A DISSERTATION ON

"ASSOCIATION OF CHOLELITHIASIS, CHOLEDOCHOLITHIASIS AND HYPOTHYROIDISM"

Dissertation submitted to

THE TAMIL NADU Dr.M.G.R.MEDICAL UNIVERISTY

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with partial fulfilment of the regulations

for the Award of the degree

M.S. (General Surgery- Branch- I)

DEPARTMENT OF GENERAL SURGERY

THANJAVUR MEDICAL COLLEGE

APRIL 2016

CERTIFICATE

This is to certify that the dissertation entitled "**ASSOCIATION OF CHOLELITHIASIS, CHOLEDOCHOLITHIASIS AND HYPOTHYROIDISM"** is a bonafide original work of **Dr. V. L. Aishwarya** in partial fulfilment of the requirements for M.S.Branch–I (General Surgery) Examination of the Tamil Nadu Dr. M.G.R. Medical University to be held in APRIL 2016 under my guidance and supervision in 2014-2015

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DECLARATION

I *Dr. AISHWARYA.V.L* hereby solemnly declare that the dissertation titled "ASSOCIATION OF CHOLELITHIASIS, CHOLEDOCHOLITHIASIS AND HYPOTHYROIDISM**"** is done by me at Thanjavur medical College, Thanjavur during 2014-2015 under the guidance and supervision of

Prof.Dr.K. SATHYABAMA, M.S. This dissertation is submitted to The Tamil Nadu Dr.M.G.R Medical University, Chennai towards the partial fulfillment of requirements for the award of M.S.

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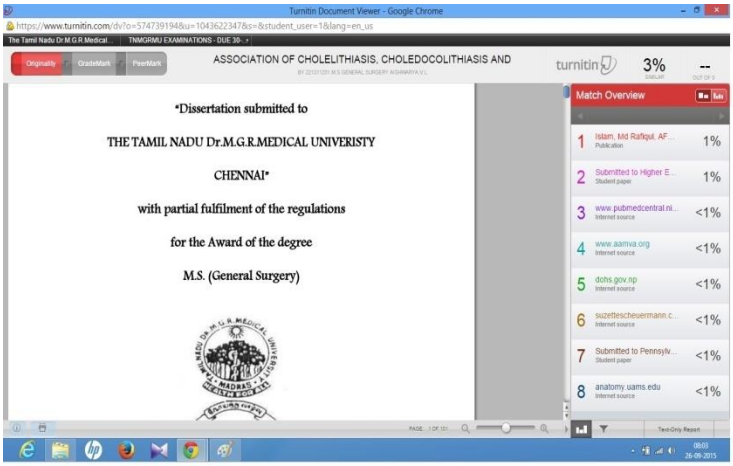

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LIST OF ABBREVIATIONS

GB - - Gall Bladder

CBD - - Common Bile Duct

SO - - Sphincter of Oddi

CCK - - Cholecystokinin

USG - - Ultrasonogram

CECT - - Contrast Enhanced Computed Tomography

MRCP - - Magnetic Resonance Cholangiopancreaticography

ERCP - - Endoscopic Retrograde Cholangiopancreaticography

PTC - - Percutaneous Transhepatic Cholangiography

TSH - - Thyroid Stimulating Hormone

TH - - Thyroid Hormones

TR - - intranuclear Thyroid Receptors

LDL - - Low Density Lipoproteins

HDL - - High Density Lipoproteins

HIDA - - Dimethyl Iminodiacetic Acid

CONTENTS

CHAPTER 1

INTRODUCTION

1. BACKGROUND

Gallstones are the most common biliary pathology, can be divided into three main types: cholesterol, pigment (black, brown) or mixed stones. In the USA and Europe, 80%cholesterol or mixed stones, where as in Asia, 80% are pigment stones. Cholesterol or mixed stones contain 51 – 99 % cholesterol plus admixture of calcium salts, bile acids, bile pigment and phospholipids. Gallstones may be single or multiple, large or small those containing calcium salts are radio-opaque. Single stones are uncommon but usually consist mainly of cholesterol and arise due to a disorder of the physio-chemical equilibrium which normally maintains cholesterol in micellar form in the bile.

Many studies were done to identify risk factor for biliary lithiasis in the west have focused on hypersaturation of cholesterol in bile in nucleation process a critical step in the genesis of bile stone.

