Chapter 2

Immunogenetic Basis of Cholecystitis

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/67365

Abstract

Cholecystitis is an inflammation of the gallbladder caused by many causes like stone that is cholesterol gallstone and sometimes the cause is due to bacterial infection also known as acalculous cholecystitis. The risk factors for this disease are female, 40, fatty, fair, aging, diabetes mellitus, pregnancy, oral contraceptive and the most common factor is the interaction between genetic and environmental factors. Genetic factors include human leukocyte antigens, ethnicity, race and single nucleotide polymorphism in genes involved in the synthesis of cholesterol, transport and excretion.

Keywords: cholecystitis, genetic, stone, HLA, ethnicity

1. Introduction

Cholecystitis is an inflammation of the gallbladder, originated from Greek word—*cholecyst* means "gallbladder," combined with the suffix *-itis* means "inflammation," means inflammation of the gallbladder, which occurs due to calculous in 90% of the cases and the rest 10% known as acalculous cholecystitis [1]. The most common presenting symptom is upper abdominal colicky pain frequently begins in the epigastric region that may radiate to the right shoulder and then localizes to the right upper quadrant of the abdomen associated with nausea and vomiting while acalculous cholecystitis may present with fever and sepsis only [2], jaundice may occur suggesting choledocholithiasis [3]. Immunocompromised patients and elderly patients may have vague symptoms that may not include fever or localized tenderness [4]. The pathogenesis of cholecystitis is blockage of the cystic duct with one or multiple gallstones form when substances in the bile form crystal-like particles. They can range from the size of a grain of sand to the size of a golf ball resulting in accumulation of bile and increased pressure within the gallbladder. Many factors contribute in the pathogenesis such as concentrated bile, increased pressure inside the gallbladder and secondary bacterial infection by

gut organisms, predominantly *Escherichia coli* and *Bacteroides* species irritate and damage the gallbladder wall, causing inflammation and swelling of the gallbladder. This leads to reduce normal blood flow to areas of the gallbladder, leading in cell death due to insufficient oxygen supply to tissues [5]. The importance of chronic inflammation of the gallbladder (chronic cholecystitis) and cholelithiasis is related to its association with gallbladder cancer [6]. Thus, it is important to deal with its etiogenesis.

2. Causes

Cholecystitis is a gallbladder inflammation, which is most commonly caused by gallstones, tumor or scarring of the bile duct [7]. The greatest risk factor for calculous cholecystitis is gallstones and the risk factors for gallstones include female sex, increasing age more than 60, pregnancy, oral contraceptives, obesity, diabetes mellitus, ethnicity like Native North American or Mexican American ethnicity, rapid weight loss and drugs like hormonal replacement therapy in women during menopause. Cholesterol gallstones, accountable for about 90% of gallstones, due to supersaturation of bile with cholesterol stand for a multifactorial disease with a significant genetic component (**Figure 1**) [8].

A genetic factor in the vulnerability to gallstones was recognized as early as 1937 [10]. These stones were formed due to interactions of lithogenic alleles of gallstone susceptibility genes in DNA and many environmental factors [11]. The genetic cause may be due to fibroblast growth factor receptor 4 (FGFR4) polymorphism, which is a genetic risk factor contributing

