New Insight into Genetic and non genetic Pathogenic Mechanisms Underlying Gallstone Formation

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Abstract

Background: 10–20% of the population in Europe carries gallbladder stone. Many gallstones are asymptomatic, but symptoms and severe complications occur in more than 40% of patients above the age of 40 years, necessitating laparoscopic cholecystectomy. The cholelithiasis prevalence is even higher in most Hispanic populations of Central and South America, and in American Hispanics with native American ancestry. Overall, gallstone disease represents a serious load for healthcare systems; annually, an estimated 700,000 and more than 190,000 cholecystectomies are done in the United States of America and Germany respectively. Also, the average of the prevalence was 4-12% in Middle Eastern countries.

Purpose of review: to highlight the role of genetic and non genetic risk factors for gall stone formation. These highlights are extrapolated from recently published and well respected studies and systematic reviews.

Conclusion: causes, mechanisms of cholelithiasis and its correlation with the pathogenesis of related diseases are discussed and reviewed

Keywords: Gallstone Formation, Genetic, Epigenetic

INTRODUCTION

Biliary stone disease is widespread in western developed countries, where 15% of adults carries gallstones [1]. In European countries, gallstones are among the most frequent reasons for gastrointestinal disease hospitalisation. [2]. Moreover, gallstone disease is expensive to treat, particularly when symptoms or complications arise [1].

Biliary stone disease is a common digestive system condition. In the early stages, gallstones are asymptomatic in about 75% of patients. Gallstones may produce symptoms including nausea, epigastric colic, diarrhoea, anorexia, etc. when they form. Gallstones may eventually move and cause potentially fatal side effects include cholangitis, acute cholecystitis, and biliary pancreatitis [3]. Cholecystectomy is necessary at this time. Yet, this therapeutic approach has drawbacks that may substantially jeopardise a patient's health and impair his general quality of life [4].

Gallstone disease is predisposed by both changeable and unmodifiable factors, including as age, female gender, race, and lithogenic (LITH) genes. Gallstones are mostly made of cholesterol in 75–80% of instances in Western nations, and they are frequently linked to broader systemic problems. [6].

Gallstone production was thought to be accelerated by five variables. They include hereditary components, elevated hepatic cholesterol secretion (leading in supersaturation of bile with cholesterol), components that encourage the formation of cholesterol crystals and solid

cholesterol crystals, gallbladder dysmotility, and components from the intestine. [5].

Anatomical considerations:

The biliary tract refers to the series of ducts via which the bile produced and expelled by the liver travels as it makes its way to the duodenum, the first section of the small intestine. The biliary tract, a typical feature of most mammals, has several small branches that converge to form the common bile duct, which is frequently referred to as the biliary tree. The portal triad is made up of the bile duct, the portal vein, and the branches of the hepatic artery. In the other two channels, bile flows in the opposite direction from the direction that the blood flows **[7]**.

Usually referred to as the biliary system or tract, this system can also be referred to as "hepatobiliary" when only the liver and bile ducts are involved. Generally speaking, the term "biliary tract" refers to all of the ducts, organs, and structures involved in the generation, storage, and secretion of bile [7]**.**

Bile canaliculi that lead to the Canals of Hering that lead to the intrahepatic bile ductule (in portal tracts or triads) that leads to the interlobular bile ducts that lead to the left and right hepatic ducts.

The common hepatic duct, which is made up of the left and right bile ducts, joins with the gall bladder's cystic duct before leaving the liver. They come together to produce the pancreatic duct and common bile duct (CBD). Then enter the duodenum through the Vater's ampulla [7].

The gall bladder:

Underneath the right lobe of the liver, which appears grey-blue in life, is where the gallbladder, a hollow cyst, is located [8]. Adult gallbladders typically measure 7 to 10 centimetres (2.8 to 3.9 inches) in length and 4 centimetres (1.6 inches) in breadth when fully inflated. About 50 millilitres are available in the gallbladder [8].

The fundus, body, and neck are the three components that make up the gallbladder. The globular base that is angled to face the abdominal wall is known as the fundus. The body is embedded in a groove on the surface of the liver's right lobe. The neck narrows to become continuous with the cystic duct, which forms the biliary tree's fusion with the hepatic duct [8].