Thyroid disorder is a prevalent condition among adult population; however, it is frequently over looked. For decade, there has been a discussion, whether thyroid disorders could cause gallstone disease. Particularly, there are several explanations for a possible relation between hypothyroidism and gallstone disease; these explanations include the known link between thyroid failure and disturbances of lipid metabolism

that may consecutively lead to change of composition of the bile. Recent studies also demonstrated low bile flow in hypothyroid subjects.

Furthermore, the sphincter of oddi expresses thyroid hormone receptors and thyroxine has a direct prorelaxing effect on the sphincter. Both low bile flow and sphincter of oddi dysfunction are regarded as important functional mechanisms that may promote gallstone formation.

The prevalence of previously undiagnosed thyroid function abnormalities has never been studied in gallstone patients before. If an increased prevalence of thyroid disorders will be found, it might have an effect on the diagnostic and therapeutic work up of patient with gallstone.

Hypothyroidism is the most common cause of secondary hypercholesterolaemia , patients with hypothyroidism have serum level of cholesterol approximately 50% higher than level in euthyroid patients and 90% of all hypothyroid patients have elevated cholesterol level.

1.2 OBJECTIVES

The purpose of this study is

1. To study the prevalence of hypothyroidism in patients presenting with CHOLELITHIASIS/ CHOLEDHOCOLITHIASIS.

2. To assess if thyroid profile is indicated in patients with biliary lithiasis.

2.1 Anatomy of the biliary system

"The biliary tree consists of the system of vessels and ducts which collect and deliver bile from the liver parenchyma to the second part of the duodenum. It is conventionally divided into intrahepatic and extrahepatic biliary trees. The intrahepatic ducts are formed from the larger bile canaliculi which join together to form segmental ducts. These fuse close to the porta hepatis into right and left hepatic ducts. The extrahepatic biliary tree consists of the right and left hepatic ducts, the common hepatic duct, the cystic duct and gallbladder and the common bile duct."

GALLBLADDER

"The gallbladder is a flask-shaped; blind-ending diverticulum attached to the common bile duct by the cystic duct. It usually lies attached to the inferior surface of the right lobe of the liver, by connective tissue. In the adult the gallbladder is between 7 and 10 cm long, with a capacity of up to 50 ml. It can hold up to 500ml of bile. It usually lies in a shallow fossa in the liver parenchyma, covered by peritoneum continued from the liver surface. This attachment can vary widely. At one extreme, the gallbladder may be almost completely buried within the liver surface, having no peritoneal covering (intraparenchymal pattern); at the other extreme, it may hang from a short mesentery formed by the two layers of peritoneum separated only by connective tissue and a few small vessels (mesenteric pattern).

The gallbladder is described as having a fundus, body, infundibulum and neck. The neck lies at the medial end close to the porta hepatis, and almost always has a short peritoneal-covered attachment to the liver (mesentery); this mesentery usually contains the cystic artery. The mucosa at the medial end of the neck is obliquely ridged, forming a spiral groove continuous with the spiral valve of the cystic duct. At its lateral end the neck widens out to form the body of the gallbladder and this widening is often referred to in clinical practice as 'Hartmann's pouch'. The neck lies anterior to the second part of the duodenum.

The body of the gallbladder normally lies in contact with the liver surface. When the neck possesses a mesentery; this rapidly shortens along the length of the body as it comes to lie in the gallbladder fossa. It lies anterior to the second part of the duodenum and the right end of the transverse colon. The fundus lies at the lateral end of the body and usually projects past the inferior border of the liver to a variable length. It often lies in contact with the anterior abdominal wall behind the ninth costal cartilage where the lateral edge of the right rectus abdominis crosses the costal margin. This is the location where enlargement of the gallbladder is best sought on clinical examination. The fundus commonly lies adjacent to the transverse colon.

