REVIEW ARTICLE

GALLSTONE DISEASE: A REVIEW

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INTRODUCTION

The present article gives a broad overview of gallstone disease and focuses on the pathogenesis, prevalence and association of the risk factors, dietary risk and protective factors, with the development of gallstones. Studies reviewed were identified by searching the Pubmed database upto 2005. The criteria for the including studies on pathogenesis, prevalence and risk factors, and dietary protective factors, were: (i) language of the article had to be English; (ii) studies should be case-control, cohort or cross sectional in design; (iii) Finally, the review focuses on studies on human populations. Although extensive research on gallstones has been conducted in animal models, no other animal besides the human is known to spontaneously develop gallstones [1]; thus while animal models may offer information on specific aspects of the lithogenic process; their findings are not considered here.

NATURAL HISTORY

Multiple gallstones were found in a mummified Egyptian priestess [2] but the disease was first described in 1507 by a Florentine pathologist, Antonio Benivenius [3]. The Swiss medic Paracelsus viewed gallstones as a consequence of "tartaric" disease [4]. In 1882, in the first open cholecystectomy Langenbuch successfully removed the gallbladder of a 43-year-old man who had had gallstones for 16 years [5]. This technique remained the gold standard therapy for symptomatic gallstones for over a century, although medical treatment with bile acids was first described in the late 19th century [6,7]. After a report of complete dissolution of gallstones by bile acids in 1937 [8] oral bile acid litholysis with chenodeoxycholic acid as a method for removing cholesterol gallstones emerged in the 1970s [9], and litholysis with ursodeoxycholic acid in the 1980s [10]. Extracorporeal shockwave lithotripsy plus oral bile acids for symptomatic gallstones was introduced first in 1986 in Munich [11]. Later, several studies proved that gallstones recur in 30–50% of cases, 5 years after bile salts therapy or lithotripsy [12,13].

Cholesterol crystals, the building blocks of cholesterol gallstones, were observed for the first time by van Lecuwenhoek in 1974 using light microscopy [14]. In 1987, Mouret [15] undertook the first laparoscopic cholecystectomy. The introduction of laparoscopic techniques to perform cholecystectomy has revolutionized this procedure. The revolutionary nature of this procedure has been unprecedented in surgical history, and has been compared to such surgical mileposts as the development of vascular surgery and organ transplantation.

As gallstones do not generate symptoms (i.e. biliary pain) in the majority of cases (60 – 80%) [16], most stones are incidentally found during routine abdominal ultrasonography [17, 18]. Asymptomatic gallstone patients are at low risk of developing symptoms, since 10% and 20% will eventually become symptomatic within 5 and 20 years of diagnosis, respectively [19,20]. Thus, the average risk of developing symptomatic gallstones is low and approaches 2.0 to 2.6% per year [21].

PATHOGENESIS

There are three types of gallstones (fig. 1 [22]) (i) Pure cholesterol stones contain at

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least 90% cholesterol, (ii) pigment stones either brown or black contain at least 90% bilirubin and (iii) mixed composition stones contain varying proportions of cholesterol, bilirubin and other substances such as calcium carbonate, calcium phosphate and calcium palmitate [23]. Brown pigment stones are mainly composed of calcium bilirubinate whereas bilirubin, calcium and/or tribasic phosphate are the main constituents of black pigment stones [24]. In Western societies and in Pakistan more than 70 % of gallstones are composed primarily of cholesterol, either pure or mixed with pigment, mucoglycoprotein, and calcium carbonate [25,26]. Pigment stones, which are more common in Asians, account for the rest of the gallstones.

The pathogenesis of all these three types of gallstones is highlighted (fig. 2). The pathogenesis of cholesterol gallstones must be briefly considered to facilitate the presentation of epidemiological risk factors such as age, gender [27], diet [28], obesity [29], decreased physical activity [30], rapid weight loss [31], and oral contraceptives (fig. 1) [32]. As is evident from the figure, these epidemiological risk factors along with reduced bile salt excretion due to cholesterol lowering drugs, or illeal resection lead to nucleation (appearance of crystals) [33,34]. The additional factors for nucleation are reduced antinucleating factors and gallbladder hypomotility [35,36]. These two factors along with mucin may contribute to aggregation of crystals and hence to the formation of gallstones [37]. Impaired motility of the gallbladder has been cited as contributing factor in the development of gallstones [38]. In theory, microscopic cholesterol crystals would regularly be washed out of the gallbladder if its contractions were effective enough. Evidence that gallbladder stasis causes the formation of stones is circumstantial in most cases, since the composition of bile is usually altered as well. Gallbladder stasis associated with high spinal cord injury [39] or with the use of the somatostatin analogue octreotide may provide more convincing examples of stasis as a cause of gallstones.

