Review Article

Review on Pathogenesis of Cholelithiasis and Drug Targets for Therapy

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ABSTRACT

Cholelithiasis is the condition/disease which occurs due to the presence or formation of gallstones; they may be either in the gallbladder (cholecystolithiasis) or in the common bile duct (choledocholithiasis). It is one of the most prevalent gastrointestinal diseases, with a substantial burden to health care system. Cholelithiasis disease may occur because of many different disorders like obesity, genetic factors, high cholesterol and fat diet intake, lack of fiber intake, being overweight, high sedentary life styles, lack of exercise. A calculus (as of cholesterol) formation in gallbladder is very common but avoidable conditions leads to the gallbladder cancer, there are different biomarkers are considered in gallbladder cancer such as CA 19-9, CA 15-3, CA-242, CA-50 and Arginase. This is very rare condition and occurs very less in people who suffer with gallstones. The pathogenesis is related such as; the cholesterol secretion in to the bile is increased across the transmembrane of the gallbladder through the transporters of gene leads to increase in the concentration cholesterol in bile and decrease in the bile volume. This elevated level of cholesterol in bile promotes the process called supersaturation and further gives in result of crystal formation. It is diagnosed with ultrasonographic technique, as there is no promising treatment for cholelithiasis which has made challenge to treat disease there is a only few drugs like ursodeoxycholic acid (UDCA) and Chenodeoxycholic acid drug (CDCA). Cholelithiasis disease treatment is cost effective in the global, and is remedial but in avoidable conditions leads to the death. So, this review mainly focused on complications, biomarkers and possible curable treatment based on the ongoing reports.

Keywords: Choledocholithiasis, cholecystolithiasis, CA 19-9, CA 15-3, CA-242, CA-50, UDCA, CDCA.

INTRODUCTION

The formations of different stones in gallbladder are known as gallstones. These gallstones formation in the gallbladder, common bile duct & hepatic duct is the condition, where the stones block the common bile duct or hepatic duct is called cholelithiasis disease. Liver makes extra cholesterol as above the normal level in abnormal condition and it gets incorporated into bile, produced by the liver. From the liver it gets secreted in gallbladder. Once the foods enter, it senses the gallbladder to release bile, and released bile further helps in digestion process. The high cholesterol secretion in bile leads to supersaturated cholesterol, the process called supersaturation. Once the supersaturation process occurs the formation of crystals will happen. These crystals further forms into cholesterol stones.

Cholelithiasis disease is common disease and it is a considerable disease in many people, this disease occurs most in elaborated countries. Mainly the gallbladder stones are isolated clump of frozen blend of cholesterol crystals, calcium crystals, mucin, nitrogenous organic compounds and bilirubin crystals which made human beings to suffer for long time[1]. The stone formation in the gallbladder is the harder condition which makes further blockage of common bile duct, and hepatic duct is called gallstone disease, this condition is the most frequent gastrointestinal disease which made a load to medical management[2].

The gallbladder stones occur in gallbladder for many different tangled reasons[3]. The formation of gallstones is such condition which is a longstanding hepatobiliary illness, the premise for which is the hinder metabolism of cholesterol, bilirubin, and bile acids in bile; this condition shows the sign of formation of gallstones in gallbladder[4]. Cholelithiasis disease is the most exorbitant treatment among gastrointestinal diseases[5].

In the gallbladder there are mainly three different types of gallstones will occur mainly based on the presence of substantial constituent: cholesterol, bilirubin, and mixed. Bilirubin is a yellow pigment so stones associated with bilirubin are called pigment stones; there are two different pigment stones will occur: black and brown. The black colored stones are formed by haemolysis and brown colored stones are formed because of biliary tract infection[6]. Cholesterol stones are occurred by different genetic factors and different risk factors.

