Review Article

Nutritional Approaches to Prevention and Treatment of Gallstones

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Abstract

Cholesterol gallstones are among the most common gastrointestinal disorders in Western societies. Individuals with gallstones may experience various gastrointestinal symptoms and are also at risk of developing acute or chronic cholecystitis. Cholecystectomy is the most frequently recommended conventional treatment for symptomatic gallstones. Bile acids (ursodeoxycholic acid or chenodeoxycholic acid) are also used in some cases to dissolve radiolucent stones, but these drugs can cause gastrointestinal side effects and there is a high rate of stone recurrence after treatment is discontinued. Lithotripsy is used in some cases in conjunction with ursodeoxycholic acid for patients who have a single symptomatic non-calcified gallstone. There is evidence that dietary factors influence the risk of developing cholesterol gallstones. Dietary factors that may increase risk include cholesterol, saturated fat, trans fatty acids, refined sugar, and possibly legumes. Obesity is also a risk factor for gallstones. Dietary factors that may prevent the development of gallstones include polyunsaturated fat, monounsaturated fat, fiber, and caffeine. Consuming a vegetarian diet is also associated with decreased risk. In addition, identification and avoidance of allergenic foods frequently relieves symptoms of gallbladder disease, although it does not dissolve gallstones. Nutritional supplements that might help prevent gallstones include vitamin C, soy lecithin, and iron. In addition, a mixture of plant terpenes (Rowachol®) has been used with some success to dissolve radiolucent gallstones. The "gallbladder flush" is a folk remedy said to promote the passage of gallstones. While minimal scientific evidence supports the efficacy of this treatment, anecdotal reports suggest the gallbladder flush may be beneficial for some people. (*Altern Med Rev* 2009;14(3):258-267)

Introduction

Gallstones are among the most common gastrointestinal disorders in Western populations. Approximately 80 percent of gallstones contain cholesterol (as cholesterol monohydrate crystals). The remaining 20 percent are pigment stones, which consist mainly of calcium bilirubinate and will not be discussed in this article. Cholesterol-containing gallstones are divided into two subtypes: cholesterol stones (which contain 90- to 100-percent cholesterol) and mixed stones (which contain 50- to 90-percent cholesterol). Each subtype may also contain varying amounts of calcium salts, bile acids, and other components of bile.

Cholelithiasis (gallstone formation) results from a combination of several factors, including supersaturation of bile with cholesterol, accelerated nucleation of cholesterol monohydrate in bile, and bile stasis or delayed gallbladder emptying due to impaired gallbladder motility. Cholesterol supersaturation can result from an excessive concentration of cholesterol in bile, a deficiency of substances that keep cholesterol in solution (i.e., bile salts and phospholipids), or a combination of these factors. Accelerated nucleation of cholesterol is

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a phenomenon not well understood. Gallbladder hypomotility may occur during pregnancy, with the use of oral contraceptives, after surgery or burns, and in patients with diabetes. However, in many cases, the cause is not clear.

While most gallstones are asymptomatic, some patients experience biliary colic, which is characterized by sudden and severe right-upper-quadrant pain (often accompanied by nausea and vomiting), occurring postprandially and lasting one to four hours. Acute or chronic cholecystitis may also occur in association with gallstones. Complications of cholecystitis may include infection, perforation, and gangrene.

The most widely used conventional treatment for symptomatic gallstones is cholecystectomy. Most patients experience a resolution of symptoms after cholecystectomy, but about 10-15 percent of patients suffer from postcholecystectomy syndrome, which is characterized either by a continuation of symptoms that had been attributed to gallbladder disease or the development of new gastrointestinal symptoms. Another conventional treatment is oral administration of a naturally occurring bile acid (ursodeoxycholic acid or chenodeoxycholic acid), that may promote gradual dissolution of radiolucent gallstones over a period of six months to two years. However, these treatments can cause various gastrointestinal symptoms and other side effects. In addition, recurrences are seen in up to 50 percent of patients after treatment is discontinued. It is generally agreed that patients with asymptomatic gallstones do not require treatment with drugs or surgery.