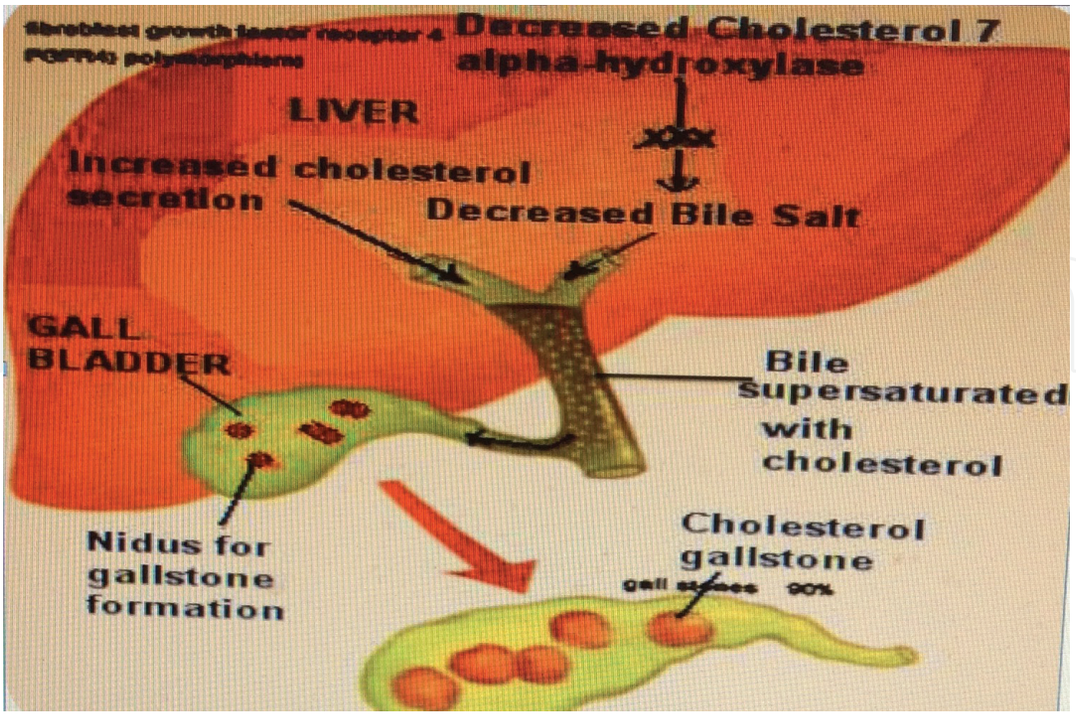

Figure 1. Formation of cholesterol gallstone [9].

to aggravation of gallstone disease by maintaining bile acid homeostasis by regulating the expression of cholesterol 7α-hydroxylase (CYP7A1). The Gly388Arg (G-388R) had a greater inhibitory activity against bile acid biosynthesis and polymorphism in it affects stabilization and activation of FGFR4 and overexpression of FGFR4, especially the G-388R mutant of FGFR4 that inhibits luciferase activity of CYP7A1 reporter [12]. Acalculous cholecystitis is related to conditions associated with biliary stasis such as critical illness, major surgery or severe trauma/burns, sepsis, long-term total parenteral nutrition, prolonged fasting, myocardial infarction, sickle cell disease, *Salmonella* infections, diabetes mellitus and patients with AIDS who have cytomegalovirus, cryptosporidiosis or microsporidiosis [13]. Genetic factors play an important role in causation of disease because around 50–70% of cholecystitis patients have a positive family history of the disease [14]. In addition to that, epidemiologic studies have showed that environmental factors and genetic elements are contributed in gallstone formation through many studies on twins, families and ethnicities with gallstone formation [15].