The gallbladder varies in size and shape. The fundus may be elongated and highly mobile. Rarely, the fundus is folded back upon the body of the

gallbladder, the so-called Phrygian cap: on ultrasound, this may be wrongly interpreted as an apparent septum within an otherwise normal gallbladder. Again, rarely, the gallbladder may be bifid or completely duplicated, usually with a duplicated cystic duct

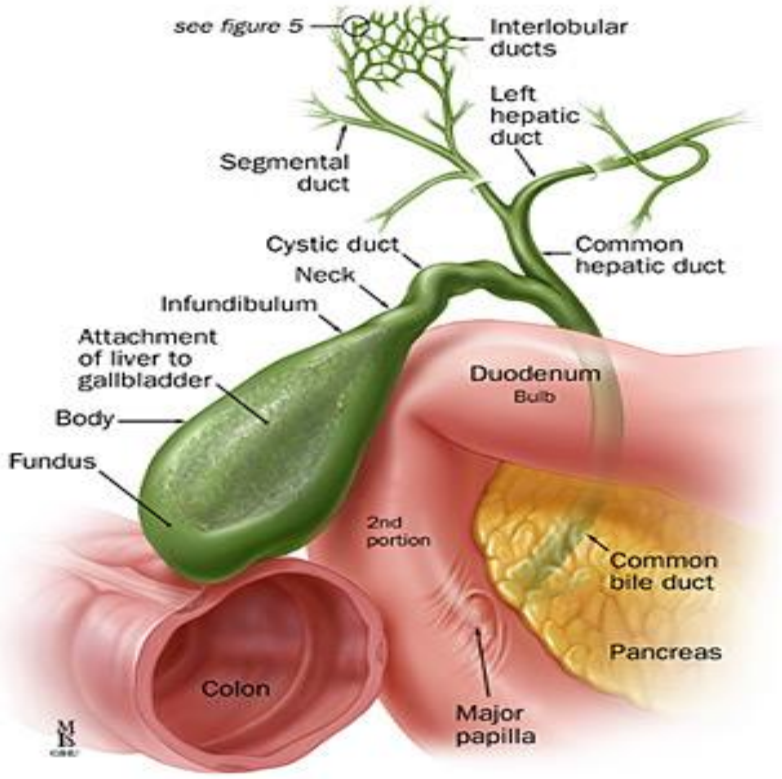


Fig 1. Overall arrangement of the intrahepatic and extrahepatic biliary tree.

CYSTIC DUCT

The cystic duct is about 3-4 cms in length and it drains into the CBD. It passes posteriorly to the left from the neck of the gallbladder, and joins the common hepatic duct to form the common bile duct. It almost always runs parallel to, and is adherent to, the common hepatic duct for a short distance before joining it. The

junction usually occurs near the porta hepatis but may be lower down in the free edge of the lesser omentum.

The cystic duct may have several important variations in its anatomy. The cystic duct occasionally drains into theright hepatic duct, in which case it may be elongated, lie anterior or posterior to the common hepatic duct, and join the right hepatic duct on its left border. Rarely, the duct is double or even absent, in which case the gallbladder drains directly into the common bile duct. One or more accessory hepatic ducts occasionally emerge from segment V of the liver and join either the right hepatic duct, the common hepatic duct, the common bile duct, the cystic duct, or the gallbladder directly. These variations in cystic duct anatomy are of considerable importance during surgical excision of the gallbladder. Ligation or clip occlusion of the cystic duct must be performed at an adequate distance from the common bile duct to prevent angulation or damage to it. Accessory ducts must not be confused with the right hepatic or common hepatic ducts.

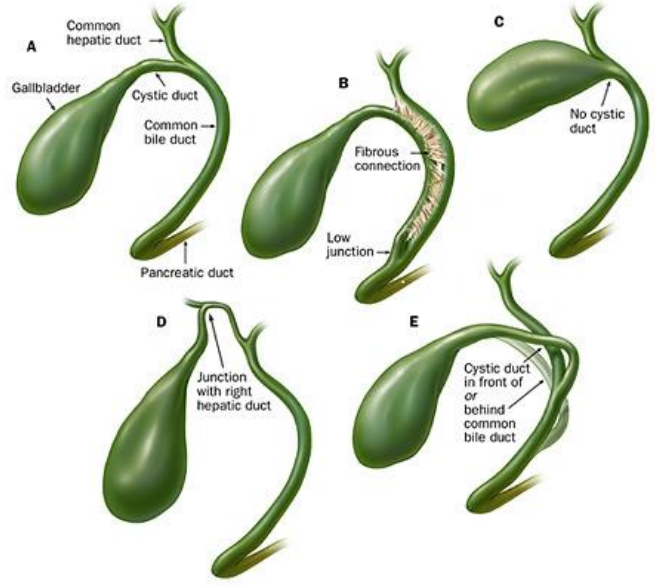


Fig 2: Anatomical variations in cystic duct

Mucosa of the cystic duct has 5–12 crescentic folds; continuous with the neck of the gallbladder. They project obliquely in regular succession; appearing to form a spiral valve when the duct is cut in longitudinal section. When the duct is distended, the spaces dilate and it appears twisted like neck of the GB.