Several layers make up the gallbladder wall. The deepest layer of the gallbladder wall is lined by a single layer of columnar cells that resemble the intestinal absorptive epithelium in appearance and feature a brush border known as microvilli. Lamina propria, a muscle layer, an outer perimuscular layer, and serosa are present below the lining epithelium. The muscularis mucosa is absent from the gallbladder, and the muscular fibres are not organised into discrete layers like they are in the intestinal system [8]. The lamina propria is a thin layer of connective tissue that lies beneath the mucosa, the inner layer of the gallbladder wall. The mucosa is made up of a single layer of columnar cells with microvilli, which are tiny hair-like attachments on the cells. Rugae, or little outpouchings formed from the mucosa, are folded and corrogated [8].

Under the mucosa, there is a layer of muscles. This is made of smooth muscle, which does not have distinct layers and has fibres that randomly sit in longitudinal, oblique, and transverse directions. To release bile from the gallbladder, the muscle fibres in this area contract. The presence of Rokitansky-Aschoff sinuses, which are deep openings of the mucosa that can pass through the muscular layer and denote adenomyomatosis, is a unique characteristic of the gallbladder wall. An outer layer of connective and fat tissue covers the muscle layer [8].

Mechanism of bile formation:

Hepatocytes produce and exude bile, a physiological watery fluid. Mostly bile salts, phospholipids, cholesterol, electrolytes, conjugated bilirubin, and water make up its composition.

[9]. Hepatocytes produce and secrete bile, which is then altered by the cholangiocytes that line the bile ducts.

In addition to having an intact biliary duct tree, active transport networks inside hepatocytes and cholangiocytes are necessary. Hepatocytes initially produce bile by secreting conjugated bilirubin, cholesterol, bile salts, phospholipids, ions, proteins, and water into their canaliculi, which are tiny tubules that connect nearby hepatocytes and eventually unite to create bile ducts [9]. The primary bile secretory mechanism is the canalicular membrane of the hepatocyte, which is made up of the cytoskeleton of the hepatocyte, carrier proteins, and intracellular organelles. Bile acids and ions are transported via the carrier proteins contained in the canalicular membrane. Molecules are actively pumped into bile by transporter proteins embedded in the canalicular membrane using energy to overcome concentration gradients. Electrochemical and osmotic gradients are produced by this active transport. As a result, water follows conjugated bile salts when they enter the canaliculus due to an osmotic gradient. Passive diffusion of inorganic ions like sodium is made possible by the electrochemical gradient. The entry of conjugated bile salts into the biliary canaliculus is the most efficient bile formation promoter. A total of 600 ml of bile flow through the body each day, 75% of which comes from hepatocytes and 25% from cholangiocytes. About 225 ml per day of the hepatocyte portion of bile flow is dependent on bile salt, and the other half is independent of bile salt. Glutathione and bicarbonate are examples of osmotically active solutes that encourage bile salt-independent bile flow [10].

Formation of bile involves two steps the first is the transport through the hepatocyte to be expelled across the canalicular membrane facing the biliary compartment, and the second is the uptake of bile acids and ions from plasma across the basolateral (sinusoidal) membrane facing the blood compartment [9].

The active transporter protein sodium-potassium ATPase on the basolateral membrane of the hepatocyte keeps gradients of sodium and potassium in place. An electrochemical gradient is created because the cell only receives two potassium ions while releasing three sodium ions [9]. While the sodium gradient strengthens the sodium-dependent taurocholate cotransporter protein, the electrochemical gradient created across the hepatocyte membrane promotes the uptake of positively charged ions. This transporter permits conjugated bile acids to enter the system. The organic anion transporter protein, however, is not dependent on sodium for the importation of organic anions. The sodium-taurocholate cotransporting protein, ion exchangers that control pH like the sodium-hydrogen exchanger and the sodium-bicarbonate cotransporter, organic anion and cation transporters, and non-esterified fatty acid transporters are just a few of the transporters embedded in the basolateral surface of the hepatocyte [9].

