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Genetic basis for cholecystolithiasis. Existing state of knowledge

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Abstract

Introduction and objective: The pathogenesis of cholecystolithiasis is not well recognized. It is postulated that coexistence of environmental factors with genetic factors in individuals predispose to this illness.
In this study the authors present the current state of knowledge about the pathogenesis of cholecystolithiasis and predisposing genetic factors such as: genes polymorphisms, genes expression and genetic mutations.
Abbreviated description of the state of knowledge: The obesity, the female sex, numerous pregnancies, diabetes, cirrhosis, type C hepatitis, coronary heart disease, long-term parenteral nutrition are well known risk factors. Also the polymorphisms in some genes are connected with cholecystolithiasis, for example: polymorphisms within *MUC1* and *MUC2* mucin genes, *ABCG8 D19H* gene encoding halftransporter. Mutated forms of some proteins such as: SLC10A2 (Solute Carrier Family 10 Member 2), increased expression of NPC1L1 protein (Niemann Pick C1 Like Protein 1) and ACAT2 (Acyl Coenzyme A-cholesterol Transferase), over expression of *SCP2* gene (Carrier Sterol Protein 2), the mutation of the *UGT1A1* gene (Uridine 5′-diphosphate-glucuronosyltransferase 1 A1) can predispose to the development of gallstones.
Summary: The incidence of cholecystolithiasis is constantly increasing. At present this disease constitutes the most frequent cause of surgical interventions in Europe, in the USA and in Australia. The lengthened life span, the rising percentage of obese individuals, suffering from diseases associated with the progress of civilization as well as the ageing of societies may influence on the development of cholecystolithiasis.

Key words

Cholelithiasis, Cholecystolithiasis, Cholelithiasis – genetics, Cholecystolithiasis – etiology, Genetic Predisposition to Disease – genetics

INTRODUCTION

Cholecystolithiasis is an illness consisting in coming into existence and the accumulation of deposits in the gall bladder [1]. According to epidemiological data, cholecystolithiasis constitutes the most frequent cause of surgical interventions in Western Europe (also in Poland), as well as in the USA, Australia and some countries of Asia. The incidence in the population of adults is estimated to be between 10–20%, women get ill 2–3 times more often than men [1]. The incidence of cholecystolithiasis amongst adults living in cities in Poland according to studies by Tomecki is estimated, on average, as 14% (including 18% amongst women and the 8.2% amongst men). At the end of life, lithiasis is stated with 22% of individuals [2].

In Western Europe and the USA, the incidence of cholecystolithiasis has grown radically over the last years. It seems that an expanding percentage of individuals with obesity influences this phenomenon, as well as the ageing of societies and the increasing life span.

The risk of cholecystolithiasis grows with age. The predisposing factors are: obesity (especially with episodes of violent slimming), the female sex, numerous pregnancies, diabetes, cirrhosis, type C hepatitis, coronary heart disease, long-term parenteral nutrition [1].

On account of the chemical structure, it is possible to divide gallstones into: cholesterol, pigmented and mixed ones. In Europe and the USA cholesterol and mixed deposits are mostly stated (70–90%) [1, 3]. For comparison, a high percentage of pigmented stones appear in Asia. The pathogenesis of cholecystolithiasis is not fully explained. It is known, though that there must exist environmental factors which at predisposed genetically individuals provoke the illness.

This study is an attempt to collect the current state of the knowledge on the pathogenesis and predisposing genetic disorders to falling ill with cholecystolithiasis.

State of knowledge. Cholesterol undergoes dissolving in bile, when it is included into micellar structures or into bubbles arising from the lecithin, bile salts and phospholipids (mainly phosphatidylcholines). In the moment, when bubbles and micelles are fully saturated with cholesterol, there comes to its precipitation. It isn't enough for forming stones, however. So that deposits could come into existence, an additional factor must work – specific protein (pronucleating factor) which is in the mucous of the mucous membranes of the gall bladder of individuals with the tendency to lithiasis. This way mucous membranes of the gall bladder can support creation of lithiasis or protect from it, depending on individual abilities to absorption of phospholipids and cholesterol from

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bile. To sum up, precipitating of crystals of cholesterol from bile saturated with it, is regarded as the crucial phenomenon in formation of gallstones.