2.1. Genetic factor

Cholecystitis had been found in certain area of the world and had an epidemiological distribution raises an issue of genetic or chromosomal factors associated with it [16]. The frequency of diseases of the gallbladder, gallstones (cholelithiasis), cancer of the gallbladder and other biliary tract system diseases is more common in western countries (North America, Europe and Africa) [17]. This may be due to general response to some dietary or other environmental risk factor, suggesting a gene-environment interaction. The role of diet was attributed to the consumption of high-calorie, high-fat, low-fiber diets and insufficient exercise [18]. There was an epidemic of gallbladder disease among Amerindians and peoples genetically related to them [19]. The existence of this epidemic indicates a genetic basis of this disease. In addition to that, the prevalence of cholecystitis in geographically associated distribution may be related to genes of aboriginal Amerindian origin, the degree of Amerindian admixture. The person from New World genotype will do cholecystectomy by age 85 years and this constitutes about 40% in Mexican-American females and increased the risk of gallbladder cancer. Thus, genetic factor can be considered as Carcinogenic reason in New World peoples as any major environmental exposure [20]. The genetic effect in gallbladder diseases starts from chromosomal changes in gallbladder cells that leads to gallbladder cancer either acquired or inherent genetic instability in normal cells of the gallbladder causing mutational events that result in neoplastic transformation of normal cells and provide such cells with a selective growth over normal cells that leads to carcinoma of the gallbladder [21].The cause was due to loss of heterozygosity in the 3p, 8p, 9q and 22q chromosomal regions of cancer patients [22]. Other study demonstrated chromosomal aberrations were confined on chromosome 1's long arm and translocation from the long arm of chromosome 4 to the long arm of chromosome 6. These aberrations constitutes about 16.6% and may be due to environmental effects, infections and inflammation [16]. The frequency of gallbladder disease was increased in Eastern populations like China, this may be due to the diet of the Chinese in Taiwan is already Westernized and differences among genetic populations [23]. The effect of genetic factor in the development of acute acalculous cholecystitis was manifested by infection with Epstein–Barr virus and development of disease [24]. Other microorganism that causes acal-

culous cholecystitis is *Lactococcus garvieae* that is recognized as a freshwater fish bacteria, is now regarded as zoonotic microorganism in human. The genome sequence of *L. garvieae* is draft genome sequence of *L. garvieae* LG-ilsanpaik-gs201105, with a total genome size of 1,960,261 bp in 53 contigs and a 38.1% average G-C content [25]. These extracellular bacteria phagocytosed by antigen presenting cells like macrophages, dendritic cells and B cells that processed them and presented with Major histocompatibility complex class II molecules to T cells. Human leukocytes antigens (HLA) (**Figure 2**) is one of the genetic factor that cause cholecystitis, studies into the genetic characteristics of patients with chronic cholecystitis made the significance of hereditary load in the development of cholecystitis and to identify genetic markers (B (III) blood group), type Hp 1-1, HLA-A3, HLA-A30 and HLA-B5, and genetic protectors (O (I) blood group), HLA-B8 and HLA-B14 of the disease [26].

The class II molecule of HLA is a heterodimer consisting of two chains, an alpha (DRA) and a beta chain (DRB), both anchored in the membrane of the cell wall. HLA DRB1 plays a central role in the immune system by presenting peptides derived from extracellular proteins and the class II molecules are expressed in cell wall of antigen presenting cells B lymphocytes, dendritic cell and macrophages. The beta chain is approximately 26–28 kDa and is encoded by six exons. Exon 1 encodes the leader peptide; exons 2 and 3 encode the two extracellular domains; exon 4 encodes the transmembrane domain and exon 5 encodes the cytoplasmic tail. Within the DR molecule the beta chain contains all the polymorphisms of HLA that specifying the peptide binding specificities. Allelic variants of DRB1 are linked with many diseases [27]. Cholecystitis patients and control groups were typed for identifying the DRB1* alleles using DNA-based methodology (PCR-SSOP). Allele's frequencies of HLA-DRB1 for cholecystitis patients and control group. There was an increased frequency of HLA-DRB1*03:01 in patients with cholecystitis compared with healthy controls (p = 0.0442, odd ratio = 4.1111, 95% CI: 1.0372–16.2949); also there is an increase in the HLA-DRB1*13:01 in patients with cholecystitis while the control group did not have this allele, thus this allele is predisposing allele to diseases development. The highest frequencies belong to HLADRB1*03:01 and

