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CHOLELITHIASIS DEVELOPMENT AND PROGRESSION IN ELDERLY PATIENTS WITH CORONARY HEART DISEASE

Abstract. Gallstone in older adults with coronary artery disease is a significant medical problem due to a variety of factors, including age-related changes in metabolism and comorbidities. Studies show that the presence of coronary heart disease can aggravate the course of cholelithiasis, increasing the risk of complications such as cholecystitis and pancreatitis. In this regard, special attention should be paid to early diagnosis and preventive measures aimed at reducing the likelihood of gallstone formation and improving the quality of life of patients. A meta-analysis of one of the studies shows a significantly increased risk of cardiovascular disease among patients with a history of cholecystectomy. The researchers suggest that interested scientists should also continue to address this issue. According to the findings, women may have a higher risk of cardiovascular disease than men. There is also evidence that cholecystectomy may increase the risk of cardiovascular disease. However, the authors believe that further research in this direction should be continued.[1]

Key words: Gallstones, adult, heart disease, meta-analysis, association

The world's greatest cause of death is cardiovascular disease (CVD). Heart and blood vessel diseases, such as stroke and ischemic heart disease (IHD), are collectively referred to as CVD. Age, obesity, body mass index (BMI), low serum high density lipoprotein (HDL) cholesterol levels, diabetes mellitus (DM)11, inadequate physical activity, smoking, excessive alcohol consumption, and high blood pressure are some of the risk factors for CVD that have been identified. An elevated risk of GD is also linked to certain risk factors.

At cohort-specific baselines, 1000 participants out of 229 (6.2%) women (Nurses' Health Study [NHS] and NHS II) and 1449 out of 437 (3.3%) men (HPFS [Health Professionals Follow-up Study]) reported a history of gallstone disease.[2]Consistently across the 3 cohorts, participants who reported a history of gallstone disease were more likely to be older, current smokers, regular aspirin users, less physically active, to consume less alcohol, to have a higher body mass index, and to have a history of 8 hypertension, diabetes, or hypercholesterolemia. Across ≤30 years of follow-up, we confirmed 21 incident CHD cases. In general, the crude incidence rates of total CHD were nearly double among participants who had reported gallstone disease compared with those who had never reported gallstone disease. There was a significant age-adjusted association between a history of gallstone disease and CHD risk in each cohort. After multivariable adjustment, the associations between history of gallstones and CHD were largely attenuated but remained significant in each cohort: NHS (hazard ratio [HR] [95% confidence interval. An interim meta-analysis of these 3 cohorts revealed that the results in women When we limited the exposure to a history of cholecystectomy only, its association with total CHD risk was similar to when our definition of gallstone disease included both history of gallstones and cholecystectomy (data not shown). In secondary analyses of the total CHD subgroup definitions (fatal or nonfatal myocardial infarction and revascularization), multivariable-adjusted analyses of the individual outcomes revealed significant associations between a history of gallstone disease and myocardial infarction in older women from NHS. There were significant associations between a history of gallstone disease and revascularization in both women and men. The results did