The gallstone disease is landscaped by Swiss medic Paracelsus as a concomitant of tartaric disease[7]. The severe condition of cholelithiasis disease causes the gallbladder cancer which is also known as gallbladder carcinoma. The gallbladder carcinoma is rarely occurring melanoma which is seen in rare population with the

incidence[8]. The gallbladder carcinoma is detected in last stage and survival rate is 5-years[9].

PREVALENCE OF DISEASE

The prevalence of gallstone disease (cholelithiasis) deviates from one country to other, since it is a most common condition in human beings all over the global[10].The prevalence in western countries according to the incidence sweep from 7.9% in men and 16.6% in women[11].In different countries like Asian, Africa it deviates according to the reported incidence, it is nearly 3% to 15% in Asian country and 5% in African country[12, 13]. And in china it is from 4.21% [14]. The percentage of prevalence according to the incidence will be in different age so the in western countries the adult people get into formation of gallstones approximately 10-15% associated with a 1% and 4% of symptoms of getting gallstones in a year[15]. The treatment of gallstone disease is expeditiously changing as the day surgery cases are registering spontaneously. The formation of gallstones in the human gallbladder is clinically tranquil, the people with gallstones suffer by pain in sometime nearly about 20% population; and 1% to 2% people will get into severe condition of gallstones and get under surgery to remove gallbladder. In American country the people are suffering or will suffer by the gallbladder stones, the range is nearly about 20 to 25 millions of people[16-19].

The gallbladder disease made a population as a heavy load to the health system; the cost for the treatment of this disease expenditure is nearly 6.2 billion per year in the U.S, and in last 3 decades that has been increased high than 20% [16, 20, and 21]. By the estimation 1.8 million cases of gallbladder stones are get admitted in to the hospital as a serious case for every year, this disease is a dominant disease which makes the human beings to suffer more among the gastrointestinal disorders[22]. In serious case, the condition of disease some time becomes as very complicated, so in complicated case the death may happens, the death rate is about 0.6%, as a low rate. In the U.S, for 2004 there was a less incidence related to gallstone disease has been occurred but 1950, nearly about 5,000 people was died[21]. The treatment for gallstones is the mainly is to remove gallbladder which contains gallstones, in serious case the gallbladder should remove to avoid complications, so the removal of gallbladder is by surgery it is the most preferable treatment to avoid gallstones this procedure has been followed since from 1950 in elaborated, advanced countries[23]. The surgery treatment for gallstone disease is nothing but cholecystectomy that is laparoscopic cholecystectomy which is considered in the year of 1989 and still it is considerable list[23, 24, & 25]. In the U.S, the performing of cholecystectomy is more frequent to treat gallbladder stones, it is considered as an overuse to remove gallbladder stones; nearly about 750,000 surgery accomplished for every year[25, 26]. The performing surgery was highly considerable matter though it is high it was constant in the late year of 1990 and even it may be diminished in the U.S[27].

The formation of gallstones in human beings is common all over the world. The incidences happens relating to gallstone disease is deviated from one country to other country based on the race, the countries like Africa, America, western Countries, U.S; the American population get gallstones at some time, the percentage occurs in this country is nearly about 10% to 20% [28]. After formation of gallstones, the more people will not get or do not come to know about any symptoms: the 80% of the patients will not feel any pain in the gallbladder, common bile duct or any other serious worst conditions such as inflammation, chronic fibrosis in gallbladder, and inflammation in the pancreases[29]. The gallstone detection in patients is normally performed by using the ultrasonographic method; the procedure is more common in all over the world. This method not only performs the detection of stones, along with that condition of the disease state will also be explained. The ultrasonographic studies are carried out in different countries but the Western Europe is the country which follows this method in highest. In other countries like Bergen, Norway and Schwedt, Germany it is performed from 5.9% to 21.9%[30].

