.5 kg) and severe ( $\geq 9$  kg) fluctuations in a single weight cycle to increase the risk of cholecystectomy by 31 and 68%, respectively. Alterations of the ratio of choles-

terol to bile salts within the gallbladder were observed in the setting of weight fluctuations and in rapid weight loss [37], reflecting increased hepatic cholesterol secretion and synthesis as well as a reduced secretion of bile salts [18]. An impairment in gallbladder motility also occurs, which triggers the formation of biliary sludge [37, 38].

## Prevention and Treatment of Gallstones in Obesity

### *The Role of Cholecystectomy*

Cholecystectomy is the gold standard treatment for symptomatic gallstones, and it is often but not routinely carried out during bariatric surgery in obese patients. There has been a reduction in the rate of simultaneous cholecystectomies in recent years due to the morbidity and mortality associated with the procedure as well as a high reintervention risk [39]. Studies have reported concomitant cholecystectomy to result in longer operation times, longer hospital stays, and higher complication rates [39, 40]. The risk of secondary cholecystectomy was demonstrated to be 6.8% (with 5.3% of these cases presenting with symptoms) after laparoscopic Roux-en-Y reconstruction, as reported in a meta-analysis of 13 studies, 12 of which were retrospective [41]. Other studies have shown the incidence of cholecystectomy to range from 3.3 and 14.7% in the 6–24 months after bariatric surgery [42, 43]. Generally, the morbidity and mortality for cholecystectomy in obese patients not undergoing bariatric surgery do not appear to be higher than those of the general population [44]. There have been previous reports of increased procedure times and postoperative morbidities in obesity; however, these did not differ significantly compared to non-obese controls [45]. Recently, Reeves et al. [44] reported a small increased odds of hospital admissions in patients with severe morbid obesity (BMI >50) compared to patients with a BMI between 30 and 40, but this increased risk was only modest (OR = 1.10; 95% CI 1.02–1.19;  $p < 0.001$ ).

As such, the recent German consensus guidelines for gallstone disease recommend simultaneous cholecystectomy only in obese patients with symptomatic gallstones [39, 46], as do the European guidelines [47]. These risks do, however, differ depending on the type of bariatric surgery, with the laparoscopic Roux-en-Y surgery displaying a higher risk than either gastric banding or sleeve resection [48]. Two recent studies corroborated the guideline recommendations; Della Penna et al. [49] followed up 61 patients with asymptomatic gallstones treated with ursodeoxycholic acid (UDCA) for 6 months after bariatric surgery (either laparoscopic Roux-en-Y gastric bypass or sleeve gastrectomy). Cholecystectomy was required in 1 patient only who had undergone sleeve gastrectomy. Another patient reported symptoms during the 6-month fol-

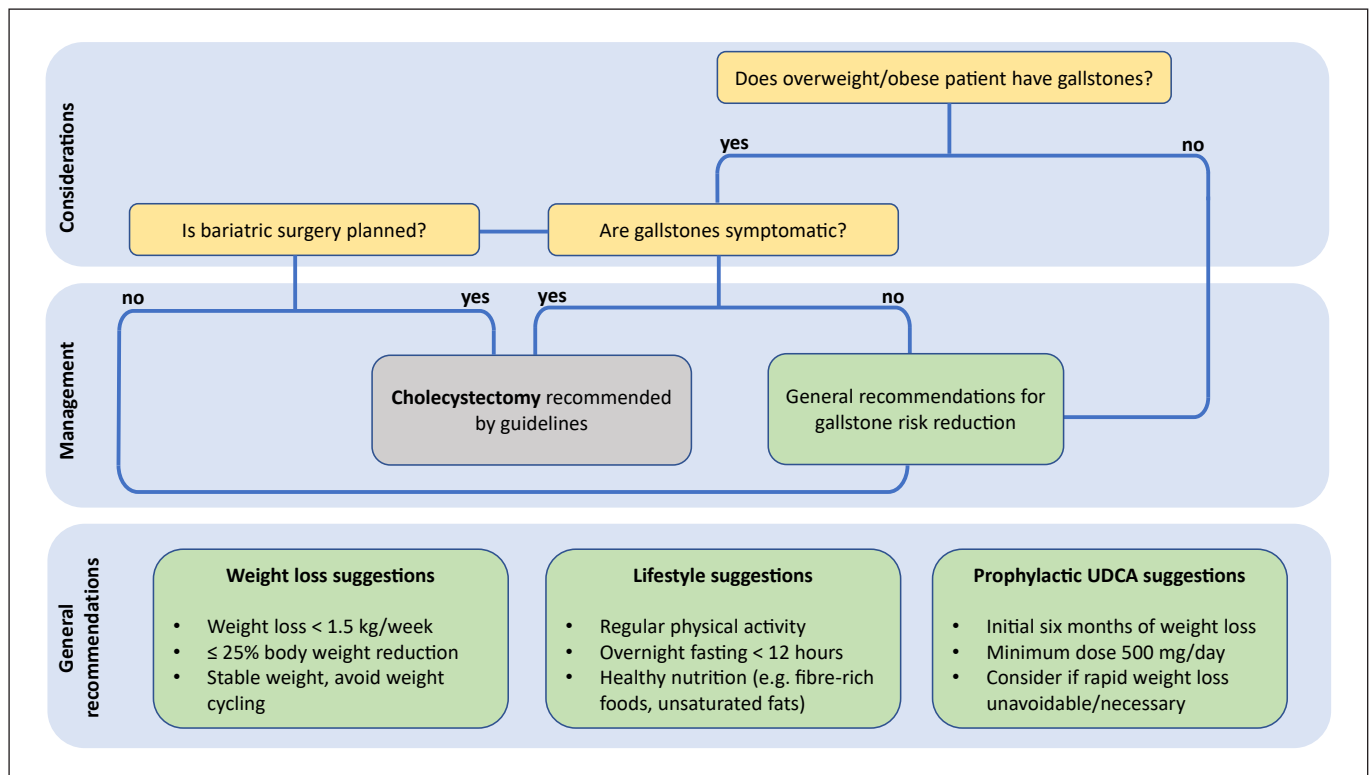
low-up after sleeve gastrectomy but did not require cholecystectomy. The remaining 59 patients remained asymptomatic with UDCA prophylaxis.