Dietary Factors

Obesity and Weight Loss

Obesity is associated with an increased risk of gallstones.[1] Weight loss may reduce the risk of gallstone formation in overweight individuals, but excessively rapid weight loss (i.e., more than three pounds per week) may promote the development of gallstones or increase the risk that silent gallstones will become symptomatic. The increased risk associated with rapid weight loss may be due to an increase in the ratio of cholesterol to bile salts in the gallbladder and to bile stasis resulting from a decrease in gallbladder contractions.[2]

Food Allergy

One practitioner stated as early as 1941 that food allergy is a common cause of gallbladder disease, and that failure to recognize food allergy has resulted in many unnecessary cholecystectomies.[3]

That the gallbladder can be a target organ for allergic reactions has been demonstrated in experimental animals. In one study an allergic reaction was induced in the gallbladder of a Rhesus monkey by administering an intravenous injection of cottonseed protein after passively sensitizing the gallbladder. The reaction was characterized by edema, hyperemia, increased mucus secretion, and eosinophilic infiltration.[4] A similar reaction was seen in the gallbladder of rabbits sensitized to sheep serum and then inoculated with sheep serum into the gallbladder cavity.[5] These reactions were called "allergic cholecystitis" by the researchers who performed the two studies.

In addition to potentially evoking an inflammatory response, food allergy or intolerance might cause delayed gallbladder emptying, an abnormality known to play a role in the pathogenesis of cholelithiasis. This possibility is suggested by a study of patients with celiac disease. Six healthy volunteers, six patients with untreated celiac disease, and six patients with celiac disease controlled on a gluten-free diet, drank a liquid fatty meal after an overnight fast. The mean time until the gallbladder emptied by 50 percent was approximately 20 minutes in the healthy individuals and patients with diet-controlled celiac disease, as compared with 154 minutes in the patients with untreated celiac disease ($p<0.02$).[6] These results indicate that patients with celiac disease have a gallbladder emptying defect that can be reversed by consumption of a gluten-free diet.

In an uncontrolled trial, identification and avoidance of allergenic foods eliminated gallbladder symptoms in 100 percent of 69 patients with gallstones or postcholecystectomy syndrome. Sixty-nine patients (ages 31-97 years) with gallstones or postcholecystectomy syndrome were placed on an elimination diet consisting of beef, rye, soy, rice, cherry, peach, apricot, beet, and spinach; fat intake was not restricted. After one week on the diet the patients were challenged with individual foods. If a food evoked typical "gallbladder symptoms," that food was discontinued and not retested for several weeks. All components of each person's diet were

tested, and each symptom-evoking food was retested several times. All 69 patients were symptom-free within one week of starting the elimination diet, with improvements usually occurring in 3-5 days. Egg, pork, and onion were the most frequent offending foods, with reactions occurring in 93-, 64-, and 52-percent of patients, respectively. Table 1 lists the most common offending foods and percentage or patients reacting. Between one and nine foods were eventually eliminated from each person's diet (average 4.4).[7]

Although long-term follow-up information was not provided for these patients, this study suggests food allergy is an important factor in the development of gallbladder-related symptoms. The author of this report pointed out that, since each patient had different food allergies, the standard dietary recommendation to avoid fatty, greasy, and rich foods may not always produce satisfactory results in patients with gallbladder disease.

Dietary Cholesterol and Fat

In a three-week randomized trial, increasing intake of cholesterol (over a range of 500-1,000 mg per day) resulted in increasing biliary cholesterol saturation in both healthy volunteers and patients with asymptomatic gallstones.[8] This rise in biliary cholesterol saturation would presumably increase the risk of gallstone formation.

