

Studies on gallstone in China

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INTRODUCTION

Gallstone is one of the common primary diseases of bile system. Chinese researchers have done comprehensive and thorough studies on it, but there are still some problems we have not solved. It is necessary to review the achievements we have made in this field recently, to summarize the experiences and find the tendency so as to provide a sound foundation for the researches in the new century. Due to the popularization of molecular biological research methods, a rapid development of modern imaging techniques and medical equipment, the basic and clinical studies of cholelithiasis have set foot on the fast lane. Studies on the cause of cholelithiasis formation and its prevention have covered areas from epidemiological investigation at macroscopical level to molecular biological researches at microcosmic level. Clinical studies include prevention and treatment of cholelithiasis with traditional Chinese medicine, popularization of micro-injury surgery, treatment of complicated calculus of bile duct, and other aspects.

PRESENT SITUATION

Studies on pathogenesis of gallstone

Study on the cause of cholelithiasis formation is an important field of studies on gallstone over a long period of time in China, and it will hold a very important position in the future. Formation of gallstone is a complicated pathologic process, which involves many factors. Researches in this field consist of epidemiological investigation, studies on components of gallstone, biliary elements which cause stone formation, anatomy and physiology of bile system, etc.

Han *et al*^[1] found that formation of gallbladder stones is related to age, metabolic disturbance of fat and damage of gallbladder emptying function in a case-control study on 66 cases of asymptomatic gallbladder stones. To know the morbidity of gallbladder stone in the young is essential to the study of the pathogenesis and prevention of cholelithiasis. Shi *et al*^[2] found a morbidity of gallstone of 0.94% in 522 young students by an epidemiological investigation, which is significantly lower than in adults. By ultrasound scanning study, we also found that the gallbladder volume of young female is smaller than that of male ($P < 0.01$), and the rate of cystic contraction 1 hour after meal is also lower than in male. The result supports that the gallbladder contractility of

female and fatty is weakened significantly, which is one of the key factors of accumulation of bile and inducement of gallstone. Kuang *et al*^[3] studied the relation between asymptomatic HBV carrier and gallstone, and found that serum HBV-M positive detectable rate in patients with gallbladder stone is higher than normal control group. He thinks that infection of HBV could be an inducer of gallstone formation. Zhu *et al*^[4] investigated the incidence of gallstone in 672 fatty liver patients diagnosed by B-ultrasonography and 14610 non-fatty-liver subjects simultaneously, and found that the incidence increases in fatty liver patients obviously because of metabolic disturbance.

Wu *et al*^[5] used X-ray diffraction analysis to measure human gallbladder bile stone. The results are as follows: particulate gallbladder bile stone is chiefly composed of crystalline material containing cholesterol; sandy bile stone is mainly made up of noncrystalline material containing bile pigment or porphobilinogen. They compared the results with those in the early 1980's and found that the proportional number presented a rise in cholesterol bile stone. They thought that the main reason is the increase of cholesterol intake, metabolic disturbance of cholesterol, and descending incidence of biliary ascariasis and bacterial infection. They also determined bilirubin level by spectrophotometry and determined cholesterol contents by TLC scanning in 31 cases of human biliary calculus, and found that 31 cases of gallstone were all mixed bilestones primarily containing pure cholesterol or cholesterol bilestones^[6,7]. Shi *et al*^[8,9] studied black bilestones by Fourier Transform Infrared Spectroscopy and found that known organic constituent and inorganic constituents of black stones were the same, but their contents are varied. They think that black stone contains quite a few of protein, and that might be the key constituent to form black stone.