Due to appearing of high concentrations of bile proteins in bile at patients with numerous cholesterol stones their participation in the pathogenesis of cholelithiasis was suggested. It was suspected that they were shortening the time for the crystallization of bile in the gall bladder and through this process they predispose to the development of lithiasis. The so-called pro-embryonic proteins including among others: M and G immunoglobulins [4, 5], α 1-antichymotripsine and mucin [6], haptoglobins [7], or α 1-acidic glycoprotein [8]. Proteins protecting from the development of cholelithiasis (so-called anti-embryonic) were recognized in the form of A1 apolipoprotein [9] and A immunoglobulin [10]. However the latest publications reject this view of the participation of above mentioned proteins in the pathogenesis of cholecystolithiasis at people, confirming the significance of saturation of bile with cholesterol [10]. Mucin remained the only protein, able to potentially play a role in the forming of gallstones [11, 12].

Chuang S.C. et al. examined the connection between polymorphisms of single nucleotides (SNPs) of *MUC1-MUC4* genes of mucin and cholecystolithiasis [13]. The project included 475 subjects (Chinese men) and 941 individuals from the control group. They chose one polymorphism within the *MUC1* gene, two within *MUC2* and five within *MUC4*. They concluded that polymorphisms within *MUC1* and *MUC2* genes were connected with cholecystolithiasis at men, but not at women; an impact of polymorphisms of the MUC4 gene wasn't proved as for the forming of stones [13].

Impaired postcibal emptying of the gall bladder can impact on the remaining of bile in the bladder and predispose to depositing the crystals of cholesterol, and their increase or the aggregation for the forming of stones. Tennert V. et al finally turned down the role of the gene of A cholecystokinin (CCKA) in the pathogenesis of cholecystolithiasis (earlier research informed about the role of over expression of this gene in formation of gallstones), limiting it to rare cases of monozygotic patients [14]. Reducing the contractibility of the wall of the gall bladder results from the impaired binding of cholecystokinin with CCK-1 receptors as a result of surrounding holes of receptors with precipitates of cholesterol [15]. Inflammation of the wall of the gall bladder also predisposes to lithiasis [16]. However it was hard to confirm *Helicobacter spp* role in the forming of gallstones at people, although lithogenic influence of infection was demonstrated in the mouse.

The intestinal absorption of the bile salts may also play a role in the pathogenesis of cholecystolithiasis. Gälman C. et al observed the elevation of the synthesis of cholesterol and bile salts in the population of patients with cholelithiasis in Chile [17]. They described this process as secondary to the increased intestinal loss of bile salts preceding creating gallstones [17]. The mechanism of the phenomenon was explained by Bergheim et al and by Renner et al, as the effect of the reduced expression of ASBT (Apical Sodium-dependent Bile acid Transporter), ILBP (cytosolic Ileal Lipid Binding Protein) and OST α and β (Basolateral Organic Solute Transporter) in enterocytes of slim women with cholecystolithiasis [18, 19].

These proteins are responsible for the sodium dependent reabsorption of bile acids in cells of the epithelium of the small intestine [18, 19]. Recently, the next protein was identified responsible for a transport of bile acids, whose mutated form can predispose to the development of gallstones – SLC10A2 (Solute Carrier Family 10 Member 2). The research was conducted on the sizeable group of patients with cholecystolithiasis in Germany [20]. Similarly, the elevated cholesterol absorption in the small intestine can predispose to cholecystolithiasis. The high content of cholesterol in the diet increases its secretion to bile and reduces the synthesis of the bile salts which increases the risk of lithiasis. Increased expression of NPC1L1 protein (Niemann Pick C1 Like Protein 1) and ACAT2 (Acyl Coenzyme A-cholesterol Transferase) in the jejunum can support the forming of gallstones, which was observed in the Chinese population.

NPC1L1 protein is responsible for processes of biosynthesis, the intestinal absorption and the transport of cholesterol, but ACAT2 is responsible for its estrification [21]. Confirming the role of the elevated cholesterol absorption in the pathogenesis of cholecystolithiasis was obtained in the study with ezetymib (Etezimibe ®) [22]. This substance belongs to a new group of medicines reducing the concentration of lipids in plasma which selectively suppress absorbing cholesterol and related plant sterols in intestines.

The aim of ezetymib on the molecular level is to be a carrier of sterols, Niemann-Pick C1-Like 1 (NPC1L1) protein which plays a role in uptaking cholesterol and phytocholesterols in the intestine. The medicine is combined with the striated border of the small intestine and hinders absorbing cholesterol, reducing the number of cholesterol transported from intestines to the liver. The study showed that the inhibition of the cholesterol absorption in the intestine prevented formation of gallstones and reduces saturation of bile with cholesterol at patients with cholecystolithiasis [22].