In observational studies, higher intake of saturated fat or trans fatty acids was associated with an increased incidence of gallstones.[9-11] In contrast, higher intake of polyunsaturated or monounsaturated fatty acids was associated with decreased risk.[12] The apparent protective effect of polyunsaturated fatty acids is consistent with experimental observations, in which hamsters fed an essential fatty acid-deficient diet had a high incidence of cholesterol gallstones and lithogenic bile (diets low in essential fatty acids are, in general, also low in polyunsaturated fatty acids).[13,14] In addition, in patients with gallstones, supplementation with 11.3 g per day of fish oil (which is high in polyunsaturated fatty acids) decreased the cholesterol saturation of bile by 25 percent.[15] While both omega-3 and -6 polyunsaturated fatty acids may be protective, further research is needed to determine the optimal amounts and ratios of these fatty acids.

Table 1. Foods Evoking Symptoms of Gallbladder Disease

Offending Food	Percent of Patients Reacting
Eggs	93%
Pork	64%
Onions	52%
Fowl	35%
Milk	25%
Coffee	22%
Oranges	19%
Corn	15%
Beans	15%
Nuts	15%
Apples	6%
Tomatoes	6%

Refined Sugar

Observational studies in humans have found that higher intake of refined sugars such as sucrose and fructose is associated with a higher frequency of gallstones.[16-19] While the association between refined sugar intake and gallstones could be due in part to the fact that consuming large amounts of sugar can lead to obesity, there is evidence that refined sugars are themselves lithogenic. In rabbits fed a lithogenic diet containing 34-percent sucrose, replacing sucrose with starch protected against the development of gallstones.[20] In another study in rabbits, replacing dietary sucrose with starch decreased the total weight of gallstones by 48 percent in females and 20 percent in males, although these differences were not statistically significant.[21] In patients with gallstones randomly assigned to consume a diet high or low in refined carbohydrates (providing a mean of 106 g per day versus 6 g per day of refined sugar), the cholesterol saturation of bile was significantly greater on the diet high in refined carbohydrates ($p<0.005$).[22] However, another study was unable to confirm those findings.[23] Although it has not been proven that consuming

refined sugar promotes gallstone formation, it would be prudent for people at risk of developing gallstones to avoid excessive intake of refined sugar.

Vegetarian Diet

In a cross-sectional study, the prevalence of gallbladder disease (asymptomatic gallstones or history of cholecystectomy) was significantly lower in female vegetarians than female omnivores (12% versus 25%; $p<0.01$).[24] In addition, a 20-year prospective study of 80,898 women found that increased consumption of vegetable protein was associated with a decreased risk of having a cholecystectomy.[25] A separate evaluation of the same cohort of women found that increasing consumption of fruits and vegetables was associated with a decreased incidence of gallstones. Similar results were seen for both total fruits and total vegetables examined separately.[26] In hamsters fed a lithogenic diet the incidence of gallstones was decreased in a dose-dependent manner by progressively replacing casein (a milk protein) with soy protein in the diet.[27,28] These observations suggest that consumption of a vegetarian diet, and particularly vegetable protein, may decrease the risk of developing gallstones.

Dietary Fiber

In observational studies, higher intake of fiber was associated with a lower prevalence of gallstones.[29,30] In addition, supplementation of the diet with 10-50 g per day or more of wheat bran for 4-6 weeks decreased the cholesterol saturation of bile in healthy volunteers, individuals with constipation, and patients with gallstones.[31-33] Bran is thought to work primarily in the colon, decreasing the formation of deoxycholic acid by intestinal bacteria and increasing the synthesis of chenodeoxycholic acid.[34] Deoxycholic acid appears to increase the lithogenicity of bile, whereas chenodeoxycholic acid decreases lithogenicity and has been used therapeutically to promote dissolution of gallstones. Based on these observational and biochemical studies it would be reasonable to recommend a high-fiber diet as part of a comprehensive nutritional program for preventing gallstones.

Caffeine

In dogs, administration of caffeine in drinking water at a concentration of 1 mg/mL prevented the development of gallstones induced by feeding a high-cholesterol diet. The protective effect of caffeine appeared to be due in part to stimulation of bile flow.[35]

Two large, prospective cohort studies found consumption of caffeinated coffee may protect against the development of symptomatic gallstones. Compared with non-coffee drinkers, the reduction in risk associated with consumption of two or more cups of coffee per day was 40-45 percent in men[36] and 22-28 percent in women.[37] Consumption of decaffeinated coffee was not associated with lower gallbladder disease risk, suggesting the beneficial effect of coffee is due to caffeine. A large cross-sectional study found little or no protective effect of coffee consumption;[38] however, cross-sectional studies tend to be less reliable than prospective cohort studies.