In case of pigment gallstone excess bile pigment production due to haemolytic anemias may lead to pigment precipitation which in addition to mucin leads to aggregation and gallstone formation [40]. The biliary calcium concentration plays a part in bilirubin precipitation and gallstone calcification [41,42]. Many patients with gallstones have increased biliary calcium, with supersaturation of calcium carbonate [41]. Calcium salts of bilirubin and carbonate are more soluble at a lower pH. The gallbladder not only concentrates bile, but also acidifies it. Failure of acidification may promote the calcification of gallstones [42,43]. Stewart et al. reported that most pigment stones contained bacteria that produced beta-glucuronidase, slime, and phospholipase, factors that facilitate stone formation; so bacteria have a major role in Western pigment gallstone formation. Furthermore, gallstone color did not predict composition or bacterial presence [44].

PREVALENCE

The incidence of gallstone disease in selected populations of different countries is summarized (table-1). These epidemiological studies have suggested a marked variation in overall prevalence between different populations. Generally it can be concluded that majority of the patients belong to Western Caucasian, Hispanic, and Native American populations, whereas Eastern European, African American, Japanese, and Pakistani populations are less affected [45-64]. More than 4 Male to female ratio (table-1) is evident from Maxican American at 20 – 39 years age group [46], United States at age 30 – 39 years [52] and Pkistani population at the age 30 – 44 years [53]. In North America the Native American population had the highest prevalence of cholelithiasis [49]. 73% of female Pima Indians over the age of 25 years had gallstones. Similar were the findings for Chippewa and Mimac Indians [57,58]. Prevalence data of Multicenter Italian study

on cholelithiasis (MICOL) showed that of the 46139 subjects screened ultrasonogaraphically, 29739 (64.46%) had gallstones [60]. In the Sirmone study an overall prevalence rate of 11 percent in Italian subjects between the ages of 18 and 65 years was noted [61]. Ultrasound examinations were repeated on the same patients with five year intervals. The ten year cumulative incidence of new gallstones was 4.6 percent. In the United Kingdom, 20 – 35 % of women and 7 – 15 % of men developed gallstones during 1989 [48]. While in Netherlands according to Russo (1984) 14000 Cholecystectomies were performed yearly [65,66]. About 75 % of the gallstones occurring in the western world were cholesterol gallstones [67]. The incidence of cholelithiasis in the people of Pakistan is increasing [53,67]. In Southern Sindh (Pakistan) the overall surgical incidence for cholelithiasis was found to be 9.03% (95% CI, 8.6 - 9.4), with females being 3.3 times more prone to develop gallstones as compared to males [53]. It has been reported by Samra et al. that out of 400 diseased gallbladder patients 320 (80 %) had gallstones [68].

FACTORS INFLUENCING GALLSTONE DISEASE

Risk Factors

Several risk factors are involved in gallstone formation (table-2), such as having given birth, estrogen replacement therapy, oral-contraceptive use, and rapid weight loss [69-72]. Similar to atherosclerosis, the risk of gallstone disease increases with age, obesity, type 2 diabetes, dyslipidaemia (hypertriglyceridaemia and low HDL [high density lipoprotein] serum cholesterol), hyperinsulinaemia, hyperparathyroidism, sickle cell anemia, spinal cord injury, cirrhosis, choletasis, cholecystitis, somatostatin, down's syndrome, wilson's disease and sedentary lifestyle [73,74]. All these conditions are risk factors for the metabolic syndrome, of which gallstone disease is deemed as just another complication [75-85]. The consumption of the high calorie diet that is more common in the West is clearly a key factor in gallstone disease. Indeed, gallstone composition has changed over the past decades in East Asian countries, with a prominent increase in the prevalence of cholesterol gallstones, possibly because dietary habits have become more unhealthy [86,87]. However, there is still little agreement about the risk of specific dietary components for gallstones [88]. The difficulty in estimating the ingestion of specific dietary constituents by individuals could account for the large variability in data for humans [74]. Studies on the association between total fat intake and risk of cholesterol gallstone disease have reported either positive [89] or non-significant [90] conclusions. A high intake of cis-unsaturated fats was associated with a lower risk for gallstone disease in men [91] Additional dietary factors associated with gallstone disease are cholesterol, highly refined carbohydrates, alcohol, and dietary fibre [74,92-96].