ETIOLOGY

The gallstone disease is a condition which is caused by several factors or different causing factors. There are several different factors are involved to cause gallstones, the main factor for the formation of gallstone is gender; the females are more susceptible to get gallstones compared to males. The valid reason is to get gallstone in female is due to estrogen, the estrogen level increases the cholesterol secretion and leads to cholesterol supersaturation, further causes the formation of crystals, stones. The other different causing factors are genetic factors, age, and race. The formation of gallstones not only occurs by age, genes & race but also they are associated with other addition factors; like being overweight, glucose intolerance, insulin resistance, drinking alcohol, diabetes mellitus, lack of fiber intake, high consumption of cholesterol and fat diet, sudden loss of weight, due to intake of drugs, during pregnancy time[31]. As above mentioned, there are different factors are reasons to get gallstones whereas the four major reasons to form stones in the gallbladder are:

1. Bile contains too much cholesterol and gets supersaturation, the supersaturation of bile with cholesterol forms stones.
2. Precipitation of cholesterol and crystallization.
3. Hypo motility of gallbladder leads to abnormal function.
4. Improper circulation of bile acids; such as enterohepatic circulation.

RISK FACTORS

The gallstone disease is associated with different risk factors such as loss of sudden weight, after giving birth to child, therapy of oestrogen-replacement and using other oral contraceptives[32-35]. The eating more cholesterol and fatty foods is the main important factor for the formation of cholesterol stones, and it is more common in western countries. Cholesterol stones are more common in human beings compared to other two stones like pigment stones and mixed stones. There several modifiable risk factors and unmodifiable risk factors take place in the formation of cholesterol stones in the gallbladder.

Modifiable risk factors:

- Obesity
- high alcohol taking
- lose of weight suddenly
- eating high cholesterol food
- eating less fiber diet
- smoking
- sedentary lifestyle
- inactiveness of gallbladder
- intake of drugs

Unmodifiable risk factors:

- gender
- age
- past history of family
- ethnicity
- genetic problem

Ethnicity:

Race is also one of the considerable factors among the different factors which cause gallstones. The mainly there are three major different stones will occur in gallbladder; cholesterol stones, pigmented stones and mixed stones. According to the reported data the prevalence plays a very important role to develop gallstones. The western countries people are more preferable to get cholesterol stones and Asian country people are more preferable to pigmented stones there are two pigmented stones such as brown and black pigmented stones, but the western people will get most brown pigmented stones.[36] Based on the reported data's the risk factors are considered as considerable in different countries, like North America, western countries, Asian country, Africa. According to the report the women's are more subjected to get gallstones compared to men's, the nearly about 64.1% women's are susceptible to gallstone disease, and in men it is about 29.5%, which is reported data of North American Indians[37]. The people in South America are also more preferable to gallstone disease it ranges with extreme percentage of 49.4% in women and 12.6% of prevalence in men[38]. In White Americans the gallstone disease occurs in the percentage of 16.6% in women and in 8.6% men in[39].

Age:

Gallstone formation is not only associated with gender, even it associated with the age. Age matters a very important role in the formation of gallstone, as the age increases the reported patients with gallstones are also increased, as it is included in the causing sign for gallstone disease.[40] Getting gallstones is not only in adults or in elders it also seen in children's but such conditions are very rarely seen in children's. The situation is unexpected and the symptoms are not particular[41, 42]. Every year according to reported studies the gallstone disease is increasing as after the people who are crossing 20 years[43]. The people who are 40 years in age are specifically suffers from the gallstones mainly in older people[44, 45]. As according to types of gallstones, the formation of gallstones deviates with age of the human beings. The beginning the cholesterol stones will occur and later the cholesterol stones gets converted to black or brown pigment stones in final or last stage. In last stage of disease, the cholecystectomy is performed to remove inflamed gallbladder[46]. The age matters in gallstone disease as age increases the secretion or deposition of cholesterol in bile also gets high[47].