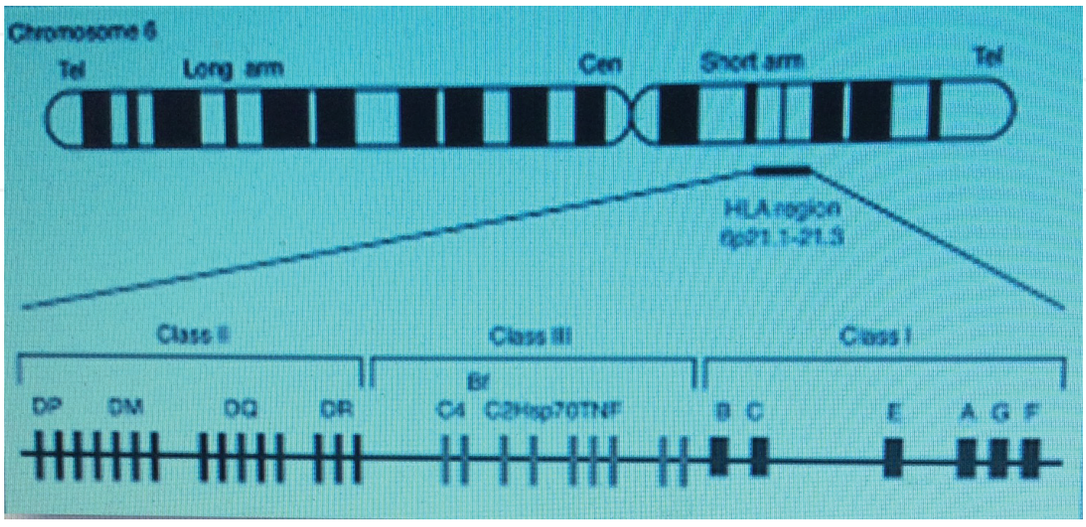

Figure 2. Major histocompatibility complex on chromosome 6: class I, class II and class III.

HLA-DRB1*13:01 that are 0.14 and 0.16, respectively. This demonstrated the role of chromosome 6 in gallbladder disease by HLA typing. Thus, HLA-DRB1*13:01 is significantly higher than control group [28]. In other populations, HLA A3, HLA A30, HLA B5, HLA B8 and HLA B14 are associated with this disease [29]. Human leukocyte antigens are important in determining immune response whether cellular or humeral. The HLA-DR antigen expression on macrophages and monocytes plays an important role in antigen presentation to T-helper lymphocytes [29]. In fact, these cells require both HLA-DR and exogenic antigens on the macrophage surface to initiate proliferation. Thus, HLA-DR is a major histocompatibility complex class II cell surface receptor that is up-regulated in response to signaling during an infection. Therefore, decrease of human leukocyte antigen-DR leading to increased gallbladder inflammation and sepsis [20]. The cholecystitis pattern of genotypic variability in an admixed population is a function of the gene frequencies of the original contributing parental populations, the number of loci involved in a trait of interest, the mating pattern relative to those loci and the amount of admixture between populations. Native peoples of the New World, including Amerindians and admixed Latin Americans such as Mexican-Americans, are highly susceptible to cholecystitis. This pattern differs from that generally associated with Westernization, which suggests a gene-environment interaction [30]. Among women with cholecystitis, the risk is highest among American Indians, followed by Hispanics, non-Hispanic whites and non-Hispanic blacks. Men differ from women by having lower risk in all ethnic groups and by having a similar prevalence between Hispanics and non-Hispanic whites. Genetic markers have not been identified that would explain differences in risk among ethnic groups. Patients with HLA typing haplotype HLAB*07 and DRB1*15 have a higher level of IgG4 in patients with primary sclerosing cholangitis [31]. Allele like HLA-DRB1*13:119 and 14:57 are either new alleles or ambiguous allele that assign with high number. According to IMGT/HLA, these two alleles occur in Native Indian.