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not change materially when we evaluated the associations separately among participants not taking lipid-lowering medication (interim 3-cohort meta-analyzed HR [95% CI], in those who were not obesity. who were nonsmokers , in those without diabetes mellitus or in those with normal blood cholesterol levels. However, obesity status and disease status of diabetes mellitus and hypertension significantly modified the association between gallstone disease and CHD risk (all P for interactionof English-language articles resulted in 124 citations from PUBMED and from EMBASE, with 16 duplicates. We screened the titles and abstracts using general inclusion criteria as described in the Materials and Methods section in the online-only Data Supplement. We identified 40 abstracts for further full-text review and eventually included 4 prospective cohorts for final meta-analysis. Together with the current study, a total of 3 cohort studies were included in our meta-analysis. Characteristics of the 3 prospective cohorts included in the meta-analysis are shown in Table I in the online-only Data Supplement. We detected significant heterogeneity among these study results (I 2 =72%, P for homogeneityIn our 3 prospective studies of 1000 women and men, we found that a history of gallstone disease was associated with a 17% increased risk of CHD, independent of traditional risk factors. The associations were consistent in both men and women and modified by obesity and hypertension and diabetes status. Results from the meta-analysis incorporating previously published data from 4 additional prospective cohort studies further confirmed our findings. Significant associations between gallstone disease and CHD risk were also observed in crosssectional studies18,19 and other prospective cohort studies in Asian17,20 and German16 populations. The most recent and largest prospective study to date emerged from the China Kadoorie Biobank study,20 which involved 199292 men and 288081 women, followed up for a median 7.2 years. Authors reported 23% higher risk of ischemic heart disease for participants with gallstone disease at baseline, as compared with those withoutthe disease, which is an estimated risk consistent with our present results in the US cohorts.[5] As to other cardiovascular outcomes, both ultrasound-diagnosed gallstones and cholecystectomy were related to a 30% higher risk in overall mortality and 49% higher risk in cardiovascular mortality in a large US population,[6] and participants who had gallstone disease had a 28% higher risk in developing ischemic stroke and 33% higher risk in hemorrhagic stroke in a nationwide study in Taiwan[8].24 In our analyses, the increased risk of incident CHD among gallstone patients was attenuated to a large degree but remained significant after we adjusted for these risk factors, and when we repeated main analyses among populations free of obesity, diabetes mellitus, and hypertension and among those with healthier lifestyle and dietary habits after stratifying by these factors. Our results were similar when we limited the disease to cholecystectomy, and it might suggest that cholecystectomy might not ameliorate the deleterious influence of gallstone diseases on CHD risk. Our observed associations were modified by obesity, diabetes mellitus, and hypertension status, with perhaps counterintuitively stronger associations observed among the presumably healthier subsets of the population, ie, those without obesity, diabetes mellitus, and hypertension. In addition, because cholesterol is the main component of most gallstones and atherosclerotic plaques, and the use of statins seems to prevent gallstone formation,[5] we included hypercholesterolemia as a covariate in our statistical models and also conducted sensitivity analyses among the participants who had normal blood cholesterol levels, as well as among those not taking lipid-lowering medications, and yet the association of gallstone disease and CHD risk remained significant. Taken together, these observations may point to pathways independent of these important risk factors that link gallstone disease to CHD. Further research is warranted to explore potential mechanisms. The potential mechanisms for the association of gallstone diseases with CHD may, at least, include the primary metabolic pathway and the bacterial pathway. Take an example in the metabolic pathway, among patients with gallstones, especially those with cholesterol gallstones, their bile acid and lecithin secretion rates tend to be depressed and cholesterol secretion rates elevated,[7] which could indicate enhanced cholesterol

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synthesis and therefore increase cardiovascular disease risk. In the bacterial pathway, gut microbiota dysbiosis may directly link gallstone disease to CHD risk. The presence of gallstones is related to microbiota dysbiosis in gut and biliary tract (maybe via biotransformation of secondary bile acids),[7] for example, an overgrowth of the bacterial phylum Proteobacteria. [9] At the same time, gut microbiota dysbiosis is found to be linked to a wide range of metabolic disturbances, including an increased risk of obesity and cardiovascular disease.[9] Of note, the bacterial link may be a targeted pathway through which diets influence both diseases. For example, circulating trimethylamine N-oxide, which is a gut flora–generated metabolite of red meat intakes, inhibits bile acid transporters in mouse liver and at the same time promotes atherosclerosis.

Our results indicate that the gallstone patients who were not affected by obesity, diabetes mellitus, or hypertension had a greater increased CHD risk compared with those who were affected by these diseases. The underlying mechanisms remained to be further explored. Patients with obesity, diabetes mellitus, or hypertension had a higher absolute risk of CHD; therefore, the increased risk attributable to gallstone disease might be relatively less than those without these diseases. In addition, patients with obesity, diabetes mellitus, and hypertension might modify their lifestyle to be healthier after disease diagnosis, and such modifications might also attenuate the relation between gallstone and CHD.

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