The formation of cholesterol stones in the gallbladder is because of the supersaturation of cholesterol in bile, which is occurred by the result of diminished effect of bile synthesis by the liver. As the bile secretion decreases the cholesterol deposition in the bile gets supersaturated with less volume of bile in gallbladder, the reason for the decreased bile secretion is because of the ineffective action of enzyme which is named as cholesterol 7 alpha-hydroxylase (CYP&A1)[48]. There are different receptors takes place in the pathogenesis of gallstones in the gallbladder and mainly the pregnant X receptor (PXR) which is called as xenobiotic receptor is involved in the formation of gallstones[49].

Gender:

Gender plays very important role in the formation of gallstones, the women are more preferable to get gallstones compared to men. After menopause the gallstones occurs in women in most of conditions[50]. The female sex hormones are involved in the gallstone disease for women, such as using oral contraceptives, estrogen replacement therapy and parity for gallstone formation[51-53]. The gallbladder function is associated with female sex hormones mainly in the bile secretion of hepatic duct. The both estrogens and progesterone involves in the secretion of cholesterol in bile, the cholesterol secretion is increased mainly by estrogen and bile salt secretion is reduced by the progesterone. The gallbladder functions such as motility and emptying is get altered by these hormones and leads to the improper function of gallbladder. The use of 4th generation progestin, and some other oral contraceptives,

drospirenone increases the degree of risk factors[54]. Women who are pregnant, during their pregnancy time the female sex hambone level get increased and leads to the formation gallstones in bile ducts in the percentage of nearly about 5% to 30%. The other different factors are also takes part during pregnancy such as obesity, cholesterol and increased in lipoproteins, metabolic disorders[55, 56]. The chance of getting gallstone mainly in reproductive aged women is more compared to men about the percentage of 2-3 times[57].

Genetic factors:

The gallstone formation in gallbladder is the most important considerable factor[58]. According to the report the family history shows the high result of risk to get gallstone formation which is 5 times more in patients. The different studies like preclinical study, Murine study has been shown that the main reason for stone formation is the genes which are called lithogenicity genes[59]. In preclinical study the mice were used to do the experiment. In process of gallstone formation there are two different entrants are involved. And they are genes such as apolipoprotien B mRNA-editing protein and peroxisome proliferators' receptor gamma which takes part in gallstones formation, considered as risk factor. The lipids are the main considerable constituents for liver disease, when there is damage in liver the lipids get release into the blood and gets raised in level this condition indicates the liver disease. So, the alteration in the lipid profile and genetic conditions are more promoting factors to get gallstones[60, 61]. There are many different genes are involved in the gallstone disease; such as APOA1-75 G/A polymorphism is type of gene involved in the formation of stones in the gallbladder and the condition deviate in sex. While the other type of gene is like APOA1M2 and APOC3 S is does not take part in gallstone formation. The important condition in pathogenesis of gallstones is significantly related to the elevated level of lithogenicity, the process of mutations in the encoding of gene causes the decrease in the secretion of lecithin in the bile which leads to the high of lithogenicity[62, 63].

Obesity & being overweight:

The pathogenesis of gallstone is mainly associated with the obesity and being overweight. The people who are high in weight and with obesity get the more chance to get gallstones, so these are considered as important risk factors[64-67]. The bile is more important to dissolve cholesterol secretion, but in cholelithiasis condition especially the people with obesity have altered mechanism that is elevated level of cholesterol production and releasing it into the bile. The cholesterol which is produced is straightly correlative to the increase in weight[68].The process of lypolysis is very important function in cholelithiasis which is regulated by the transmembrane receptor is also called beta3-adrenergic receptor which is exhibit in adipose tissue. The main function of the gallbladder is the contraction and relaxation, this function is associated with the different genes and one of the gene takes part in gallbladder contraction process is ADRB3 which exhibited high level in the tissue of the gallbladder.

