

Editorial

Aetiopathogenesis of gallstone disease in Sri Lanka: what do we know?H. Weerakoon¹¹ Department of Biochemistry, Faculty of Medicine and Allied Sciences, Rajarata University of Sri Lanka.**Abstract**

Pathogenesis of gallstones (GS) involves a complex interaction between multiple genetic and exogenous risk factors. As the prevalence, disease burden, aetiopathogenesis, and the complications of GS disease vary across different populations, a better understanding of the disease, specific to a given community is imperative. Though some of the initial studies reveal a higher incidence of pigment and mixed cholesterol GS over pure cholesterol stones among Sri Lankans, GS disease is largely underexplored in local context. Therefore, the prevalence, disease burden and aetiology of the GS disease in Sri Lanka need to be rigorously studied. Further research on exploring the possible factors triggering the development of GS on a pigment nidus is essential in discovering the aetiopathogenesis of GS among Sri Lankans, and will be the key in identifying effective preventive measures.

Keywords: Gallstones, Aetiopathogenesis, Mixed cholesterol gallstones, Pigment gallstones.**Copyright:** © 2021 H. Weerakoon.  This is an open-access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium provided the original work is properly cited.**Funding:** None**Competing interests:** None**Received:** 09.08.2021**Accepted revised version:** 12.08.2021**Published:** 15.08.2021✉ **Correspondence:** harshitw83@yahoo.com<https://orcid.org/0000-0002-8699-133X>

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Pathogenesis of gallstones (GS) is multifactorial and involves a complex interaction of numerous genetic and exogenous risk factors. It is an asymptomatic disease, with only ~20% of patients developing the symptomatic GS. However, the symptomatic GS causes several upper gastro-intestinal surgical casualties resulting in hospital admissions and surgical interventions accounting for a significant health care cost. Moreover, the morbidity caused by both the disease and the inpatient treatment adversely affects the patient's quality of life, as well as their psycho-social circumstances [1–3].

GS disease is a common condition in western countries where most GS are rich in cholesterol. In the west, the highest prevalence of GS is reported among North American Indians (~70%) [1,2]. Genetic factors leading to the supersaturation of bile is a leading cause for the pathogenesis of cholesterol GS in these populations. Apart from ethnicity, gender and age are the other two main non-modifiable risk factors of GS. It is a disease

common among females, and the prevalence of symptomatic GS increases with advancing age. However, familial and genetic risk factors account only for ~30% of cholesterol GS. On the other hand, modifiable risk factors like obesity, type 2 diabetes mellitus, dyslipidaemia, use of oral contraceptive pills, high parity, overnutrition, and sedentary lifestyle act as the main risk factors of cholesterol GS. These risk factors increase the biliary cholesterol secretion or change the composition of bile and the motility of the gallbladder, favouring cholesterol crystallization. Moreover, with a significant overlap of metabolic changes between cholesterol GS and the metabolic syndrome, it is considered as a part of metabolic syndrome [1–4].

GS detected in patients from some other parts of the world are compositionally different to the west. For an example, brown pigment stones consisting of calcium bilirubinate, palmitate, and stearate, and mucin are commonly found among East Asians. The development

of these stones is known to be associated with infections, including parasitoses in the biliary tract [3]. Moreover, pigment and mixed cholesterol stones are found as the commonest types in some South Asian populations, including Sri Lanka [5–7]. Pigment stones are rich in calcium bilirubinate and phosphate, while mixed stones are composed of alternative crescentic pigment and cholesterol layers [8]. Compared to cholesterol stones, the pathogenesis of pigment and mixed stones is largely underexplored. Patients with chronic haemolytic anaemia are more prone to develop pigment stones due to increased biliary bilirubin excretion [1–3]. Ethnic and community differences in terms of prevalence and the chemical composition of GS across the world indicate the significant influence of exogenous risk factors on the pathogenesis of GS. Though a low and intermediate prevalence of GS was detected among Black Africans (5%) and Asians (20%), respectively, a rise in the disease prevalence has been reported from some of these regions as well [1–3,9]. Apart from the improved case detection through novel diagnostic approaches, westernization of their dietary habits can also be a significant contributor to this rising prevalence [1–3].