The Swedish Obese Subjects study [50] also supports the recent guidelines, reporting an overall low cumulative incidence for cholecystectomy after bariatric surgery. This nonrandomized, controlled study compared standard of care with the effects of bariatric surgery [50]. Overall, 3,597 participants who had not undergone previous or concomitant cholecystectomy at the time of inclusion were analyzed. The cohort was divided into 2 groups: 1,755 patients received bariatric surgery (gastric bypass,  $n = 236$ ; vertical banded gastroplasty,  $n = 1,202$ ; and gastric banding,  $n = 317$ ). The control group ( $n = 1,842$ ) received the usual treatment for obesity, including lifestyle advice. UDCA was not provided to any of the groups. During 26 years of follow-up, modest weight changes were observed in the control group (3% fluctuations), in contrast to the surgical group where weight loss averaged 25% at 2 years and 16% at both 10 and 15 years. Symptomatic gallstone incidence differed significantly ( $p < 0.001$ ), with the surgery group reporting 307 first-time events versus 252 in the controls. A similar trend was observed for complicated gallstones and the rate of cholecystectomies, with 172 versus 144 first-time events ( $p < 0.006$ ) and 230 versus 170 cases ( $p < 0.001$ ), respectively. The above risks were more pronounced during the first 5 years after surgery.

Given the invasiveness of the standard treatment for gallstone disease, a greater emphasis on the prevention of gallstones is required and it is discussed in the following sections within the context of excess body weight.

### *Diet and Physical Activity*

Steady weight reduction (i.e., <1.5 kg/week) is recommended in the setting of obesity and gallstone risks (as discussed in Rapid Weight Loss and Weight Cycling). The increased risks of gallstones have been illustrated with 2 popular weight reduction methods, i.e., bariatric surgery and very low-calorie diets [26–28, 51], with approximate risks of 30 and 25%, respectively [26, 28]. Randomized controlled trials in obese patients have demonstrated these risks to be mitigated to a certain degree when weight loss diets have a higher fat content [37, 52, 53]. General nutrition-related recommendations include reducing the energy density of the diet (particularly avoiding saturated fats and sugar) and instead consuming fiber-rich foods such as wholegrains, fruits, or vegetables [54–59]. Reducing energy-dense foods, particularly those high in sugar, has shown beneficial effects on both weight and gallstone risk [60]. A high dietary glycemic load increases the risk of gallbladder stone formation [61–63]. In contrast, fiber-rich foods reduce the risk of cholecystectomy in women [64, 65]. Additionally, a reduction in the



**Fig. 1.** Suggested approach based on clinical evidence and guideline recommendations to reduce the risk of gallstone disease in overweight/obese patients undergoing weight loss.

lithogenicity of hydrophobic bile salts was demonstrated with consumption of high-fiber and calcium-rich foods [66]. However, fiber supplementation during weight loss did not lead to significant benefits in terms of gallstone development in a randomized study with obese participants [67]. Other foods reported to reduce the risk of cholecystectomy include legumes, olive oil [68], and nuts [69].