Diet:

The reason for getting gallstones also mainly associated with the eating of more cholesterol and fat foods[69].Even consumption of extreme carbohydrates is also the reason for gallstone formation. So, to avoid this condition there are several ways are there, they are like drinking coffee, eating high fiber content food, and unsaturated fats. The best example for the diet consumption related to the formation of gallstone is the western population, in western countries the people eat lots of carbohydrates food, and food with less fiber content, these people are more common towards to get gallstones due to the consumption of such foods. The one more reason for the gallstones is the change in the diet which leads to the formation of cholesterol stones later gets converted to pigment stones. Even the extend duration of parenteral nutrition enhances the gallbladder function that is contraction and leads to the increase in gallbladder stones[70].

Sudden weight loss:

The sudden weight loss is also the one of the main cause for getting stones in the gallbladder. The weight loss is specifically low compared to normal weight deviates and leads to the formation of gallstones the weight loss should not cross 1.5kg in a week is the condition for the formation of gallstones in human beings[71-77]. The percentage of this condition varies with country to country and nearly about 7% to 16% of population is considered with symptoms of getting gallstones. The valid reason for sudden weight loss is mainly associated with intake of food; the managing food may avoid the formation of gallstones.

Drugs:

There are several drugs which cause the gallstone formation; the long period of consuming drugs may cause the stones in gallbladder. Examples like; octreotide is the one type of drug which causes the gallstones, by altering the gallbladder function such as motility of the gallbladder[78]. The corticosteroid treatment is for extended duration is the important reason to get gallstones which raises the level of lipid profile in the blood such as total cholesterol level, triglyceride level, low density lipoproteins. If bile does not dissolve the secreted high level cholesterol, it gets supersaturated with bile and the concentration of cholesterol in bile gets elevated and further leads to the formation of stones in the gallbladder. The bile composed of lecithin and phospholipids which helps to dissolve the deposited cholesterol in bile, if the abnormal secretion of both phospholipids and lecithin's are incapable to dissolve cholesterol. In cancer treatment condition there is high chance of getting gallstones. The main specific reason for the gallstone disease in drug intake condition is enzyme which is responsible for the

breakdown of cholesterol in the bile and excretion bile from the gallbladder, if the improper function of enzyme leads to the superstation process of cholesterol.

PATHOGENESIS OF GALLSTONE DISEASE

The process involved in the formation of stones in the gallbladder is due to several different factors. The different factors include such as obesity, more cholesterol diet and fat diet intake, lack of exercise, being high weigh, sudden loss of weight. Due to some drugs and in pregnancy time, after giving birth to child, age, gender, races these are all considered as important causing factors for cholelithiasis disease[79, 80]. The cholesterol secretion in to the bile is increased across the transmembrane of the gallbladder through the transporters of gene leads to increase in the concentration cholesterol in bile and decrease in the bile volume. This elevated level of cholesterol in bile promotes the process called supersaturation. The further supersaturation process causes the formation of different types of crystals, mucin gels and gallstones. The improper function of gallbladder such as decrease in motility of gallbladder further enhances the decrease in empty of gallbladder. There are different types of gallstones will form in the gallbladder based upon the constituents deposition in gallbladder. They are cholesterol, pigmented and mixed stones. The pigment stones are two types, differ in color they are brown and black pigmented stones which are formed by the excess level of bilirubin secretion in bile leads to pigment stone formation. The mainly nucleation process is involved in the supersaturation process it is due the accumulation of inorganic salts, excess level of calcium and phosphates. This nucleation process further leads to the formation of small nuclei's in the gallbladder. While the formation of cholesterol stones in the gallbladder is by the other important reason that is elevated level of cholesterol, lipids and bile salts in the bile of gallbladder[81]. The supersaturation of cholesterol in the bile leads to form the cholesterol stones, these cholesterol stones are the results of increase in the secretion of bile acids, lecithin and cholesterol[82]. There are different proteins are involved in the transportation of cholesterol, bile acids and lecithin or phospholipids. These three genes as proteins are named as an ABCG5/G8, CYP7A1 AND ABCB4. The ABCG5/G8 is responsible for the transportation of cholesterol into the bile through the transmembrane; the CYP7A1 is mainly responsible for the transportation of bile acids into the bile through the transmembrane. And ABCB4 gene transports the lecithins nothing but phospholipids into the bile. When there is abnormal condition occurs than the gene expression gets altered compared to normal expression. The ABCG5/G8 gene expression increases with increase in cholesterol deposition into the bile in abnormal condition and bile acids; lecithin gets secreted in normal level. Similarly the gene CYP7A1 expression decreases along with decrease in the secretion of bile acid, which is responsible for the solubalization of cholesterol. And the other ABCB4 gene expression gets decreases which results in the decrease of lecithin it is also mainly responsible for solubalization of cholesterol secreted into the bile.