Bile formation process occurs in the canalicular membrane of hepatocytes via proteins of transporters belonging to ABC (ATP- binding cassette) family which enable the secretion of cholesterol, phospholipids and the salts of bile acids. ABCG5 and ABCG8 transporters play the key role in this process (transporters of sterols in the intestine and the liver). *ABCG5* and *ABCG8* genes encoding appropriate proteins – halftransporters. They give rise to a heterodimer which is the functional transporter, being located in the canalicular membrane of the hepatocyte and responsible for the secretion of cholesterol to bile. Polymorphisms of *ABCG5* and *ABCG8* genes predispose to the development of cholecystolithiasis, which was confirmed in numerous studies.

As first a polymorphism of *ABCG8* D19H gene (Asp19His), with research carried out on the Caucasian population was described. In the Chinese population a Q604E polymorphism of the *ABCG5* gene was described [23, 24]. Rudkowska I. et al analysed polymorphisms of A632V, T400K, D19H, M429V and C54Y of the *ABCG8* gene and Q604E of the *ABCG5* gene. Attention was paid to a connection between the polymorphism of *ABCG5/G8* genes and cholecystolithiasis, but also the hypercholesterolemia, with response to the diet and the hypolypemic treatment [25]. Katsika D. et al conducted analysis of polymorphisms of the *ABCG5* Q604E gene and *ABCG8* D19H in the population of Swedish twins, both mono- as well as dizygotic ones. They combine the risk of cholecystolithiasis with the *ABCG8* D19H polymorphism – this variant is regarded as the most predisposing one [26].

The connection with the ABCG5 Q604E polymorphism did not demonstrate the statistical significance [26]. Stender S. et al examined 62279 patients as for the polymorphism of

the *ABCG8* gene and stated that the D19H polymorphism was predisposing to symptomatic cholecystolithiasis and the cholangiocarcinoma [27]. Schafmayer C. et al carried out *ABCG5* and *ABCG8* genotyping on the large population of individuals with cholecystolithiasis and control group without lithiasis. The examination confirmed the participation of genes mentioned above in the pathogenesis of cholelithiasis [28]. Van Erpecum K.J. et al obtained similar results [3]. Krawczyk M. et al showed that genetic factors were responsible for around 25% of full risk of lithiasis. They emphasize the role of genes as transporters of cholesterol of *ABCG5/G8* as main genetic factors of cholelithiasis at people [29].

The *ABCG5* and *ABCG8* gene expression is regulated by the nuclear LXR (Liver X receptor). In the mouse's model the activation of this receptor increases the risk of gallstone formation [30]. Nevertheless the significant studies are absent concerning the LXR role in the pathogenesis of lithiasis at people. Increase in the expression of the hepatic LXR alpha receptor and of *ABCG5* and *ABCG8* genes was observed at slim patients with cholecystolithiasis in China. It correlated with the indicator of saturation of bile with cholesterol [31]. A small group of participants was a downside of this study, though. The role of the LXR in the pathogenesis of cholelithiasis at people is poorly recognized and will require further research.

The next family of proteins which may be related with cholecystolithiasis is a ABCB family [33]. The uniqueness of ABCB group consists in the fact that it contains both full transporters as well as halftransporters. ABCB1 (MDR/PGY 1) protein, called glycoprotein P, is the first human transporter which was cloned and exactly characterized. ABCB1 isoform is associated with the phenomenon of the multi-drug resistance, while ABCB4 is a transporter of the phosphatidylcholine or a lipase expelling this phospholipid to the bile. ABCB5 – B8 proteins are located in mitochondria, where they participate in the iron metabolism and are responsible for a transport of precursors of proteins. They were connected with cholecystolithiasis at patients with the metabolic syndrome [32]. *ABCB4* and *ABCB11* proteins are located in the liver and are responsible for a secretion of bile acids.

ABCB11 subfamily (historical names: BSEP – Bile Salt Export Pump, SPGP – sister's form of P glycoprotein) is located in the the canalicular membrane of hepatocytes and is responsible for a secretion of the bile acids to bile. Mutations within the *ABCB11* gene are manifested as family, progressing, intrahepatic cholestasia of the second type (BRIC2 – benign recurrent cholestasis type 2). At these sick individuals characteristic, more frequent appearance of cholecystolithiasis was observed, due to the insufficient amount of salts of bile acids in bile [33].

ABCB4 protein (MDR3 – Multi Drug Resistance 3 P-glycoprotein) performs the role of the transporter of the phosphatidylcholine through the canalicular membrane of the hepatocyte to the bile. Mutations of the *ABCB4* gene were connected with the predisposition to ductal and intrahepatic cholelithiasis in a young age (below 40 years of age) and with the greater risk of the recurrence of lithiasis after cholecystectomy. Some part of patients with the mutation display serious anomalies of the structure of the bile duct without constricting [34].