Protective Factors

Diet not only is the risk factor for gallstone disease but a protective factor as well [97-117]. In an experimental study in gallstone patients, vitamin C supplementation (2 g per day for two weeks) had induced changes in bile composition and prolongation of nucleation time, suggesting that vitamin C supplementation may also influence the conditions for cholesterol crystal formation in humans [97]. Other epidemiological studies report similar results [98-100]. A small case-control study had found an association between lower dietary intake of ascorbic acid and gallbladder disease in women, but not in men [98]. Thus, the association between ascorbic acid status and cholelithiasis has been reported only in women, and may be the result of a biological interaction between ascorbic acid status and sex hormones [98 – 100]. However, these findings may also reflect the lower prevalence of gallbladder disease among men.

Coffee affects several hepatobiliary processes that are involved in cholesterol

Table-1: Distribution of gallstone patients by age and sex in different ethnic populations.

Population	Age (years)	Male %	Female %	Male : Female
Mexican–American [45]	20 – 39	2.6	13.8	1 : 5.3
1982 – 1984	40 – 59	9.7	26.4	1 : 2.7
(n = 1380)	60 – 74	15.5	44.4	1 : 2.9
Puerto Ricans [46]	20 – 39	2.0	9.0	1 : 4.5
1982 – 1984	40 – 49	3.3	21.2	1 : 6.4
(n = 582)	60 – 74	11.1	12.1	1 : 1.1
	20 – 29	2.3	2.5	1 : 1.1
Rome, Italy [47]	30 – 39	2.0	5.9	1 : 3
1981 – 1982	40 – 49	6.7	10.9	1 : 1.6
(n = 2320)	50 – 59	14.7	17.8	1 : 1.2
	> 65	14.4	25	1 : 1.7
	20 – 29	-	3.9	-
Bristol, England [48]	30 – 39	-	6.4	-
1987 – 1989	40 – 49	4.7	6.5	1 : 1.4
(n = 1896)	50 – 59	7.5	14.2	1 : 1.9
	60 – 69	11.5	22.4	1 : 1.9
	15 – 25	0	12.7	0
	25 – 34	4.4	73.2	1 : 16.6
Pima Indian [49]	35 – 44	11.1	70.8	1 : 6.4
1967 – 1968	45 – 54	31.9	75.8	1 : 2.4
(n = 596)	55 – 64	66.3	62.0	1 : 0.9
	> 65	67.8	89.5	1 : 1.3
	0 – 19	1.0	0	0
	20 – 29	1.0	3.0	1 : 3
Okinawa, Japan [50]	30 – 39	2.5	3.5	1 : 1.4
1984	40 – 49	2.0	3.0	1 : 1.5
(n = 2727)	50 – 59	1.5	4.0	1 : 2.7
	60 – 69	4.5	9.0	1 : 2
	> 70	15.0	9.5	1 : 0.6
	20 – 29	1.3	4.4	1 : 3.4
United States [51]	30 – 39	1.1	5.2	1 : 4.7
1988 – 1991	40 – 49	5.9	8.2	1 : 1.4
(n = 14,000)	50 – 59	7.3	11.9	1 : 1.6
	60 – 74	17.2	16.4	1 : 10
	< 14	1.6	0.5	1 : 10
	15 – 29	11.8	15.5	1:4.3
Hyderabad, Pakistan [67]	30 – 44	27.9	39.0	1:4.6
1999 – 2001	45 – 59	32.5	31.6	1:3.2
(n = 2066)	60 – 74	21.9	11.2	1:1.7
	≥75	4.1	2.1	1:1.7

*(Prepared after review of papers [45-50,67]).