When the cholesterol secretion is increased with decrease in the bile acids and lecithin the condition further leads to the supersaturation. This superstation process occurs due to the high cholesterol secretion in bile which causes the low bile concentration, as cholesterol secretion increases the concentration of bile gets decreases and leads to the supersaturation of cholesterol. The further nucleation process occurs with formation of small nuclei which is the beginning step for the stone formation in gallbladder stone disease[83]. In nucleation process there are two processes are involved; promote nucleation and inhibit nucleation. In promoting nucleation mucus glycoproteins and heat labile proteins are involved where as in the inhibition of nucleation the apolipoprotien and lecithin's are involved[84, 85]. The nucleation process leads to the formation of unilamellar vesicles, and precipitization of cholesterol leads the formation of monohydrate crystals which results in the micro stones. These micro stones fuse together or combine together and lead to the formation of big cholesterol stones[86].

GALLBLADDER CANCER

The formation of stones in the gallbladder is most common but the gallbladder cancer is very rare condition which occurs very less in people who suffer with gallstones. It is very uncommon seen condition; most of the cases are related with the inflammation of the gallbladder with major stones and with very serious pain of right upper abdomen part, right shoulder part, stomach pain, nausea and vomiting. Gallbladder cancer specially occurs in the last stage of the disease which cannot be predicted, the symptoms are very less in early stage. The survival rate in cancer of gallbladder is nearly about the 5-years and about 5%[87].

DIFFERENT BIOMARKERS IN GALLBLADDER CARCINOMA

The gallbladder cancer is very rare and it is uncommon, based on the reported data the cancer of gallbladder is very less. The cancer of gallbladder is deviate from male to female. The surgical removal of gallbladder is the only way to get rid of gallbladder cancer. The process of cancer begins with different types of molecules called as biomarkers and they mainly involve in this process. The different types of biomarkers are CA 19-9, CA 15-3, and CA 242, CA 50, CA 125, arginase and mucins. These all biomarkers are the important biomarkers among different types of biomarkers.

CA 19-9

The CA 19-9 is one of the biomarker which is considered as the leading one. This biomarker plays role in causing different cancers like gallbladder cancer, biliary tract cancer and cancer of pancreatic. This is the glycoprotein which is 210 kDa malignant which is considered as carbohydrate. The CA 19-9 is not only take part in causing cancer it is even present in different site of the body. It is

exist in ovarian cyst fluid, fluid of the seminal, saliva which is mucin rich, juice of gastric, fluid of amniotic, urine, pancreatic, gallbladder[88].

CA 15-3

CA 15-3 is the important antigen which causes the cancer to gallbladder. It is a miscellaneous in nature with a 300 kDa. It is also involves in the breast cancer which is resulted by increased level of presence in serum. The high level secretion of CA 15-3 causes the different types of cancers like; cancer of ovary, cancer of gallbladder, pancreas cancer, colorectal cancer, cancer in lung, stomach cancer and cancer of uterus[89-91]. This CA 15-3 is mainly present in the high level, especially in cancer of gallbladder. While in cholelithiasis patient it is present in fewer amounts.