Admittedly, Acalovschi M. et al did not confirm the connection of polymorphisms of *ABCB4* and *ABCB11* genes with cholecystolithiasis (examining pairs of siblings with the control group) [35], nevertheless new research confirms the connection of polymorphisms of the *ABCB4* gene. Davit-Spraul A. et al. showed that mutations of the ABCB4 gene were predisposing to liver diseases, cholelithiasis included [36]. Marschall H.-U. et al obtained similar results [37].

The *ABCB4 and ABCB11* gene transcription is regulated by the nuclear FXR (NR1H4, Farnesoid X receptor). This receptor influences the concentration of the bile salts and phospholipids in bile. Blocking the receptor at the mouse dramatically increases the predisposition to creating cholecystolithiasis, on account of the low contents of bile acids salts and phospholipids in bile. Applying the synthetic FXR agonist (GW4064) at mice protects from the forming of gallstones through the increase of the bile salts and phospholipids concentration in bile [38]. Analyses of polymorphisms of the NR1H4 gene encoding FXR gave controversial results. The most frequent polymorphism – NR1H4 _ 1 in the German population doesn't increase the risk of the development of cholecystolithiasis, in the Chinese population it exerts a protective action and protects against lithiasis, and in the Mexican population it increases the risk [39].

Publications suggesting the role of the SCP2 protein in the pathogenesis of cholecystolithiasis have been published in the last years (Sterol Carrier Protein 2). The *SCP2* gene yields to the high expression at cells connected with the lipid metabolism (among others in heatocytes). Its role in the pathogenesis of the Zellweger syndrome is postulated, in which cells are characterized by a deficiency of peroxisomes and disorders of the synthesis of bile acids appear. Cui Y. et al observed over expression of *SCP2* gene at patients [40] with cholecystolithiasis compared with the control group. They concluded that this protein could play the key part in the forming of gallstones [40]. Seneshaw et al noticed that simultaneous blocking of *SCP2* and *FABP1* (Fatty Acid Binding Protein 1) genes at the mouse protects from the development of cholelithiasis [41].

Recent reports point to the potential role in the pathogenesis of the cholecystolithiasis of UGT1A1 enzyme (Uridine 5'-diphosphate-glucuronosyltransferase 1 A1). The product of this protein is responsible for coupling of bile in the liver. Krawczyk M. et al. emphasize the role of the mutation of the *UGT1A1* gene as crucial thing in the forming of gallstones [29]. Chu C.H et al and van Erpecum K.J. point to the polymorphism of the *UGT1A1* gene, which, is connected with the increase in the risk of lithiasis [42, 3].

Pathogenesis of pigmented lithiasis is a little bit different. Pigmented stones constitute about 10–30% of all gallstones and are are above all black stones (content of cholesterol under the 20%, composed mainly from calcium bilirubinate). They are observed at patients with the chronic disease, such as Gilbert's syndrome, inherited spherocytosis or hemolytic sickle cell disease. They can also come into existence at patients with the Crohn's colitis, especially after the partial resection of the small intestine, or at individuals affected with cystic fibrosis [43]. In normal conditions, majority of bilirubin (breakdown product of haemoglobin) is conjugated in the liver to bilirubin monoglucuronide, and then to water-soluble bilirubin diglucuronide. Non-conjugated bilirubin is characterized by a weak water solubility. In case of the haemolysis producing bilirubin increases even ten times which is predisposing to precipitating calcium bilirubinate by the same time to creating pigmented deposits.

CONCLUSIONS

The pathogenesis of cholecystolithiasis has basically remained unsolved. The existing knowledge on this subject doesn't explicitly allow to determine universal genetic factors which predispose to falling ill. Great population differences are being observed, as for instance, a chemical structure of the stone or disorders which in one community predispose to lithiasis, and in other exert protective action, guarding against the illness. There is a lack of multicentre trials, allowing to assess the impact of many genes to the incidence in all sorts of ethnic groups. The subject has not been not raised also with a reference to the Polish population.

Growing number of obese patients, with diabetes or the increasing life span justifies the need to undertake further research on the pathogenesis and the genetic predisposition to this illness, particularly due to the fact that it often leads to the need of the surgical intervention, frequently at patients in the advanced age and in bad general condition when such intervention is burdened very much with the greater risk of post-operative complications.

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