The study on the relationship between metabolism of bile acid and formation of gallstone^[10-12] is the subject causing great attention of scholars all the time. It had been shown that the ability of defluence was determined by the ratio of cholesterol, bile acid and lecithin. In the bile of patients who suffered from cholesterol calculus, bile salts, total bile acid pool, and contents of chenodeoxycholic acid decreased. At the same time, contents of cholyglycine rose while cholytaurine reduced, and proportion of conjugated deoxy-cholanic acid increased. All above factors promote cholesterol crystal nucleation and gallstone formation. Uniform recognition about the mechanism of bile acid dissolving bilirubin has not been obtained, but most of scholars believe that reduced bile acid is one of the key factors in gallstone formation. These results provide a solid theoretical basis to study the cause of cholelithiasis formation, prevention of gallstone and litholytic therapy. However, because some mechanisms have not been pinpointed, the effects of clinical application are not satisfactory. Lu *et al*^[13] found that fever had obvious influence on biliary elements in a study on guinea pigs. All the animals in fever group had significantly higher concentrations of total bile protein and bilirubin than that of the control groups, which is prone to gallstone formation.

Bacterial infection is very important in the forming of the gallstone. Recently, there are many research reports^[14-17]

about the function in the formation of the gallbladder stone. The content of aerobic, anaerobic, L-bacterium, and *Helicobacter pylori* of the gallbladder tissue, bile, gallstone and portal vein have been tested through the use of the immunohistochemistry and the proliferation of PCR-DNA. These results indicated that bacterial infection and the formation of gallbladder stone and the chronic inflammation of bile duct system are closely related. According to the bacterial enzymology, the formation of bilirubin gallstone is related to the content of exterior β -glucuronidase-G, which result from the proliferation of bile duct bacterial infection, the interior environment (the best pH is 7.0), and the content of inhibitor. But according to the research of Yang *et al*^[18], the interior β -glucuronidase-G, as a kind of active enzyme in human body, is one of the related factors of bilirubin gallstone.

The research of the relation between the contracting function of gallbladder and incidence of gallstone is a very important content of the study on cause of gallstone formation. Ma *et al*^[19] found that the gallbladder emptying rate is not normal in half of the gallstone patients through the observation of 100 cases of gallbladder stone patients. He considers that the function of gallbladder is mainly affected by its thickness, the location of the gallstone and the shape of the gallstone. Zhao *et al*^[20] also holds the view that gallbladder emptying rate in gallstone patients' is below the normal, and especially in the pregnant women it is lower than in the men of the same age. Xu *et al*^[21] have done a research on the change of the contractive function of gallbladder after gastrectomy, and the result showed that incidence of cholestasis, and gallstone rose because of cut of liver rami of nervus vagus, gastrointestinal reconstruction and decrease of secretion of cholecystokinin.

In recent years, many researchers have done experiments to explore the relation between the disease of gallbladder stone and human gene group with molecular biological technology, and that made the study enter into gene level. Jiang *et al*^[22] used PCR-RFLP to analyse the relation between variety of *Xba* I in Apo B Gene and blood fat. The research shows that the X⁺ allele of Apo B gene is associated with high serum cholesterol and it may be regarded as a high-risk gene of cholesterol gallstone formation. Shuai *et al*^[23] explored the relation between the expression of CCK-A receptor of gallbladder and gallbladder hypomotility in patients with gallstone. He thought that the down-regulation of gene expression of CCK-A receptor plays an important role in gallbladder hypomotility in patients with gallstone.

The relation between the change of interior or exterior hormone level and the formation of gallstone attracts the attention of scholars. Through case-control study, Luo *et al*^[24] concluded that the use of steroid contraceptives in gallbladder stone women patients aged 20-44 years and the absorption quantity of heat are the main factors of the formation of gallbladder stone. Steroid contraceptives containing estrogen and progesterone, are the reflection of the effect of exterior hormone on gallstone formation. With the help of radioimmunology, Wang *et al*^[25] have experimented on the alteration of ATCH, Cor and thyroxine of the gallbladder stone. The results showed that the formation of cholelithiasis was related to the increase of Cor, and the decrease of T3 in serum. They^[26] also proved that the cholelithiasis patients have an obvious increase in level of tyrosine peptide and cholecystokinin in serum in another experiment. Han *et al*^[1] found that the content of the insulin in gallstone patients was much higher than in non-gallstone patients, showing that the level of insulin was related with formation of gallstone.