CA 242

The CA 242 is also one of the biomarker considered to cause cancer of the gallbladder. The chemical structure of the CA 242 is not explained specifically. It is the antigen which is included as a monoclonal antibody, but is similar in the structure of carbohydrate. It is mainly exist in the mucin compound which is considered as CA 242. The gallbladder cancer occurs by the concentration of CA 242 in gallbladder, the patients who suffer with gallbladder cancer are having 42.19U/ml of CA 242 in the serum. Even it is having relationship with the ALP, total bilirubin in serum.

CA 50

The CA 50 is mainly takes part in the different cancer causing factor as a biomarker such as; cancer of bile duct, pancreas cancer, cancer of gallbladder. It is mainly considered to differentiate between the gallbladder cancers which are occurred by the benign and malignant. It is considered as a most frequent biomarker in the cancer of pancreatic.

CA 125

There are various types of glycoproteins are involved in the cancer of gallbladder. The one of the glycoprotein is CA 125, it is 200 kDa. The CA 125 is identified by the Murine monoclonal antibody which is explained by the cell line of adenocarcinoma. The CA 125 is seen in different sites of the body, such as in fetal, liquid body substances, epiglottis, bronchial and amnion[92-95]. In the cancer of the ovary the CA 125 is applied as an important precursor to cause cancer. In different cancers like breast cancer, bile duct cancer, gastrointestinal cancer, liver cancer, colorectal cancer, lung cancer and in many other cancer the CA 125 play a key role as a specifically[96].

Arginase

The arginase is also one of main biomarker which is extremely considered as important in the pathogenesis of cancer of gallbladder. It is a type of enzyme called manganese. The enzyme involved in the reaction such as arginine + water gives raise to ornithine + urea. The people who are with the gallbladder cancer are most probably with increased level of the arginase in their blood serum. In cancer there are different stages are involved based on the condition of tumors like stage I, stage II and stage III. The different stages of cancers are occurred, depends on the level of arginase in the tissue. So the stage III is mainly associated with high level of arginase in tissue.

Mucins

The mixture of carbohydrates and protein forms a glycoprotein, which is called mucins. The mucins are a bundle of molecules with increase in mass weight. The different studies which are performed have been reported such as advanced studies showed that MUC1 exhibited in malignancy of different human organs. Similarly the MUC2 is also type of mucin which is mainly present in the colon and it is exhibited in different organs including stomach. It is also takes part in the pathogenesis of cancer especially cancer related to the gallbladder.

DIAGNOSIS OF GALLSTONE DISEASE

The gallstone disease is a more common disorder, where the formation of crystals or stones in the gallbladder, common bile duct and in hepatic duct will happen. The stones are hardened in appearance; the formation of stones in gallbladder does not make any pain in human beings especially in early stage. But later the stones get bigger in size and cause the inflammation of gallbladder, necrosis in gallbladder leads to the tissue damage of the gallbladder. Once the stones get stuck or block the biliary duct it is the most serious or major problem, which leads to the rapidly sudden right upper abdomen pain, right shoulder pain.

To diagnose this disease there is the only one way which is easy and convenient method called ultrasonographic method. By using this method the stones are identified in the gallbladder or in common bile duct, hepatic duct[97].The diagnoses of gallbladder stones by ultrasonographic method is more common nearly about 95% of this method is followed in all over the world. It is more comfortable, protective, less expenditure method. The stones are usually identified in the position of liver below in which gallbladder is present [98]. By performing diagnostic method the doctor can say easily the expansion or magnitude of the stone, inflammation of the gallbladder, the width or diameter of gallbladder wall, area of the gallbladder, width of the common bile duct, hepatic duct, volume of the gallbladder and condition of the liver[99,100]. Even the types of different stones can be identified by ultrasonographic method. There are three different stones in the gallbladder; cholesterol stones, pigmented stones and mixed stones. This method is most preferably performed to detect gallstones.