Dietary lipids are mediators of gallstone risk, with unsaturated fatty acids displaying risk reduction properties and saturated and trans fats increasing the risk [70–72]. In patients with gallstones, omega-3 fatty acid supplementation reduced the cholesterol saturation index in bile [73]. Another study in obese women without gallstones who were randomized to receiving omega-3 fatty acids or UDCA or placebo for 6 weeks did not observe a reduction of biliary cholesterol saturation, despite the fact that none of the participants developed gallstones during this intervention period [74]. The omega-3 group did, however, display improved gallbladder motility in patients with hypertriglyceridemia [75]. Additionally, gallbladder hypomotility might be mitigated by reducing the time of overnight fasting to less than 12 h, as suggested by observational data [76].

Physical activity has a multitude of benefits with regard to weight loss and weight maintenance, and it has

also been studied for its direct effects on gallstone risk. In fact, several studies have reported physical activity as having protective effects on the formation of gallstones [34, 63, 77–79]. Intervention studies, however, show only modest effects: improvements in gallbladder motility were observed in a randomized study, where the intervention included moderate training, but the results were similar in the control group [80]. A lack of significant effects on gallstones was also reported in pregnant women taking part in a randomized study [81].

#### *Prophylactic Ursodeoxycholic Acid*

During the weight reduction phase, prophylactic ursodeoxycholic acid has shown great promise in reducing the formation of gallstones regardless of the method of weight loss, i.e., low-calorie diets or bariatric surgery, with reductions as high as 58% reported in randomized controlled trials [25, 29, 31, 53, 82–85]. A minimum dose of 500 mg/day is recommended, as shown in clinical trials and a meta-analysis of such trials, with this dose being more effective than 300 mg/day in reducing the risk of gallstones forming during a 6-week period but also after 3–4 months [53]. A higher dose has not shown greater benefits either, as illustrated in a randomized trial in patients receiving gastric bypass [31]. In this study, 3 UDCA doses were compared: 300, 600 and 1,200 mg/day for 6 months. The



600-mg dose was the most efficacious at preventing gallstones, with an incidence of 2 versus 13 and 6% in those receiving 300 and 1,200 mg, respectively. These findings have been corroborated [29].

Since subsequent cholecystectomy, e.g. after bariatric surgery, can be performed should gallstones become symptomatic, many patients do not receive prophylactic UDCA during the weight reduction phase in clinical practice [86, 87]. Given the benefits reported above, recent guidelines on gallstones have strongly recommended UDCA be given as a prophylaxis in the case of a high risk of sludge or stone formation when undergoing weight loss either through low-calorie diets or bariatric surgery [46, 47]. Studies suggest the first 6 months after surgery to be the most critical because they are associated with the greatest reduction in body weight, with UDCA showing mild benefits after the first 6 months that do not justify prolonged prophylaxis [88]. A recent randomized study assessed the effects of prophylactic UDCA on the incidence of gallstones in 190 patients undergoing 1 anastomosis gastric bypass [89]. These patients were randomized to either 600 mg/day of oral UDCA ( $n = 95$ ) or to a control group ( $n = 95$ ) for 6 months. The incidence of gallstones after 3 months was 0 versus 4 (4.2%) in the UDCA and control groups, respectively, and 3 (3.1%) versus 21 (22.1%) at 6 months. After 12 months of follow-up, 4 (4.2%) versus 24 (25.2%) patients in the UDCA and control groups developed gallstones, respectively ( $p < 0.05$ ). The majority were asymptomatic, with only 28.6% of participants displaying symptoms. Multivariate analyses identified UDCA as the only significant predictor of gallstone formation (HR = 0.17; 95% CI 0.06–0.48;  $p < 0.001$ ).

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## Conclusions

Excess body weight is associated with an increased risk of cholesterol gallstones. As summarized in Figure 1, sensible weight loss strategies can mitigate this risk, but rapid weight loss or weight cycling might trigger a lithogenic cascade and further increase the probability of either gallstones forming or of stones becoming symptomatic. Healthy nutrition with an emphasis on plant foods and unsaturated fats combined with regular physical activity can promote successful weight loss and weight maintenance. In the case of rapid weight loss, such as in the setting of bariatric surgery, prophylactic UDCA during the initial 6 months has been demonstrated to reduce the incidence of both gallstones and biliary symptoms. Such a strategy should benefit patients who are candidates for bariatric surgery or who for other health reasons need to undergo rapid weight loss, since recent guidelines do not recommend simultaneous cholecystectomy during surgery unless the patient has a preexisting diagnosis of symptomatic gallstones.

## Conflict of Interest Statement

The authors of the present review have nothing to declare.

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## Author Contributions

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