The majority of the transporter proteins in the hepatocytes' canalicular membrane belong to the family of ATP-binding cassette proteins. Actively carrying chemicals and enzymes into the bile are these proteins. Bile salt export pump (BSEP), multispecific organic anion transporter (MRP2), multiple drug resistance 1 and 3 (MDR1 and MDR3), ATP dependent transporter of organic cations, ATP dependent phospholipid transporter (flippase), and canalicular bicarbonate transporter are some of the pump proteins that make up this system. In addition to enzymes like alkaline phosphatase, the canalicular membrane transporters aid in pumping chemicals into the bile against concentration gradients. Moreover, there are microfilaments that constrict in order to promote bile secretion through the canaliculi. The canalicular membrane only covers 1% of the hepatocyte's surface area [11].

The transport proteins anchored in the apical canalicular region of hepatocytes are the primary regulators of bile flow and bile composition. In order to pump organic solutes into bile despite gradients of high concentrations of approximately 1:100 to 1:1000 compared to their concentration in plasma, the majority of these canalicular membrane transporters, which are

members of the ABC superfamily, must use ATP [12].

They are composed of the P-glycoprotein MDR1 (ABCB1), which transports organic cations; Floppase MDR3 (ABCB4) transfers phosphatidylcholine to the canalicular membrane's outer domain; The MRP2 [multispecific organic anion transporter (ABCC2)] pumps a number of medications and other chemical conjugates as bilirubin digucuronide; the bile salt export pump, (BSEP, *ABCB11*) which is bile salts transporter; the breast cancer resistance protein (BCRP, ABCG2), hetermeric transporters (ABCG5 and ABCG8) excrete cholesterol and plant sterols into bile [9].

Phosphatidylcholine (PC) and cholesterol make up the majority of the lipid components in bile. Having values between 97 and 320 mg/dL and 140 to 810 mg/dL, respectively. Although the canalicular membrane also contains phosphatidylethanolamine, sphingomyelin, and phosphatidylserine, PC represents nearly all biliary phospholipids in bile A canalicular floppase (MDR3 in humans) is required for PC secretion, which also depends on bile salt excretion.

There are two hypothesized methods for how PC is expelled into bile. The first is that PC enters vesicles or cytosolic transport proteins that attach to the canalicular membrane, where it is subsequently flipped to the outer leaflet by MDR3. Bile salts discharged into the canalicular lumen may directly increase PC extraction because the accumulation of PC on the outer side of the canalicular membrane is intrinsically unstable. According to a different explanation, bile salts operate to destabilise PC microdomains that have accumulated on the outside leaflet, causing vesicles to first bud and then pinch off into bile. These hypotheses account for the findings that MDR3 and bile salts are essential for phospholipid excretion [9].

Although the mechanism by which the heteromeric ABC transporters ABCG5/G8 result in the extrusion of cholesterol is still unclear, evidence suggests that this process requires micelle-forming bile salts rather than other cholesterol receptors such high-density lipoprotein (HDL) [13].

Whereas Nieman-Pick-C2, a cholesterol-binding protein produced by the biliary system, enhances biliary cholesterol secretion by boosting ABCG5/G8-mediated cholesterol transport, Nieman-Pick C1-like 1 (NPC1L1) protein on the canalicular membrane inhibits cholesterol excretion in bile [14]. It is possible that hepatic NPC1L1 regulates cholesterol homeostasis by reducing NPC2 synthesis [15].

The most important risk factor for gallstone formation is thought to be increased biliary cholesterol release as well as cholesterol supersaturation of the bile. Almost 2/3 of the daily intestinal cholesterol input (800–1000 mg) in humans is eliminated through biliary cholesterol excretion, which is carried out by the canalicular transporters ABCG5/G8. An additional 300 mg is obtained through food [16].

Mechanism of gallstone formation:

Age, female gender, race, and lithogenic (LITH) genes are unmodifiable risk factors for gallstone disease. Modifiable risk factors include obesity, insulin resistance, physical inactivity, and other diseases. Gallstones are mostly made of cholesterol in 75–80% of instances in Western nations, and they are frequently linked to broader systemic problems and the rest are pigment stones [17].

Gallstone development is not caused by a single risk factor; instead, interrelated disorders are critical in the development of cholesterol gallstones: Gallbladder dysmotility, genetic factors, hepatic hypersecretion of cholesterol, rapid phase transitions of cholesterol in bile, and altered gut microbiota are some of the other factors. Intestinal factors include cholesterol absorption, slow intestinal motility, and altered gut microbiota [18].