Research on prevention and treatment of gallstones

Research on prevention and treatment of gallstones can be divided into combined treatment by traditional Chinese medicine and modern medicine, surgery, litholytic and lithotriptic therapy. An important part of non-surgical treatments of gallstones is litholytic and lithagogue one. Great achievements have been made in extrinsic experiments of dissolving gallstones with different solvents for different components of gallstones. However, the outcome of clinical applications is not satisfactory as far as cholesterol or bile pigmental stone, litholytic treatment by oral drug in particular is concerned. Another important cause of the limited clinical application is the toxic and side effects of the litholytic. Many scholars put much emphasis on studying extrinsic lithodialysis and direct perfusion of litholytic into the biliary tract^[27-30]. The application of traditional Chinese medicine is given much attention in China. Litholytic and lithagogue treatment with Chinese herbs in clinical application is the most vigorous research field in gallstone research in China besides the researches on gallstone formation. The drugs selected can change the components of stone-forming bile, dissolve the gallstones formed, improve contractility of the gallbladder, relax sphincter of the bile duct and exert anti-inflammatory and antibacterial functions. Several medical institutions of our country^[31-37] have carried out basic and clinical experimental researches on their prepared patent Chinese drugs with litholytic and lithagogue functions. They proved that some formulae can relieve the depressed liver, normalize the function of the gallbladder, promote blood circulation to remove stagnancy, heat and dampness, and achieve purgation. Many clinicians^[38-43] have made inductions of indications and specific methods for treating cholelithiasis with Chinese herbal drugs and combined traditional Chinese and modern medicine, making its application more rational and effective. Zhou *et al*^[44] made extrinsic CT scan of cholelithiasis cases, compared the results with the chemical components of the stone, and proved that CT imaging and value can demonstrate the chemical type of gallstones. He suggested that 40HU, the critical value of judging cholesterol calculus can provide a valuable basis for non-surgical treatment, especially litholytic method.

With the popularization of laparoscopy, the age of micro-traumatic surgery has come and great changes have taken place in surgical operation and surgical ideology. Cholecystectomy has entered the stage of laparoscopy in developed countries. This tendency is becoming obvious in China. The surgical treatment of gallstones with clinical application of celioscope^[45-53] consists of peritoneoscopic cholecystectomy, peritoneoscopic choledocholithotomy, endoscopic papillectomy, and application of choledochoscopy. Indications of laparoscopy for gallstone treatment are not limited to pure gallbladder stone now. Choledocholith, acute cholecystitis, and acute pancreatitis are no longer the contraindications of laparoscopic cholecystectomy (LC). Among them, choledocholith could be treated by two methods at least. One is sphincterotomy of Oddi before LC. The other is laparoscopic choledochotomy. Sphincterotomy performed with endoscope is a simple therapy for calculus of common bile duct with a diameter smaller than 3 cm and stricture of terminal common bile duct shorter than 3 cm. Undoubtedly, application of all kinds of choledochoscopy has improved the rate of pre- and intra-operative diagnoses of biliary diseases, reduced the rate of residual bile stone, and could help patients avoid a second operation. Therefore, their application is welcome by clinicians increasingly.

Much concern is being taken in research on surgical treatment of hepatic calculus^[54-56]. As Huang pointed out, 'early-stage systemic lobectomy of liver or segmental hepatectomy' is drawing a highly

increasing attention in treating hepatic calculus, especially in early stage cases that are diagnosed by CT scanning. It is thought that the treatment procedure could achieve the aim of maximal clearance of lesions and reservation of functional liver tissues. Furthermore, most scholars^[57] think that irritating of hepatic calculus and secondary infection could result in mucosal ulcer of bile duct, or even metaplasia leading to the development of hepatic cholangiocarcinoma finally, although there are disputes about question. Therefore, the reports of present clinical studies make lobectomy of liver the key point in surgical treatment of hepatic calculus although removing obstruction, getting rid of calculus and making drainage are the principles that should be followed. Intraoperative choledochoscopy, intraoperative ultrasound, intraoperative fast pathological examination and other imaging and diagnostic methods are key measures in treating hepatic calculus.

