Gallstone disease (GD) is a major health problem in developed societies, affecting ≤15% of the general population. Although many risk factors for gallstone formation are not modifiable, obesity, diabetes mellitus, metabolic syndrome, rapid weight loss, and a sedentary lifestyle are risk factors for GD that can be changed. Moreover, the chronic use of some drugs (eg, octreotide, thiazide diuretics, and some oral contraceptives) may also increase the risk of developing GD. In contrast, long-term statin use seems to prevent gallstone formation, possibly by decreasing biliary cholesterol secretion and saturation and inhibition of cholesterol crystal formation. The rising pandemic of obesity and the metabolic syndrome is likely to lead to an increase in the prevalence of gallstones in many parts of the world in the foreseeable future.

See accompanying article on page 2232

Interestingly, in this issue of the journal, Lv et al1 examined the association between GD (as diagnosed by a standardized questionnaire) and the risk of incident ischemic heart disease (IHD) among 199,292 men and 288,081 women aged 30–79 years in the China Kadoorie Biobank study. Participants with a previous history of cancer, IHD, and stroke at baseline were excluded from the study. At baseline, 5.8% of 487,373 adult participants reported the presence of GD (men 3.7%; women 7.3%). During a median follow-up period of 7.2 years, there were 10,245 incident cases of IHD (≈90% nonfatal) in men and 14,714 (≈95% nonfatal) in women. The authors found that GD was associated with an increased incidence of IHD events (ie, a combined end point inclusive of fatal and nonfatal events), independently of multiple cardiovascular risk factors. As compared with those subjects without GD at baseline, the multivariate-adjusted hazard ratios for IHD were, respectively, 1.11 (95% confidence interval 1.02–1.22) for men with GD and 1.27 (95% confidence interval 1.20–1.34) for women with GD. Interestingly, the association between GD and incident IHD was found to be stronger in women (than in men) and in nonhypertensive compared with hypertensive individuals. In contrast, the association between GD and incident IHD was similar across subgroups stratified by age, smoking status, alcohol consumption, physical activity level, and presence of obesity or diabetes mellitus.

The relationship between GD and risk of IHD has been debated for many years, with some recent cross-sectional and prospective studies showing an independent association between GD and IHD and between GD and cardiovascular mortality and morbidity. That said, the findings described by Lv et al are timely and clinically relevant. The study extends previously published data and shows that GD independently predicts incident IHD in a prospective cohort of over 0.5 million adults from 10 geographically diverse areas across China. The major limitations of this study were the self-reported diagnosis of GD and the lack of any information about insulin resistance, dyslipidemia, use of lipid-lowering drugs, nonalcoholic fatty liver disease (NAFLD), and variation in gut microbiota. However, despite these limitations, this is the largest prospective cohort study to date examining the association between GD and risk of IHD. In addition, the follow-up duration of the study was relatively long, the authors have adjusted for many important potential confounders, and the results were consistent across clinically relevant subgroups.

The reasons for the increase in IHD risk related to GD remain largely unexplained. GD and IHD are 2 common diseases that share multiple cardiometabolic risk factors, and it is now important to understand how GD is linked to IHD. Cholesterol is the main component of most gallstones and also atheromatous plaques. Whether GD and IHD are found more frequently together because they share common risk factors or whether the pathogenesis of both is causally linked is uncertain. Gallstone formation requires dysregulation of biliary lipid secretion, biliary cholesterol supersaturation, and also gallbladder hypomotility and the presence of pronucleating factors, such as a nidus of infection. Alterations in hepatic processing of the lipid globule and availability of cholesterol for both very low–density lipoprotein and bile acid secretion could be a shared pathway for both GD and IHD. Altered bile acid metabolism associated with GD may also influence several nuclear receptors that are involved in the regulation of lipogenesis and insulin sensitivity, such as peroxisome proliferator–activated receptors, liver X receptors, farnesoid X receptor, and hepatocyte nuclear factor 4α.

An association between GD and NAFLD has been shown in recent cross-sectional studies, and mounting evidence...
suggested that NAFLD is an emerging risk factor for IHD and plays a key role in the development of hepatic insulin resistance and atherogenic dyslipidemia. Preliminary evidence also suggests that GD is associated with more severe liver damage in NAFLD patients. Additionally, some population-based studies also reveal a significant association between NAFLD and cholecystectomy, but no association between NAFLD and gallstones, suggesting that cholecystectomy might not be innocuous and may contribute to NAFLD development and progression. Increasing evidence is now suggesting a role for dysbiosis of the intestinal microbiota in obesity, diabetes mellitus, and maybe also NAFLD and IHD. Dysbiosis can increase the proportion of gram-negative bacteria in the portal circulation and also increase the production of lithogenic bile acids, both of which could increase the risk of GD. In the Figure, we have attempted to summarize the putative underlying mechanisms by which dysbiosis might mediate a link between GD, obesity, NAFLD, and IHD. A better understanding of these mechanisms would enable us to better tailor a treatment for both patients with GD and those with IHD.

In summary, although it is not proven that there is a causal link between GD and IHD, it is important that clinicians are aware of the significant association between GD and risk of IHD. For patients with GD, we suggest that a multidisciplinary approach based on a careful evaluation of coexisting cardiometabolic risk factors and monitoring for IHD and liver complications is now warranted. It is possible to speculate
that long-term statin therapy in patients with GD might exert a beneficial effect not only on IHD prevention but also on the cholesterol gallstone formation, consequently decreasing the need for cholecystectomy. However, it is likely that new randomized clinical trials are needed to test the effect of statins on GD to address this issue.

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