Other Dietary Factors

In a prospective study of 80,718 women participating in the Nurses' Health Study, increased consumption of peanuts and other nuts was each associated with a lower risk of cholecystectomy. Women who consumed five or more ounces of nuts per week had a 25-percent lower risk of having a cholecystectomy, compared with women who rarely or never ate nuts.[39]

Circumstantial evidence suggests consumption of large amounts of legumes may increase the incidence of gallbladder disease. In a study of healthy young men, consumption of a diet containing 120 g per day of legumes for 30-35 days increased biliary cholesterol saturation, compared with a control diet. This effect was due to a combination of an increase in the concentration of cholesterol and a decrease in the concentration of phospholipids in the bile.[40] In addition, Chileans and American Indians, who have some of the highest prevalence rates of cholesterol gallstones in the world, both consume legumes as dietary staples.[40] However, a case-control study conducted in the Netherlands found an inverse association between legume intake and gallstone risk. This association did not appear to be due to a decrease in legume consumption as a result of gastrointestinal intolerance to this food group.[41] Thus, the relationship between legume consumption and gallstone risk remains uncertain. The possibility that legume

consumption promotes the development of gallstones should be weighed against the known beneficial effects of legumes, which include improvements in blood glucose regulation and a reduction in serum cholesterol levels.

In healthy volunteers who rarely consumed alcohol, consumption of 39 g per day of alcohol (equivalent to 3-4 drinks daily) for six weeks decreased cholesterol saturation of bile.[42] If the same effect could be achieved with smaller amounts of alcohol, then moderate alcohol consumption might decrease the risk of developing gallstones.

In mice fed a lithogenic diet containing 0.5-percent cholesterol, feeding of garlic or onion reduced the incidence of gallstones and decreased the lithogenicity of the bile.[43] It is not known whether these findings are relevant to gallstones in humans.

Nutritional Supplements

Vitamin C

Several animal studies indicate vitamin C may help prevent gallstones. Guinea pigs developed gallstones when fed a diet high in cholesterol and low in vitamin C, but not when fed the same diet with an adequate amount of vitamin C.[44,45] Vitamin C is a cofactor for the enzyme 7α-hydroxylase, the rate-limiting step in the conversion of cholesterol to bile acids (Figure 1). Thus, vitamin C appeared to prevent gallstone formation by promoting the conversion of cholesterol to bile salts, thereby decreasing the lithogenicity of bile.[46-48] Vitamin C supplementation also inhibited cholelithiasis and accelerated the conversion of cholesterol to bile salts in hamsters.[49]

In a cross-sectional study of 7,042 women participating in the Third National Health and Nutrition Examination Survey, 1988-1994, a significant inverse association was found between serum vitamin C levels and prevalence of gallbladder disease. No such association was found in men participating in the same survey.[50] In a study of patients with gallstones, daily supplementation with 2 g vitamin C for two weeks decreased the lithogenicity of bile. Sixteen patients with gallstones scheduled for cholecystectomy received 500 mg vitamin C four times daily for two weeks prior to surgery; another 16 patients scheduled for cholecystectomy did not receive vitamin C (control group). During surgery, bile was taken from the gallbladder of each patient. Compared with control patients, vitamin C-treated patients had significantly higher concentrations of phospholipids in bile. The mean nucleation time of bile (the time required for the formation of cholesterol crystals, the first step in stone formation) was seven days in the vitamin C group and two days in the control group ($p<0.01$).[51]

These findings suggest increasing vitamin C intake decreases the risk of developing gallstones. However, additional research is needed to confirm that possibility and determine the optimal dosage.