HEPATIC BILE DUCTS

The main right and left hepatic ducts; emerge from the liver and unite near the right end of the porta hepatis as the common hepatic duct. The extrahepatic right duct, is short and nearly vertical while the left, is more horizontal and lies in segment IV. The common hepatic duct is joined on its right in an acute angle by the cystic duct to form the CBD. "The common hepatic duct lies to the right of the hepatic artery and anterior to the portal vein in the free edge of the lesser omentum.

COMMON BILE DUCT

The common bile duct is formed near the porta hepatis, by the junction of the cystic and common hepatic ducts, and is usually between 6 and 8 cm long. Its diameter tends to increase somewhat with age but is usually around 6 mm in adults. It descends posteriorly and slightly to the left, anterior to the epiploic foramen, in the right border of the lesser omentum, where it lies anterior and to the right of the portal vein and to the right of the hepatic artery. It passes behind the first part of the duodenum with the gastroduodenal artery on its left, and then runs in a groove on the superolateral part of the posterior surface of the head of the pancreas." The IVC lies posterior to the duct and the duct is occasionally embedded in the pancreatic tissue. It may lie close to the medial wall of the second part of the duodenum or as much as 2

cm from it: even when it is embedded in the pancreas, a groove in the gland marking its position can be palpated behind the second part of the duodenum.

Hepatopancreatic ampulla (of Vater)

As it lies medial to the second part of the duodenum, the common bile duct approaches the right end of the pancreatic duct. The union of the common bile duct and the main pancreatic duct follows one of the three configurations. In about 70% of people, these ducts unite outside the duodenal wall and traverse the duodenal wall as a single duct. In about 20%, they join within the duodenal wall and have a short or no common duct, but open through the same opening into the duodenum. In about 10%, they exit via separate openings in the duodenum. Circular muscle usually surrounds the lower part of the common bile duct (bile duct sphincter) and frequently also surrounds the terminal part of the main pancreatic duct (pancreatic duct sphincter) and the hepatopancreatic ampulla (sphincter of Oddi). When all elements are present, this arrangement may allow for separate control of pancreatic and common bile duct emptying. Division of the upper part of the ampulla and ampullary sphincter (sphincterotomy) may be required to allow access to the common bile duct during endoscopic retrograde cholangiography.

Calot's triangle

The near triangular space, formed between the cystic duct, the common hepatic duct and the inferior surface of segment V of the liver, is commonly referred to as Calot's triangle. It is enclosed by the double layer of peritoneum, which forms the short mesentery of the cystic duct. Since the two layers are not closely

opposed, there is an appreciable amount of loose connective tissue within the triangle. It is perhaps better described as a pyramidal ‘space' with one apex lying at the junction of the cystic duct and fundus of the gallbladder, one at the porta hepatis, and two closer apices at the attachments of the gallbladder to the liver bed. The base of the triangle, thus lies on the inferior surface of the liver. This space usually contains the cystic artery as it approaches the gallbladder, the cystic lymph node and lymphatics from the gallbladder, one or two small cystic veins, the autonomic nerves running to the gallbladder, and some loose adipose tissue. It may contain any accessory ducts which drain into the gallbladder from the liver. One must be aware of the variations in cystic duct anatomy so that we avoid accidently ligating the common bile duct.