Operations of biliary tract, especially cholecystectomy, have been widely performed in grass-root-level medical institutions, but many complications and sequelae have resulted from inappropriate handling of indications, inappropriate choice of operative methods, and malpractice during operation, even making another operation necessary. With aging of the population, more and more studies^[12,49] have been conducted on prevention and treatment of gallstones of elderly people. As to the chemical cholecystotomy started in the 1980s, Sun Shuming^[58] concluded that chemical excision is very safe after the experiment performed on pigs. The clinical study of lithotriptic therapy^[53,59,60] shows that extracorporeal shock wave lithotomy or lithotomy through sinus tract of skin after operation is effective to cure gallstone. However, these techniques and their values still need further improvement.

COMMENT AND PROSPECTIVES

Researches on causes of gallstone have been carried out for a long time with many conclusions drawn about cholesterol lithiasis and bilirubin lithiasis. Take the former as an example, almost all the cases experience three courses: cholesterol saturating, unbalance between causing and anti-causing factors; and dynamic disfunction of bile duct. Experts have worked over all aspects of that and obtained valuable findings. New research trend in this field is to discover its molecular biological and genetic nature with sophisticated research approaches. And we can expect that research in this field will become a hotspot in the up coming years, with the deepening of human genome Project. According to the status in quo, many risk factors causing the formation of gallstone have already been discovered, but in our opinion, emphasis must be laid on nation-wide big sample clinical epidemiological surveys so as to find effective measures to prevent gallstone occurrence based on integrating the basic research with clinical practice.

There is a close relationship between the research on prevention of gallstone and litholytic therapy and study on the cause of cholelithiasis formation. An effective litholytic therapy using traditional Chinese medicine could be expected if we take good advantage of the dissolving measures used abroad. But more precise basic studies on this issue are needed in China. We anticipate that, just like what has happened to other traditional Chinese medicine, researches focusing on traditional medicine curing gallstone will shift from simple summarization of clinical cases to strict double-blind case-control study using monomer components purified from raw Chinese medicine through high-tech settings.

Surgical treatment still is a consequence in gallstone treatment. As far as gall stone is concerned, laparoscopic cholecystectomy will

play a major role in the treatment of the disease for a relatively long time. At the same time, more reports on the issue will appear. Consequently, laparoscopy will be widely utilized in all branches of surgery. Basic and clinical researches on complications of this therapy, such as bile duct injury, will be further strengthened. As to the therapies for hepatic calculus, early-stage systemic lobectomy of liver or segmental hepatectomy will be commonly recognized, and the idea about curing the cases of this type will shift from treating the complications to radical surgical treatment. Furthermore, choledochoscopy, which belongs to micro-injury surgery, will play an more important role. Nevertheless, effect of lithotriptic therapy and chemical cholecystotomy in curing lithiasis should be further evaluated.

The present faults of some gallstone studies in China are the echo at low level and the lack of innovation. Therefore, revolutionary progresses are difficult to achieve. The key to better the current situation in a short time is to put more stress on prevention and treatment of gallstone, especially on issues about the integration of theory and application of basic findings to clinical practice.

SUGGESTIONS

To summarize, through the application of molecular biological techniques, studies on causes of gallstone and their mechanism at molecular and genetic level should be enhanced. A good theoretic basis for prevention of gallstone could be anticipated. In the research on prevention of gallstone and litholytic therapy, especially the application of traditional Chinese medicine, more emphasis should be laid on the basic researches of mechanism and strict double blind case-control studies. Micro-injury surgery should be especially stressed. At the same time, clinical case-control studies with vast specimens are expected to guide the gallstone therapy. As it is known that improved health situation and changing the diet structure will make the incidence of cholesterol lithiasis in gallstone increase in the coming years, researches on this issue will be strengthened. In regard to prevention of hepatic bile duct stone, more importance should be attached to researches on indication and complications of early stage systemic lobectomy of liver or segmental hepatectomy and prevention of the recrudescence of gallstone after surgery.

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