Iron

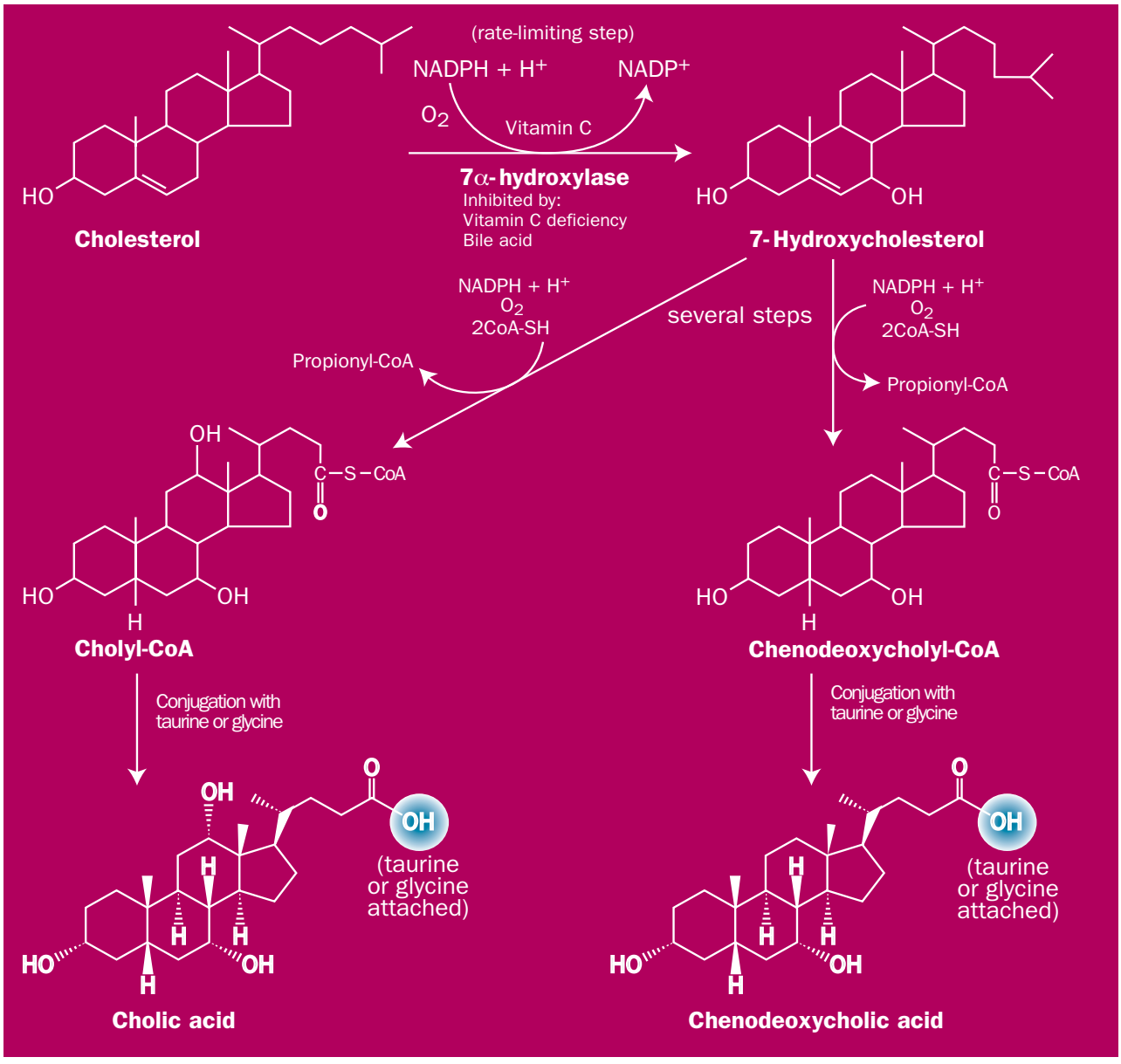
Dogs fed an iron-deficient diet had a higher incidence of cholesterol crystals in their bile than animals fed a control diet (80% versus 20%; $p<0.05$). The activity of hepatic 7α-hydroxylase (Figure 1), was nonsignificantly lower by 64 percent in iron-deficient dogs than in controls ($p=0.07$).[52] These findings raise the possibility that iron deficiency plays a role in the pathogenesis of gallstone formation in humans.