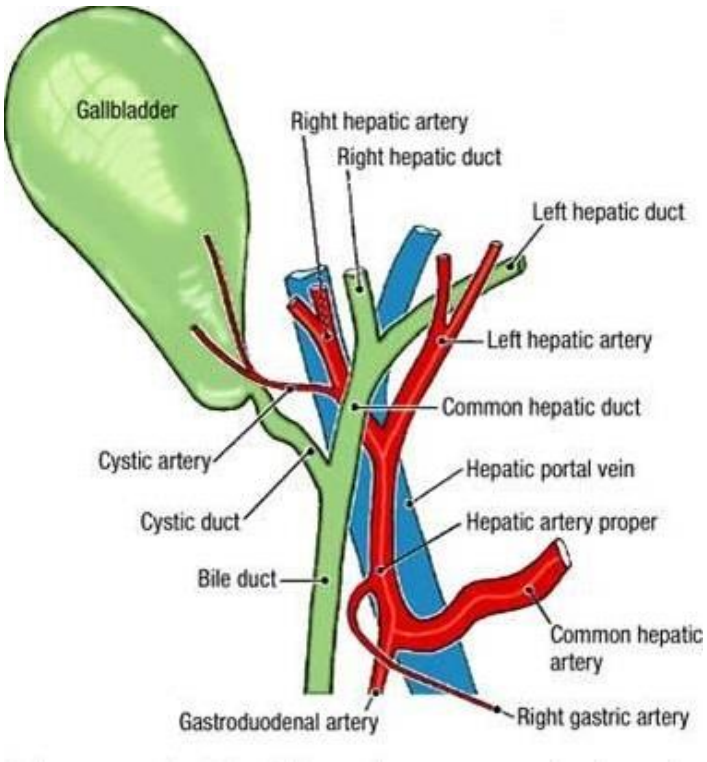


Fig3: Normal anatomy of the cystic artery

VASCULAR SUPPLY AND LYMPHATIC DRAINAGE

Cystic artery

The cystic artery usually arises from the right hepatic artery. It usually passes posterior to the common hepatic duct and anterior to the cystic duct to reach the superior aspect of the neck of the gallbladder and divides into superficial and deep branches. The superficial branch ramifies on the inferior aspect of the body of the gallbladder, the deep branch on the superior aspect. These arteries anastomose over the surface of the body and fundus. The origin of the cystic artery frequently varies. The most common variant is an origin from the common hepatic artery (Occasionally low down), sometimes from the left hepatic or gastroduodenal artery, and rarely from the superior pancreaticoduodenal, coeliac, right gastric or superior mesenteric arteries. In these cases, it crosses anterior (or less commonly posterior) to the common bile duct or common hepatic duct to reach the gallbladder. An accessory cystic artery may arise from the common hepatic artery or one of its branches and the cystic artery often bifurcates close to its origin, giving rise to two vessels which approach the gallbladder. Multiple fine arterial branches may arise from the parenchyma of segments IV or V of the liver and contribute to the supply of the body, particularly when the gallbladder is substantially intrahepatic. This makes the gallbladder relatively resistant to necrosis during inflammation which otherwise occludes the cystic artery.

These fine branches form a network which anastomoses with the vessels ascending around the common bile duct “and with the vessels from the liver parenchyma which descend with the right and left hepatic ducts.

Ductal arteries

The common bile duct and hepatic ducts are supplied by a fine network of vessels, which usually receive contributions from several sources; and which lie in close proximity to the ducts.” Disruption of the network during surgical exposure of the bile ducts over a long length frequently causes chronic ischaemia and resultant stenosis of the duct. Approaches which spare the network are necessary to avoid this complication.The common bile duct is fairly consistently supplied by two to four ascending and descending arteries which form long narrow anastomotic channels along the length of the duct: the most prominent of these are disposed into medial and lateral ‘trunks', although they may lie more anterolateral and posteromedial. The largest contributions, usually arise as one or two branches, from the retroduodenal branch of the gastroduodenal artery; as it crosses the anterior surface of the duct at the upper border of the duodenum. Three or four descending branches; supply this network from the right hepatic and cystic arteries; as these vessels pass close to the lower common hepatic duct, occasionally they are “the dominant supply to the common bile duct”.

Posteriorly, a retroportal artery often arises from the coeliac axis, superior mesenteric artery or one of their major branches close to the origin from the " aorta, and runs upwards on the posterior surface of the portal vein. It usually ends by joining the retroduodenal artery close to the lower end of the supraduodenal bile duct, but occasionally it passes up behind the bile duct to join the right hepatic artery. Wher present, the retroportal artery contributes to the arterial network supplying the supraduodenal bile duct system.

