Targets for Current Pharmacologic Therapy in Cholesterol Gallstone Disease

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Gallstone disease is one of the most frequent and costly digestive diseases in Western countries; its prevalence in adults ranges from 10% to 15%.[1–4] Despite the frequency of the condition, many patients with gallstones remain undiagnosed, although symptoms and/or complications occur in approximately a third of patients. In the United States, medical expenses for the treatment of gallstones exceeded $6 billion in the year 2000. The prevalence of gallstones seems to be rising and approximately 1 million new cases are discovered each year.[5] About 75% of the gallstones in the United States and Westernized countries, including Italy, are cholesterol gallstones.[6–8] The remaining gallstones are pigment stones that contain less than 30% cholesterol by weight, which can be subclassified into 2 groups: black pigment stones (about 20% of all gallstones, found in the gallbladder and/or bile duct, containing mainly insoluble

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bilirubin pigment polymer mixed with calcium phosphate and carbonate, and cholesterol) and brown pigment stones (about 5% of all gallstones, found mainly in bile ducts, containing calcium bilirubinate, calcium palmitate, and stearate and cholesterol).[9]

Cholesterol gallstones are associated with well-known risk factors, such as obesity, type 2 diabetes, dyslipidemia, and hyperinsulinemia,[1] which are often components of the metabolic syndrome epidemic,[10–14] which has a prevalence greater than 35% in the adult population and which continues to increase in Westernized countries.[15,16] Epidemiologic surveys have observed that cholesterol cholelithiasis is prevalent in populations consuming a Western diet (ie, enriched in saturated fatty acids, cholesterol, and rapidly absorbed refined carbohydrates), rather than a more prudent diet (ie, enriched in monopolyunsaturated fats, fruit, vegetables, and low in refined carbohydrates) associated with physical activity.[17–25] Thus, the prevalence of cholesterol gallstone disease is significantly higher in North and South American as well as European populations than in Asian and African populations.[6] In China, the prevalence of cholesterol gallstones seems to increase with the Westernization of the traditional Chinese diet.[26–28] Even in Japan, the adoption of Western-type dietary habits has resulted in a marked increase of the prevalence of cholesterol cholelithiasis over the past 40 years.[29,30] As discussed later, high efficiency of intestinal cholesterol absorption and high dietary cholesterol seem to be key and independent risk factors for the formation of cholesterol gallstones. The complex pathogenesis of cholesterol gallstones depends on the concurrent existence of hepatic hypersecretion of cholesterol into bile, leading to bile supersaturation with cholesterol, accelerated nucleation/crystallization of cholesterol in gallbladder bile, impaired gallbladder motility leading to gallbladder stasis, and increased cholesterol availability from the small intestine, as well as *LITH* genes and genetic factors.[1,31,32] A complex genetic basis plays a key role in determining individual predisposition to developing cholesterol gallstones in response to environmental factors.[33–37] Some gallstone genes might also play a potential role, including some genes governing the nuclear bile acid receptors such as farnesoid X receptor (FXR). For example, *FXR* variants seem to affect gallbladder motor function and intestinal microflora in Mexicans,[38] whereas functional variants in FXR might account for intrahepatic cholestasis of pregnancy in Whites, as well as being associated with other cholestatic and dyslipidemic disorders.[39]

From a therapeutic point of view, although gallstone disease is frequent in the general population and the costs of therapeutic interventions are high, the natural history of the disease suggests restriction of the medical treatment of gallstones to a subgroup of symptomatic patients.[1,36,40] The selection of patients eligible for medical or surgical therapy, therefore, is of key importance. The onset of biliary pain is the only suggestive marker of symptomatic gallstone disease,[41,42] although it can be difficult to distinguish between symptomatic and asymptomatic patients in a random population of patients with gallstones.[43] The diagnosis can be misleading if patients inadequately describe typical symptoms or suffer from highly atypical symptoms.[44] Previously symptomatic patients who are symptom-free for 5 consecutive years should be included in the group of asymptomatic subjects again. After this time, the risk of pain attacks gradually decreases toward values similar to those of patients with asymptomatic gallstones.[45] Classic drug therapy for cholesterol gallstones (ie, oral litholysis by the bile acid ursodeoxycholic acid [UDCA]) plays a limited role, but novel interesting therapeutic options might arise in the near future, related to the molecular mechanisms responsible for the formation of cholesterol gallstones.[1] Such novel therapeutic approaches might involve subgroups of patients permanently or temporarily at risk for gallstone formation. Recent studies in animal models and humans have found that blocking the intestinal absorption of cholesterol with