Occurrence of genetic alterations is risk factors have been associated with gallbladder disease like cholecystitis, chronic inflammation of the gallbladder, congenital biliary abnormalities and polyps. Genetic predisposing factors associated with cancer of gallbladder like mutations in *KRAS*, *TP53*, *p16*/*CDKN2A*, microsatellite instability, overexpression of COX2, VEGF, hTERT and ERBB2 genes in gallbladder cancer (GBC) [32, 33]. Chronic inflammation of the gallbladder and biliary tract infections or irritation by gallstones and progression to invasive carcinoma, tracks at the molecular level, with tumor suppressor gene silencing by DNA methylation, together with global and gene-specific loss of methylation [34]. There are different studies about lesions' methylome and gene-specific promoter methylation alterations in the following genes (*APC*, *CDKN2A*, *ESR1*, *MCAM*, *MGMT*, *PGP9.5*, *RAR*β and *SSBP2*) of DNA of the patients with cholecystitis. The acquisition of hypermethylation at gene-promoter sites (p16, APC, methylguanine methyltransferase, hMLH1, retinoic acid receptor beta-2 and p73) may lead to loss of gene function and chronically inflamed gallbladder and cancer and this hypermethylation differ in different parts of the world [35]. In addition to that, aberrant methylation of 5′ gene promoter regions is an epigenetic phenomenon that is a main method for silencing of genes, which is absent in chronic cholecystitis, whereas it is present in gallbladder disease [36]. The methylation levels seem to play an important role in the progression of chronic cholecystitis without metaplasia to chronic cholecystitis with metaplasia [37].

2.2. Genetic cause of calculous cholecystitis disease

Gallstone disease is a very common biliary tract disease in the world. Gallstones are one of the most common and mainly costly digestive diseases in the developed countries. Geographic and ethnic differences in its occurrence imply that genetic factors influence risk of gallstone formation [14]. Its prevalence in the western countries was 48% [38], whereas in Asian ones was 5.9–21.9% [39]. It is a most common cause for cholecystitis, acute cholangitis and biliary pancreatitis. It is formed due to genetic-environmental factors interactions. Genetic factors that influence gallstone formation by its implication in different metabolic pathways, have been involved from linkage studies of twins, families study and ethnicities, it had been found that this disease is more common in siblings and other family members of affected persons than spouses or unrelated controls in a ratio 3:1 [40]. Twin studies have provided a clue into the genetic effect on disease development; the rates of this disease in monozygotic twins of both sexes were higher than in dizygotic twins [41]. This involves the genetic effects of multiple *LITH* genes of susceptible alleles that interact with environmental factors. The genetic defect either oligogenic (mutations in single genes) or polygenic (mutation in multiple genes) that affect the molecular pathophysiology of cholesterol gallstone formation, defect in the physical-chemistry of bile and the physiology of biliary lipid secretion [42–44]. One of these metabolic pathways defect is MDR3 which is the phosphatidylcholine translocator across the hepatocyte canalicular membrane because phospholipids are a carrier and a solvent of cholesterol in hepatic bile. Thus a defect in the MDR3 gene due to mutations involving a conserved amino acid region represents a genetic factor involved in the formation of cholesterol gallstone disease in adults and familial intrahepatic cholestasis type-3 that characterized by production bile acid-rich toxic bile that damages the intrahepatic bile ducts [45]. Other genetic pathway disease is caused by defects of canalicular secretion of bile salts. Most of bile salts were absorbed in terminal ileum while in the liver, there is a transporter at the basolateral sinusoidal membrane called sodium-dependent taurocholate transporter and the bile salt export pump at this membrane-mediated hepatic uptake and canalicular secretion of bile salts. When there is impairment in the bile flow leads to impairment in the metabolism of cholesterol and bile acids by expression of transporter proteins and enzymes of the cytochrome P-450 system. This stimulates or inhibits the transcription of genes encoding transporters and enzymes involved in their metabolism leading to a hepatoprotective dysfunction and familial intrahepatic cholestasis type-1 results from mutations in various genes encoding hepatobiliary transport proteins while type-2 results from mutations in the bile salt export pump gene [46]. There is other genetic defect that leads to cholelithiasis, which is a mutation in ABCB4 gene (adenosine triphosphate-binding cassette (ABC), subfamily B, member 4) a major genetic risk factor in a symptomatic and recurring form of cholelithiasis in young adults [47]. Pullinger et al. [48] showed that a deletion mutation in cholesterol 7 alpha-hydroxylase enzyme (CYP7A1) was related to hypercholesterolemia resistant to 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors that lead to a loss of enzyme function which results in decrease in bile salt synthesis. This ends in increase of bile stone formation and calculus cholecystitis. Other monogenic disorder is mutations in the ATP-binding cassette (ABC) 1 gene that leads to a defect in cellular cholesterol efflux ends in Tangier disease [49, 50]. Other cause was defect in splicing of cholecystokinin A receptor (CCK-1R) resulted in