TREATMENT

The treatment for gallstone disease is mainly depends on the state of existing of stones in the gallbladder. The size of the stones also matters for the treatment, severity,

function of the gallbladder and contents of the gallbladder mainly cholesterol secretion, bile acids and lecithin secretion. The doctors now days do not give any treatment without any specific symptoms which are related to the gallstone disease.

Cholecystectomy

In the treatment of stones in the gallbladder is performed mainly by cholecystectomy. Where this method is followed with standard procedure in which it is a type of surgery where a small instrument is placed in the wall of the abdomen near to gallbladder. Or it can be even performed by open surgery method. This method is a gold standard method which is considered for the therapy of gallstones[101-103]. In the cholecystectomy the open surgery and small incision method both are very protective treatments relating with the death rates of 0.1% to 0.7%[104]. The treatment of cholecystectomy is the very high expenditure treatment for gallstone disease. As it is considered as treatment even it has a barrier.

Dissolution of gallstones by oral route therapy

There are the drugs which dissolve the stones in the gallbladder. The drugs are like CDCA which is also called Chenodeoxycholic acid and UDCA, it is called as ursodeoxycholic acid. The CDCA drug has been considered as a first treatment to dissolve gallstones, but it has exhibited many adverse effects. This drug is given as oral administration to human beings who were suffered with the stones in the gallbladder and even for liver related disease[105].

Chenodeoxycholic acid

The Chenodeoxycholic acid is also called as chenodiol. As a main bile acid it is composed with bile. It is mainly produced by the liver and gets secreted or released in to the bile which mainly helps in dissolution of stones in the gallbladder.

Mechanism of action: The Chenodeoxycholic acid contains the bile acids which are mainly responsible for the dissolution of gallstones. It gets incorporated in to bile by producing from the liver. The bile which contains a concentration of bile acids enhances the mechanism of gallstone dissolution. It is having a negative feedback action. The enzyme which is responsible for production of cholesterol and bile is mainly regulated by the mechanism of action of Chenodeoxycholic acid which is having a negative feedback action on this cholesterol synthesizing enzyme. The drug is having 81-100% bioavailability and it will take a time of 3-6 months to show a beginning effect towards gallstone dissolution. The drug get metabolized and excreted from fecal matter about 80%.

Ursodeoxycholic acid

The ursodeoxycholic acid is the one of most current drug used in all over the world for treatment of gallstone diseases and related other liver disease. It is the one of the high expenditure or cost effective drug which has been chosen to dissolve gallstones. It usually composed in the bile and it is given by oral route. The mechanism of action is very effective towards the gallstone dissolution and including other related liver diseases treatment.

Mechanism of action: The ursodeoxycholic acid drug increases the bile flow from the gallbladder; the bile gets secreted in gallbladder. The drug shows its action by increasing the flow of bile which is secreted in gallbladder from the liver. The bile dissolves the cholesterol concentration and reduces the stone formation. It is mainly decreases the deposition of cholesterol from the liver. The drug avoids the re-absorption of cholesterol by the intestines. The UDCA is having a bioavailability is about 90% which is more compared to CDCA drug. The action towards the dissolution of gallstones is similar to CDCA about 3-6 months. The drug gets metabolized and even it is excreted mainly from the fecal matter.

Agents for cholesterol lowering

The main reason is to form cholesterol stone is high secretion of cholesterol into the bile and causing supersaturation of cholesterol in the bile. So the supersaturation process leads to the formation of crystals and further big stones of cholesterol. So there are some agents which are used to lower the cholesterol secretion. The statins are the main drugs which lowers the cholesterol level. This agent shows the effect by inhibiting the enzyme which is responsible for the cholesterol production. The enzyme involved in the production of cholesterol is the 3-hydroxy-3-methyl-glutaryl-Coa reductase[106-109].

Ezetimibe is also one of the agent or drug which mainly used as cholesterol lowering agent in gallstone disease. This drug is having an effect of hypocholesterolemic and it reduces the cholesterol secretion in intestinal part.

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