Lecithin

Phospholipids increase the solubility of biliary cholesterol. Some studies have found biliary phospholipid concentrations are lower in patients with gallstones than in those without gallstones, whereas other studies have found no difference in the phospholipid content of lithogenic and normal bile.[53] Supplementation with lecithin (which contains high concentrations of phospholipids) has the potential to decrease the lithogenicity of bile by increasing biliary phospholipid concentrations.

In an uncontrolled trial, supplementation of eight gallstone patients with a relatively low dose of lecithin (100 mg three times daily) for 18-24 months was associated with a significant increase in biliary phospholipid content and a significant decrease in biliary cholesterol levels. In one patient, gallstones decreased in size and changed in shape, but no changes were seen in the other patients.[54] In another study, daily administration of 4.5 g soybean lecithin for three weeks resulted in a nonsignificant eight-percent improvement in the cholesterol saturation index of bile.[55] It is not clear whether the changes observed in these studies are of clinical value, and there is at present no strong evidence to support the use of lecithin to prevent or treat gallbladder disease.

Figure 1. Conversion of Cholesterol to Bile Acids



Other Factors Associated with Gallstones

Hypochlorhydria

Hypochlorhydria is common in patients with gallbladder disease,[56] occurring in 52 percent of 50 patients with gallstones in one study.[57] While there is no evidence hypochlorhydria contributes to the pathogenesis of gallstones, it may be responsible in part for some of the nonspecific symptoms associated with chronic cholecystitis, such as belching, bloating, abdominal pain, and nausea. In hypochlorhydric patients, hydrochloric acid-replacement therapy with meals may relieve these symptoms.[58] Hydrochloric acid is usually administered as betaine hydrochloride. The dosage of betaine hydrochloride recommended for hypochlorhydric patients varies among different practitioners from 600 mg per meal to 3,000 mg or more per meal.[59]

Rowachol®

Rowachol® is a proprietary preparation that contains six plant monoterpenes (Table 2). Each capsule contains 100 mg of the mixture. Rowachol has choleretic properties (i.e., it stimulates bile production by the liver) and inhibits the formation of cholesterol crystals in bile.[60,61] In clinical trials, treatment with Rowachol for six months resulted in complete or partial gallstone dissolution in 29 percent of 27 patients with radiolucent gallstones. In addition, Rowachol enhanced the efficacy of chenodeoxycholic acid in dissolving gallstones, allowing for the use of lower (and better tolerated) doses of chenodeoxycholic acid. Rowachol could presumably also be used to enhance the efficacy of ursodeoxycholic acid.

Table 2. Monoterpene Content of Rowachol

Constituent	Percent of Total Content
Menthol	32%
Menthone	6%
Pinene	17%
Borneol	5%
Camphene	5%
Cineol	2%
Base of Olive Oil	33%

Twenty-four patients with radiolucent gallstones received one capsule of Rowachol per 10 kg body weight per day, in most cases for six months. Seven patients (29%) showed radiological and/or surgical evidence of partial (n=4) or complete (n=3) gallstone dissolution. No side effects were seen and there was no laboratory evidence of hepatotoxicity or hematological abnormalities.[62]

Thirty patients with radiolucent gallstones and a functioning gallbladder were treated for up to two years with a combination of Rowachol (1 capsule twice daily) and chenodeoxycholic acid (7-10.5 mg per kg body weight per day). The dosage of chenodeoxycholic acid was slightly lower than the usual 750 mg per day in order to minimize side effects and cost. The treatment was well tolerated; only one patient reported diarrhea. Stones disappeared in 11 patients (37%) within one year and in 15 patients (50%) within two years. In comparison, in the National Cooperative Gallstone Study, in which chenodeoxycholic acid was given alone at a dose of 750 mg per day, complete dissolution was seen in only 13.5 percent of patients after two years. The authors of this report concluded that a combination of medium-dose chenodeoxycholic acid and Rowachol is economical, effective, and likely to have fewer adverse effects than higher doses of chenodeoxycholic acid alone.[63]