non-functional receptor and stasis of bile in gallbladder [51]. Additional defect was mutations in the ATB7B gene leads to copper accumulation and Wilson's disease [52]. A genome-wide association (GWA) study of more than 500,000 SNP identified a coding variant rs11887534 (D19H) of the sterol transporters ABCG5/G8 on the canalicular membrane of hepatocytes as a risk factor for cholesterol gallstone development [10]. In addition to that, polymorphisms of the apolipoprotein (APO)-E (three allelic variants, e2, e3 and e4) e4 genotype is a genetic risk factor for cholelithiasis [53], Apo-B and the cholesteryl ester transfer protein are result in familial type III hyperlipoproteinemia (HLP III) [54].

Thus, in conclusion, there are a large number of genetic polymorphisms (SNPs) that causing calculus cholecystitis starting from cholesterol transporter [55], plasma transport [56], cholesteryl ester transfer protein [57] and cholesterol uptake [58], bile acid synthesis [59], transporter [60] and bilirubin excretion [61], mucin affect the formation of the gallstone genetically [62], gallbladder motility [63] and hormone receptor [64]. Thus, genetic study provided an insight toward the pathogenesis of the calculus cholecystitis.

2.3. Immunologic causes

The role of immune system on development of calculus and cholecystitis is manifested by cell-mediated immunity (Th1 cell) exerting its effect on formation of cholesterol gallstone and local inflammation [65]). It was first be confirmed by Lee and coworkers [66]. The proinflamatory cytokines had an effect on mucin production. Regarding immunoglobulins (particularly IgM and IgG), it had been found that they promote crystal nucleation [67]. This immune mechanism in the biliary system was altered due to the presence of multiple microbial flora [68] and other bacteria like enterohepatic *Helicobacter* spp. as *H. pylori* [69].This bacteria-induced disease through stimulation of adaptive immunity by Th1-mediated proinflammatory immune response and secretion of cytokines [70] and increased immunoglobulines production that alters mucin production [71]. In addition to that innate immunity also had an important role in defense mechanism against cholecystitis represented by Toll-like receptors by initiating and directing immune response to bacteria, lower expression of TLR4 in chronic cholecystitis in the glandular and luminal epithelium of gallbladder enhancing cholecystitis [72]. CXCL16 (membrane-bound molecule) was detected on gallbladder epithelia, CXCR6(+)/CD8(+) T cells and CXCR6(+)/CD68(+) macrophages were upregulated due to *E. coli* infection through Toll-like receptor 4. This is due to role of the scavenger receptor class A on macrophages that phagocytes *E. coli* followed by foamy changes and that bacterial infection causes the upregulation of CXCL16 in gallbladder epithelia, leading to the chemoattraction of more macrophages via CXCL16-CXCR6 interaction [73].

3. Conclusions

Inflammation of the gallbladder whether calculus or acalculous is a complex process mediated by genetic and environmental factors. Cholecystitis required a strong involvement of a genetic factor whether in the immune response infection against pathogen, formation of a

stone and defense mechanism against inflammation. Understanding the concept of genetic factor leads to a novel diagnostic tools, treatments and preventive measures.

Conflict of interest

The author confirms that there are no conflicts of interest.

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