Cystic veins

The venous drainage of the gallbladder is rarely by a single cystic vein There are usually multiple small veins. Those arising from the superior surface of the body and neck lie in areolar tissue between the gallbladder and liver and enter the liver parenchyma to drain into the segmental portal veins. The remainder form one or two small cystic veins, which enter the liver either directly or after joining the veins that drain the hepatic ducts and upper bile duct. Only rarely does a single or double cystic vein drain into the right portal branch.

Lymphatics:

Numerous lymphatic vessels; run from the submucosal and subserosal plexuses on all aspects of the gallbladder and cystic duct. Those on the hepatic aspect of the gallbladder connect with the intrahepatic lymph vessels. "The remainder drain into the cystic node, which usually lies above the cystic duct in the tissue of Calot's triangle. This node, and some lymphatic channels which bypass the cystic node, drain into a

node lying in the anterior border of the free edge of the lesser omentum. Hepatic nodes collect lymph from vessels that accompany the hepatic ducts and the upper" part of the bile duct. The inferior hepatic and upper pancreaticosplenic nodes receive lymphatics from the lower part of Common bile duct.

INNERVATION

The gallbladder and the extrahepatic biliary tree are innervated by branches from the hepatic plexus. The retroduodenal part of the common bile duct and the smooth muscle of the hepatopancreatic ampulla are also innervated by twigs from the pyloric branches of the vagi.

Referred pain: In common with other structures of foregut origin, pain caused by stretch of the common bile duct or gallbladder is referred to the epigastrium. Involvement of the overlying somatic peritoneum produces pain which is more localized to the right upper quadrant.

GALLBLADDER

The fundus of the gallbladder is completely covered by a serosa, and the inferior surfaces and sides of the body and neck of the gallbladder are usually covered by a serosa. If the gallbladder possesses a mesentery the serosa extends around the sides of the body and neck onto the superior surface and continues into the serosa of the mesentery, whereas the serosa is limited to the inferior surfaces only if the gallbladder is intrahepatic. Beneath the serosa is subserous loose connective and adipose peritoneal tissue. The gallbladder wall microstructure

generally resembles that of the small intestine. The mucosa is yellowish-brown and elevated into minute rugae with a honeycomb appearance. In section, projections of the mucosa into the gallbladder lumen resemble intestinal villi, but they are not fixed structures and the surface flattens as the gallbladder fills with bile. The epithelium is a single layer of columnar cells with apical microvilli; basally, the spaces between epithelial cells are dilated. Many capillaries lie beneath the basement membrane. The epithelial cells actively absorb water and solutes from the bile and concentrate it up to ten-fold. There are no goblet cells in the epithelium. The thin fibromuscular layer is composed of fibrous tissue mixed with smooth muscle cells arranged loosely in longitudinal, circular and oblique bundles. Gall bladder does not have submucosal layer and a muscular layer.

BILE DUCTS

The walls of the large biliary ducts consist of external fibrous and internal mucosal layers. The outer layer is fibrous connective tissue containing a variable amount of longitudinal, oblique and circular smooth muscle cells. The mucosa is continuous with that in the hepatic ducts, gallbladder and duodenum. The epithelium is columnar and there are numerous tubuloalveolar mucous glands in the duct walls.