Genetic factors:

The Swedish Twin Registry study on 43 141 twin pairs born between 1900 and 1958 presented for the first time conclusive evidence for the role of genetic variables in humans [19]. Around 25% (95% confidence interval (CI) = 9%-40%) of the phenotypic variation among twins was caused by genetic variables, 13% (95% CI = 1%-25%) by common environmental factors (such as childhood food), and 62% (95% CI = 56%-68%) by individual environmental factors [19].

The most significant gallstone risk factor is cholesterol supersaturation of bile. The ATP-dependent hemitransporters ABCG5 and ABCG8, which are enmeshed in the hepatocanalicular membrane of the hepatocyte, pump hydrophobic sterol compounds into bile [20].

In mixed micelles and vesicles made of bile acids and phosphatidylcholine, found in hepatic bile, cholesterol is solubilized [21]. The phosphatidylcholine translocator ABCB4 and the bile salt export pump ABCB11, respectively, allow these lipids to enter the bile [20]. When the ratio of biliary cholesterol to bile salt and/or phosphatidylcholine is upset, mixed micelles can no longer properly absorb cholesterol, and cholesterol will precipitate.

In humans, a variation of the hepatobiliary cholesterol transporter ABCG8 (p.D19H) was found to be the most significant genetic risk factor for the development of gall stones [22]. The final transport protein is changed from aspartic acid to histidine as a result of the mutation, which causes the nucleotide guanine to be replaced by cytosine at position 55 (c.55G>C) (p.D19H). The ABCG8 gene's p.D19H variation is carried by around 5% of Europeans. The genetic link has so far been confirmed in many international cohorts, including those from China [26][27], India [25], Sweden [19], and Germany [22]. Hence, this genetic variation constitutes a widespread risk factor for gallstones in the world [24].

Further GWAS meta-analysis susceptibility loci for gallstone disease were found, all of which carry minimally elevated risk. These comprise a sulfo-conjugation enzyme for bile salts and cholesterol 7-hydroxylase, the rate-limiting enzyme for the manufacture of bile salts (SULT21) [28]. Besides these frequent variations, it has been shown that rare mutations in the ABCB4, ABCB11, CFTR (cystic fibrosis transmembrane conductance regulator, also known as ABCC7), or the CYP7A1 gene might result in gallstones through impairing bile production and composition.

NPC1L1 is responsible for absorbing cholesterol from the intestine. According to a Danish study involving 67 385 members of the general population, NPC1L1 gene variations are linked to lower plasma LDL cholesterol concentrations, which protect against ischemic vascular illnesses, but also to a higher incidence of biliary stones [29]. Another study on the Chinese population discovered that symptomatic gallstone carriers had a considerably greater minor allele frequency of the p NPC1L1 polymorphism g.1679C>G (rs2072183) than did healthy controls. Moreover, this modification was related to decreased hepatic NPC1L1 mRNA expression, which brought to cholesterol supersaturation [30].

Gallstone sufferers in a particular subgroup who have low phospholipid-associated cholelithiasis (LPAC) syndrome. Cholelithiasis at a young age (40 years), concomitant gallbladder, bile duct, and/or intrahepatic cholesterol gallstones, and recurrence of biliary symptoms after cholecystectomy are the hallmarks of LPAC syndrome [31]. LPAC syndrome is one of the phenotypic spectrum of ABCB4 deficiency, which also results in severe cholestatic liver disorders in children, and is brought on by mutations of the ABCB4 gene [20].

Bile's altered lipid components:

Gallstones made of cholesterol form when micelles and vesicles cannot dissolve the cholesterol in supersaturated bile, which leads to the precipitation of solid cholesterol crystals mostly from

multilamellar vesicles [32].

Insulin resistance, which increases 3-hydroxy-3-methylglutaryl coenzyme A reductase activity, increases the risk of cholesterol gallstone formation and turning on the genes that cause cholesterol secretion: both ABCG5 and ABCG8 [34]. Gallstone prevalence is likely to be high in diabetes patients due to these molecular pathogenic pathways [35], as well as a condition called gallbladder hypomotility and autonomic neuropathy [36]. Because oestrogen increases oestrogen receptor and the G protein-coupled receptor 30 while lowering bile acid production, women get more gallstones than men do [37,38].