gallstone formation. Coffee components stimulate cholecystokinin release [101], enhance gallbladder motility [101,102], inhibit gallbladder fluid absorption [101], decrease cholesterol crystallization in bile [103], and perhaps increase intestinal motility [104]. Moreover, diterpines present in coffee may down-regulate the hepatic low density lipoprotein receptors [105] and decrease 3-hydroxyl-3-methylglutaryl Co-A reductase activity [106]. Thus, metabolic studies suggest that coffee consumption influence gallstone formation [101, 107]. Epidemiological studies are not conclusive in this respect; some studies have shown a positive association between coffee intake and risk of gallbladder disease [108,109]. It is important to consider the possibility that the observed relationship between coffee intake and gallstones may be owing to a coffee avoidance by individuals with symptomatic disease or due to the existence of upper gastrointestinal symptoms related to both coffee use and gallstones.

Several epidemiological studies have indicated a reduced risk for gallstones in

subjects with moderate alcohol consumption [31,36,110-112]. Alcohol lowers bile cholesterol saturation with the result of a reduction in cholesterol gallstone formation. A protective effect of alcohol against gallstones has also been explained by an increased conversion of cholesterol to bile acids and by alterations in the type of bile acids undergoing enterohepatic circulation [112-114]. In addition, it has been shown that low plasma high density lipoprotein (HDL) cholesterol concentrations increase the risk for the formation of cholesterol stones [115]. Therefore, increase of HDL cholesterol plasma levels, induced by moderate alcohol consumption [116], may reduce the risk of gallbladder disease. In contrast, alcoholism is a major risk factor for the development of liver cirrhosis, which on its own is associated with pigmented gallstones [36].

Nuts are rich in several compounds that may protect against gallstone disease. The association between nut intake and cholecystectomy was examined by Tsai et al. in a large cohort of women [117]. They studied nut (peanuts, other nuts, and peanut butter) consumption in relation to the risk of cholecystectomy in a cohort of 80,718 women from the Nurses' Health Study who were 30-55 y old during 1980 to 2000 and had no history of gallstone disease. During 1,393,256 person-years of follow-up from 1980 to 2000, they documented 7831 cholecystectomies. After adjustment for age and other known or suspected risk factors, women who consumed > or =5 units of nuts (1 unit = 1 oz or 28.6 g nuts)/wk (frequent consumption) had a significantly lower risk of cholecystectomy (relative risk: 0.75; 95% CI: 0.66, 0.85; P for trend < 0.0001) than did women who never ate nuts or who ate <1 unit/mo (rare consumption).

A large number of epidemiological studies have shown that insoluble fiber intake is inversely associated to gallbladder disease [61,118,119]. Fiber may protect against gallstone formation by speeding intestinal transit and reducing the generation of

Table-2: Major factors influencing gallstone formation [69-96].

Independent	Increasing age
	Female gender
	Race
	Family history
Dietary	High calorie
	Low fibre
	Low cis-unsaturated fats
	High refined carbohydrates
Life style	Low grade physical activity
	Prolonged fasting
	Rapid weight loss
	Pregnancy and parity
	Oral contraceptives
Associated conditions	Metabolic syndrome
	Obesity
	Diabetese mellitus
	Hyperinsulinism
	Hyperparathyroidism
	Sickle cell anemia
	Spinal cord injury
	Cirrhosis
	Cholestasis
	Cholecystitis
	Somatostatin
	Down's syndrome
	Estrogen replacement therapy
	Gallbladder or intestinal stasis, or both
Protective Factors	Ascorbic acid
	Coffee
	Alcohol
	Nuts
	Fibers
	Buckwheat protein