Twenty-two patients with radiolucent gallstones and a functioning gallbladder received two or three capsules per day of Rowachol plus chenodeoxycholic acid (375 mg at bedtime, equivalent to a mean of 38% of the recommended dose) for 12 months. The combination was well tolerated; only one patient discontinued treatment because of gastrointestinal side effects. Thirteen patients (59%) had complete (n=6) or partial (n=7) dissolution of stones.[64]

Rowachol at a dosage of three capsules per day, alone or in combination with chenodeoxycholic acid or ursodeoxycholic acid, was also used with some success by one group of investigators to dissolve radiolucent stones in the common bile duct. However, during the treatment, eight of 31 patients required emergency hospitalization for biliary colic, obstructive jaundice, pancreatitis, or cholangitis. These complications were successfully managed and all but one patient continued with the treatment. The investigators concluded that dissolution therapy may be considered in patients with radiolucent common bile duct stones when endoscopic sphincterotomy or surgery is not feasible. However, careful attention to potential complications is required while stones persist.[65,66]

Rowachol has been on the market for more than 50 years and has not been reported to cause any serious side effects.[59] The usual dosage is 2-3 capsules daily. Larger doses are not recommended as they may increase biliary cholesterol saturation.[67]

Gallbladder Flush

A gallbladder flush (also called a liver flush) is a folk remedy that is said to promote the passage of gallstones.[68,69] Several different versions are used. One method is to fast for 12 hours and then, beginning at 7 p.m., ingest four tablespoons of olive oil followed by one tablespoon of lemon juice every 15 minutes for a total of eight treatment cycles. Another method is to consume only apple juice and vegetable juice (no food) during the day until 5-6 p.m., and then ingest 18 mL of olive oil followed by 9 mL of fresh lemon juice every 15 minutes until eight ounces of oil have been consumed. Some practitioners use *Cascara sagrada* and garlic/castile enemas in combination with the olive oil and lemon juice treatment. According to published and anecdotal reports, patients often experience diarrhea and abdominal pain from this treatment, and by the next morning they typically pass multiple soft green or brown spheroids that have been presumed to be gallstones.

However, in most cases these spheroids were not subjected to chemical analysis and the patients did not undergo follow-up evaluations to document they no longer had gallstones. Analysis of one group of passed "gallstones" revealed they consisted of 75-percent fatty acids and contained no cholesterol, bilirubin, or calcium. Further experimentation suggested the spheroids were "soap stones," created by the interaction of digestive enzymes with certain components of olive oil and lemon juice.[70] Analysis of another spheroid passed after a gallbladder flush revealed it was not a gallstone.[71]

One case report did document ultrasonographic evidence of a reduction in the number of gallstones following the ingestion of olive oil and lemon juice,[72] and there are several other anecdotal reports of gallstones resolving on follow-up ultrasound evaluation after a gallbladder flush.[73] If this treatment can promote the passage of gallstones, then it might also cause stones to become trapped in the common bile duct, potentially leading to a medical emergency. However, to this author's knowledge, such an adverse effect has not been reported.

Conclusion

The evidence reviewed in this article suggests that the risk of developing gallstones can be reduced by maintaining an ideal body weight and by consuming a diet similar to diets recommended for preventing other common diseases, such as heart disease, diabetes, and hypertension. Certain nutritional supplements may also help prevent gallstones, but the evidence supporting that possibility is not strong. Based on the available evidence, it would be reasonable to recommend 500-2,000 mg per day of supplemental vitamin C for patients at risk of developing gallstones, in order to reduce the lithogenicity of their bile. Iron status should also be assessed, and deficiencies should be treated appropriately. In patients with symptomatic gallstones, identification and avoidance of allergenic foods appears to be a viable alternative to cholecystectomy. In most cases, food allergies can be identified by an elimination diet followed by individual food challenges. A mixture of plant terpenes may also be useful for dissolving radiolucent gallstones, particularly when used in combination with a bile acid.

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