Nuclear receptors such as the Farnesoid X receptor (FXR) and liver X receptor (LXR) function as bile acid sensors and regulate crucial processes of cholesterol and bile acid metabolism. FXR expression is impacted by hepatic insulin resistance [39], and because hepatic ABCG5 and ABCG8 are activated, biliary cholesterol release is increased when LXR is active [40]. Humans can also express ABCG8 differently; for example, twins with the homozygous or heterozygous ABCG8 D19H genotype have a higher risk of gallstone disease [41]. Moreover, the ABCG5 Q604E polymorphism was linked to the features of the insulin resistance syndrome in men [42].

Biliary aquaporins may have an impact on the function of bile concentrating (AQPs) [43]. According to Asai et al research [44], cholesterol gallstone development in the animal model is enhanced by hepatic levels of the transcription factor hypoxia-inducible factor 1 subunit (HIF1A). Suppression of hepatic AQP8 can have an impact on decreased water secretion from hepatocytes. The same study also revealed that human gallstone patients with and without nonalcoholic liver steatosis have activated HIF1A.

Intestinal cholesterol absorption change:

With varying degrees of effectiveness, the small intestine absorbs both dietary and released biliary cholesterol [45]. The equilibrium between the influx and efflux of intracellular cholesterol molecules across the brush border membrane of the enterocyte determines the expression of sterol transport proteins, which are key intestinal components that are regulated by numerous genes [45].

High intestinal cholesterol absorption efficiency and high cholesterol lithogenic diets are two separate risk variables that affect cholesterol gallstone development in mice [46].

The aberration could be caused by altered cholesterol transporters expressed on enterocytes' brush boundary membrane. With the different forms of the Niemann-Pick type C1-like protein (NPC1L1) transporter, cholesterol uptake in animal models is hampered. [48]. By lowering intestinal cholesterol absorption and lowering biliary cholesterol saturation, ezetimibe, a powerful NPC1L1 selective inhibitor, lowers cholesterol absorption through the enterolymphatic circulation of cholesterol. So, even when given a lithogenic diet, ezetimibe-treated gallstone-prone animals do not develop cholesterol gallstones. [49].

Moreover, patients with gallstones exhibit greater or unaltered de novo production of cholesterol and markedly decreased cholesterol absorption [50]. In risk groups, the development of gallstones may be preceded by this metabolic profile. In addition, insulin resistance contributes through influencing the homeostasis of cholesterol. It increases cholesterol production while decreasing intestinal cholesterol absorption, and the impact is not reliant on obesity [50].

Included in maintaining cholesterol homeostasis is osteopontin (OPN), a soluble cytokine and matrix-associated protein that is found in a variety of tissues and bodily fluids [51]. Due to decreased intestine NPC1L1 expression and intestinal cholesterol absorption, Lin et al study showed that OPN knockout mice are unaffected by a lithogenic diet [52].

Microbiota in the gut:

The human gastrointestinal tract is home to 10^{14}–10^{15} bacteria, which are thought to outnumber host cells by a factor of 10 to 1 [58]. An estimated $3.8•10^{13}$ bacteria are present in a 70 kilograms male overall [59]. More than 1000 distinct bacterial species make up the gut microbiota [60], and although they vary greatly between populations, a core microbiota made up of only several of these bacterial species may be found in large cohorts of healthy people.

Concern over the microbiota and its correlation with disorders of the gut, especially those of the liver and biliary system, has grown recently [61].

It's important to consider how the gut flora may affect the aetiology of cholesterol gallstones.

By comparing the bacterial composition of the gut, bile, and gallstones from 29 patients with cholesterol gallstones to the gut of 38 healthy participants, Wu et al [53] studied the composition of these microbial communities by examining 299 217 sequences of the 16S ribosomal RNA gene from bacteria. Proteobacteria, a phylum of gut bacteria, were found to be significantly up, whereas Faecalibacterium, Lachnospira, and Roseburia species were found to be significantly down.

Increase in the content of the hydrophobic and lithogenic secondary bile acid deoxycholate is explained by the presence of Gram-positive anaerobic bacteria with higher 7-dehydroxylation activity in the cecum of gallstone patients, according to results of additional research [54].