GS disease among Sri Lankans is largely underexplored. We still do not have data to understand the prevalence of the disease in our population, including the disease burden. Only a limited number of studies are available in the literature to describe GS disease among Sri Lankans. These studies demonstrate that GS is a disease prevalent mostly in middle-aged females and early development of symptoms in females [10,11]. These basic epidemiological factors are consistent with the global presentation of symptomatic GS disease. Fourier transform infrared (FTIR) spectroscopy, X-ray powder diffraction (XRD), atomic absorption spectrophotometry (AAS), and scanning electron microscopy (SEM) based chemical composition and microstructural analysis of the GS recovered from a cohort of patients residing in central hills of Sri Lanka showed a high incidence of pigment and mixed cholesterol with only ~10% pure cholesterol GS [6]. Female gender, moor ethnicity, and body mass index (BMI) over 25 kg/m² were identified as the factors associated with mixed cholesterol GS over black pigment GS [10]. Moreover, patients with either pure cholesterol or mixed cholesterol GS showed significantly high serum triacylglycerol levels than those who had pigment GS [12]. However, the other common risk factors like positive family history, high fasting blood glucose, high parity and use of oral contraceptive pills in females, smoking and alcohol intake in males were not significantly different between pigment and

mixed cholesterol GS patients [10]. Interestingly, irrespective of the type of GS, most of the patients in this cohort were overweight and obese according to the South Asian BMI cutoffs indicating their high predisposition to non-communicable diseases, including cardiovascular diseases [10].

An in-depth analysis of the chemical composition and the microstructure of the GS recovered from Sri Lankan patients revealed the presence of a pigmented nidus rich in calcium bilirubinate, carbonate, and phosphate as the origin. This was observed not only in pigment GS but also in most of the mixed cholesterol stones [6]. Hence, the precipitation of calcium salts seemingly is a significant initiating step in the pathogenesis of GS among Sri Lankans. However, the majority of the patients with pigment or mixed cholesterol stones with a pigment nidus were not the patients who were diagnosed with known risk factors of pigment GS [6,10]. This highlights the requirement of further exploration into the development of GS from a pigment nidus in our population. The biliary microbiome can also affect GS pathogenesis [13,14]. Though it has not led to species characterization, a higher number of bacterial isolates were identified in cultured bile obtained from patients with pigment stones compared to cholesterol stones in one of the Sri Lankan studies [15]. Toxic heavy metal excretion through bile as a cause not only for GS but also for gallbladder carcinoma is also under investigation [16–18]. Gallbladder carcinoma is one of the devastating complications associated with GS in some populations, including North Indians [19]. Therefore, histopathological examination of the gallbladder specimens removed during cholecystectomies due to GS is routinely carried out in many countries. However, according to a Sri Lankan study, gallbladder cancer was found in only 0.8% of the specimens [20,] and thus, gallbladder carcinoma in association with GS seems to be a rare presentation in our population. Further to that, our initial studies identified a significantly high concentration of Pb²⁺ in pigment stones compared to mixed and pure cholesterol stones [6]. These key findings indicate the possible role of the biliary microbiome and toxic heavy metals in the pathogenesis of GS in our population. Identification of the influence of toxic heavy metals may help us to understand the environmental effects on the pathogenesis of GS. However, these studies have looked into the effect of individual factors but not the combined effect of multiple factors.

Control of modifiable risk factors like dietary and lifestyle habits are recommended as the main strategy of prevention of pathogenesis of cholesterol GS [1–3]. Pharmacological options used in reducing the cholesterol crystallization in bile are not generally recommended as a primary preventive strategy of cholesterol GS considering the cost-effectiveness. Identification of community-specific risk factors for GS disease for a given community/ ethnic group is pivotal as a fundamental step of disease prevention. Moreover, GS is not a solitary disease in the majority, but a presentation of a group of diseases categorized under metabolic

syndrome [1–3]. Overweight is a common association of GS disease in Sri Lanka irrespective of the type of GS, and hence the implementation of health care measures to control overweight and obesity may impact positively on control and prevention of GS disease in our community. Simultaneously, the prevalence of GS disease in Sri Lanka should be assessed to identify the actual disease burden. More importantly, understanding specific aetiological/risk factors for the progression of GS formation on a pigment nidus will be pivotal in implementing effective preventive and control measures of GS disease in Sri Lanka.

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