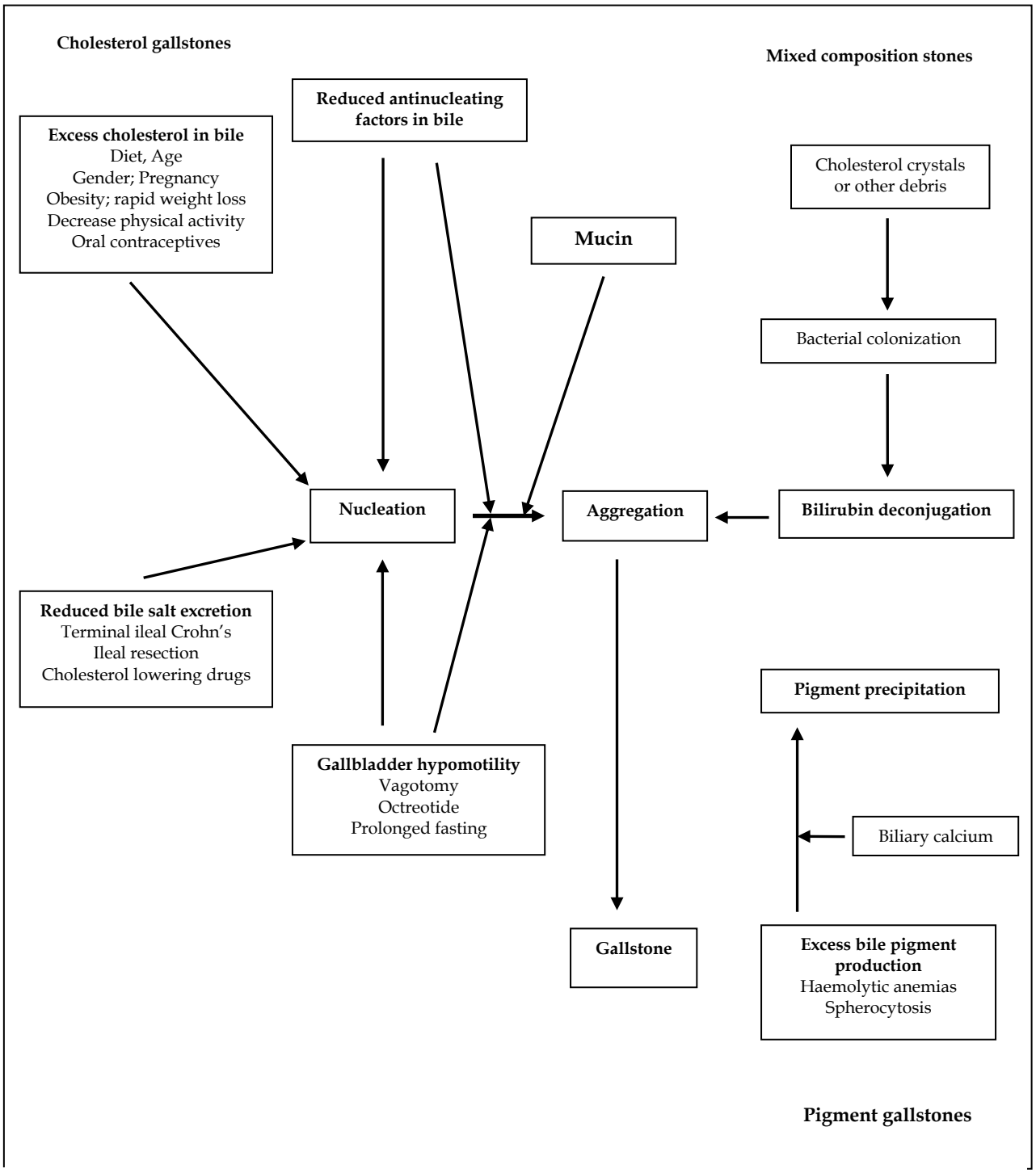
*(Source: [22]).

Fig. 1: Gallstones vary from pure cholesterol (white), through mixed, to bile salt predominant (black).

secondary bile acids such as deoxycholate [118-120], which has been associated with

increased cholesterol saturation of the bile [121,122].

A study with hamsters demonstrated that buckwheat protein has strong gallstone-preventive and cholesterol-lowering activities in plasma and gallbladder. It further suggests that these effects of Buckwheat protein are mediated by enhancing bile acid synthesis and faecal excretion of neutral and acidic steroids. Buckwheat protein might be useful for the treatment of both hypercholesterolemia and gallstone



(Configured after review of papers [27-44]).

Fig. 2: Pathogenesis of cholesterol, pigmented and mixed composition gallstones.

formation. Because buck wheat protein contains higher amounts of amino acids such as arginine and glycine than do casein and SPI [123,124], further study is required to examine whether these components relate to the effects of buck wheat protein.

CONCLUSIONS

Gallstone disease is a prevalent and costly disease. It has emerged as a complex disorder, involving the liver, gallbladder, and intestine. In spite of numerous well-defined risk factors for gallstones, the growing global epidemic of obesity and metabolic syndrome will probably increase rate of gallstone disease worldwide.

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