Patients with a history of cholecystectomy had lower levels of the genus Roseburia spp. than do controls. Moreover, the uncultivated genus Oscillospira spp. enriches the microbiota of gallstone sufferers. While the phylum Bacteroidetes exhibits the reverse effect, this last genus has a positive correlation with the concentration of the secondary bile acids and a negative correlation with the primary bile acids [55].

In their work on mice, Wang et al reported dysbiosis in the form of decreased Firmicutes levels and a decreased Firmicutes to Bacteroidetes ratio [56].

The microbiota can be impacted by environmental toxins that are consumed with food. This action could affect the pathogenetic causes of gallstones. An aberrant gut microbiota can result from an 8-week exposure to organochlorine pesticides such dichlorodiphenyldichloroethylene (P,p'-DDE) and -hexachlorocyclohexane, according to Liu et al [57].

dysmotility of the gallbladder:

Gallbladder dysmotility, another risk factor for the development of cholesterol gallstones, is connected to a number of clinical disorders [62,63,64].

Gallbladder emptying in patients with gallstones was delayed and had an expanded postprandial residual volume, according to research on the relationship between fasting and postprandial states [64,65].

The following abnormalities result from long-term supersaturation of cholesterol in bile: absorption of cholesterol into the muscular layer of the gallbladder, decreased back diffusion of cholesterol into bile, and inhibition of action potentials and Ca2+ ions [67].

Moreover, research on animals revealed that restricting the buildup of triacylglycerol in the gallbladder wall boosts its contractile strength and inhibits the development of gallstones [68].

Inadequate smooth muscle relaxation and contractility are thought to be related to lipotoxicity of gallbladder [69,70]. Moreover, high cholesterol absorption may lead to cell proliferation and inflammatory cell infiltration in the gallbladder mucosa and lamina propria [64,73]. Gallbladder dysmotility is a risk factor for gallstone recurrence even after successful extracorporeal shock-wave lithotripsy and/or oral bile acid dissolution therapy [74,75], as it provides ample time for the production of cholesterol nuclei and gallstone growth [76,77].

Reduced postprandial gallbladder emptying and accelerated cholesterol precipitation, crystallisation, and gallstone development are observed in CCK mutant animals fed a lithogenic diet. In addition, mice had larger gallbladder volumes when they weren't eating, longer transit times through their intestines, and better intestinal cholesterol absorption from supersaturated bile. Similar results are produced by the CCK-1R antagonist devazepide [78,79].

Cholecystokinin receptor genetic variations and a decrease in their density may be linked to cholesterol cholelithiasis in humans [80,81].

Patients with gallstones have significantly less interstitial cells of Cajal (ICC), enteric glial cells, mast cells, and other key cell types controlling gallbladder intrinsic innervations [82,83].

Gallbladder dysmotility, which causes cholesterol gallstones to form, involves the cyclic changes in gallbladder size that occur when fasting and during the postprandial emptying and refilling phase. Good gallbladder relaxation, mediated by duodenal release of vasoactive intestinal peptide and human fibroblast growth factor 19 protein, is necessary for postprandial refilling (FGF19; FGF15 in mice) [84]. With approximately 23-fold higher quantities in bile than in serum, FGF19 affects the ileum, cholangiocytes, and the gallbladder epithelium [85,86].

Bile acids must enter the terminal ileum and activate FXR before there can be an increase in FGF19 entering the portal circulation. Fibroblast growth factor receptor 4 (FGFR4) and its co-receptor β-klotho are subsequently activated by FGF19 [87]. This route promotes smooth muscle relaxation, which results in gallbladder replenishment before to the next meal [64,84].

The G protein-coupled bile acid receptor 1 (GPBAR-1) found in the gallbladder epithelium and smooth muscle [91] and which is stimulated by intraluminal hydrophobic bile acids [89] is another factor in the relaxation of the gallbladder wall. This effect is independent of FGF19 [90]. Gallbladder smooth muscle contraction is prevented by hydrophobic bile acids through stimulating GPBAR-1 receptors and opening an ATP-sensitive potassium channel [92]. The amount of the bile acid pool is less in GPBAR-1 knockout mice, and they respond to GPBAR-1 slowly and affected by dietary lithogenesis [90].

By interacting neurohormonal systems involving the liver and intestines, the gallbladder regulates the enterohepatic circulation of bile acids during periods of fasting [64,93]. Low amplitude small phasic contractions produced by vagal-motilin stimulation cause a 20–30% reduction in gallbladder volume compared to fasting. [94,95]. In contrast to healthy control participants, cholesterol gallstone patients may have altered fasting gallbladder motility [74] as a result of less effective propagating myoelectric complexes cycles and aberrant motilin release [64,96]. With faster bile acid recycling and enhanced bile acid pool hydrophobicity, the fasting motility deficit may increase the direct hepatic production of lithogenic bile to the small intestine [97].

DIETARY FACTORS AND LIFESTYLES:

It has been noted that the high caloric, low fiber and high lipid westernized diet increases the incidence of gallstone disease [98]**.** Gallstone disease was linked to high calorie, total fat, saturated, and monounsaturated fatty acid diets, according to a case-control research using questionnaires [99].

With a 7% increase in the prevalence of symptomatic gallstones with each unit increase in BMI, increased BMI per se constitutes as a well documented risk factor for gallstone disease (particularly in women) [100]. These modifications may have an impact on crucial stages in the aetiology of cholesterol gallstones, such as biliary cholesterol supersaturation [101] and gallbladder mucin production triggered by hypertriglyceridemia [102]. Additionally, individuals who are overweight and obese frequently experience gallbladder dysmotility, which results in

larger fasting gallbladder volumes and decreased postprandial gallbladder emptying, which causes gallbladder stasis, a condition that is known to increase the risk of developing gallstones [103,104].

Patients who are obese are more likely to develop gallstones after undergoing bariatric surgery, such as the Roux-en-Y gastric bypass (RYGB) technique [108,109], or while rapidly losing weight from very-low-calorie diets that contain less than 800 kcal per day [105-107].

The consumption of fast food at least once per week [100] and meat consumption [98] have been identified as new risk factors for the symptomatic development of gallstones, and these dietary factors also appear to have an impact on the likelihood of developing gallstone disease. Moreover, consuming a lot of sweet foods and refined sugars may put both men and women at risk for gallstone disease [110-112]. The mechanism entails hyperinsulinemia, elevated hepatic cholesterol synthesis, and cholesterol release into bile [113,114], which results in biliary cholesterol supersaturation [115]. These are the main pathogenic processes that lead to the development of cholesterol gallstones.

A significant ultrasonographic investigation in pregnant women [116] has demonstrated the link between a high carbohydrate and fructose intake and the development of gallstones. Compared to women in the lowest quartile, women in the top quartile of total carbohydrate intake were more likely to develop gallstones. An increased incidence of incident sludge/gallstones was associated with a high diet of fructose, but not sucrose, lactose, or galactose, and this association was unrelated to overall carbohydrate consumption [116].

Gallstone sufferers consume less fibre than healthy individuals [111], which may increase the chance of developing cholesterol gallstones. Deoxycholic acid and lithocholic acid, which are secondary (lithogenic) bile acids, are produced more frequently as a result of the process, which may also have an adverse effect on intestinal motility [117,118]. Consuming fats with an animal origin is also thought to have a harmful effect. Butter consumption and consumption of all visible fat on meat were both positively linked with cholelithiasis [119]. Gallstone disease and total and saturated fat intake have been linked in French individuals, according to research [120].

Since vitamin C facilitates the conversion of cholesterol into bile acids by liver 7-hydroxylation, it modulates the hepatic and biliary pathways of cholesterol homeostasis. The likelihood of developing cholesterol gallstones has been linked to a reduction in vitamin C consumption [121–123].

Gallstone incidence was reported to be higher in people who consumed more beans [124,125]. The mechanism suggests a rise in biliary cholesterol secretion and a drop in serum total and very low density lipoprotein cholesterol concentrations. The plant steroids saponins found in beans promote the production and crystallisation of biliary cholesterol [126,127].

Conclusion:

Identifying and understanding the pathogenic risk factors of gall stone formation pave the way for adopting certain measures for prevention of this prevalent and costly disease.

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