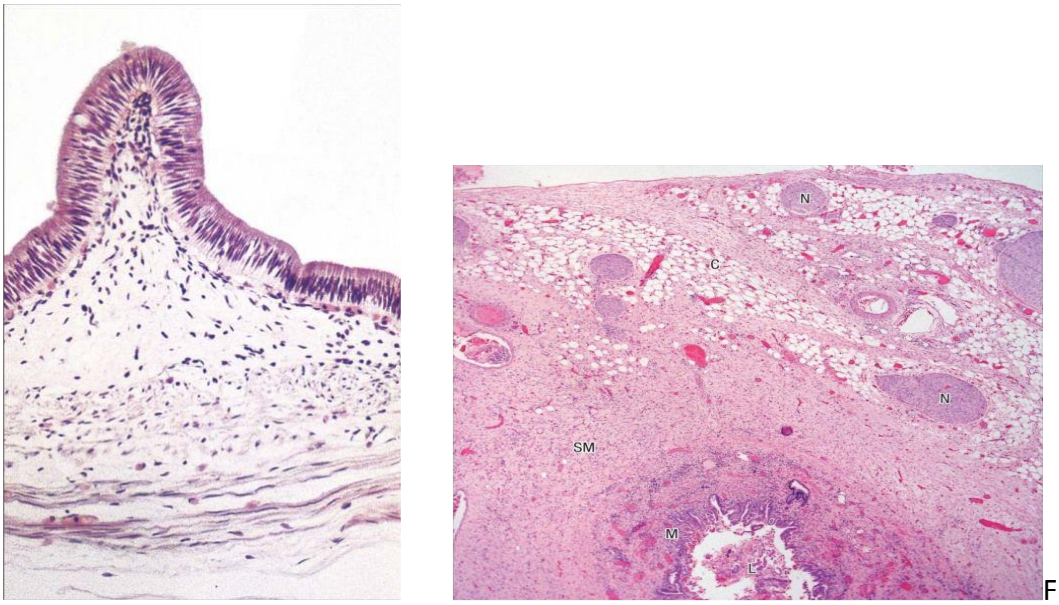


Fig 4: *Low power micrograph showing the gallbladder wall and the human common bile duct structure*.

Sphincter of Oddi:

The sphincter of Oddi regulates flow of bile; into the duodenum, prevents the regurgitation of duodenal contents into the biliary tree, and diverts bile into the gallbladder. It is a "complex structure that is functionally independent from the duodenal musculature and creates a high-pressure zone between the bile duct and the duodenum.

The sphincter of Oddi is about 4 to 6 mm in length and has a basal resting pressure of about 13 mmHg above the duodenal pressure. On manometry, the sphincter shows phasic contractions with a frequency of about four per minute and amplitude of 12 to 140 mmHg. The spontaneous motility of the sphincter of Oddi is regulated by the interstitial cells of Cajal through intrinsic and extrinsic inputs from

hormones and neurons acting on the smooth muscle cells. Relaxation occurs with a rise in CCK, leading to diminished amplitude of phasic contractions and reduced basal pressure, allowing increased flow of bile into the duodenum. During fasting, the sphincter of Oddi activity is coordinated with the periodic partial gallbladder emptying and an increase in" bile flow; that occurs during phase II of migrating myoelectric motor complex.

2.2 Physiology of biliary system

BILE:

The amount of bile secreted per day is 500- 1000ml. Bile serves two important "functions: First, bile plays an important role in fat digestion and absorption, because bile acids in the bile do two things:

(1) Bile emulsifies fat into smaller particles which can be attacked by lipase enzyme secreted from the pancreas

(2) They aid in absorption of the digested fat end products through the intestinal mucosal membrane.

Second, bile serves as a means for excretion of several important waste products from the blood." These include especially "bilirubin", an end product of haemoglobin degradation; and excesses of cholesterol.

SECRETION OF BILE:

Bile is secreted in two stages by the liver:

(1) The initial portion is secreted by the principal functional cells of the liver, the hepatocytes; this initial secretion contains large amounts of bile acids, cholesterol, and other organic constituents. It is secreted into minute bile canaliculi that originate between the hepatic cells.

(2) Next, the bile flows in the canaliculi toward the interlobular septa, where the canaliculi empty into terminal bile ducts and then into progressively larger ducts, finally reaching the hepatic duct and common bile duct. From these the bile either empties directly into the duodenum or is diverted for minutes up to several hours through the cystic duct into the gallbladder. In its course through the bile ducts, a second portion of liver secretion is added to the initial bile. This additional secretion is a watery solution of sodium and bicarbonate ions secreted by secretory epithelial cells that line the ductules and ducts. This second secretion sometimes increases the total quantity of bile by as much as an additional 100 per cent. The second secretion is stimulated especially by secretin, which causes release of additional quantities of bicarbonate ions to supplement the bicarbonate ions in pancreatic secretion (for neutralizing acid that empties into the duodenum from the stomach).

STORAGE OF BILE:

Bile is normally stored in the gallbladder until required in the duodenum. The maximum volume that it can hold - 30 to 60 milliliters. Nevertheless, as " much as 12 hours of bile secretion (usually about 450 milliliters) can be stored in the gallbladder because water, sodium, chloride, and most other small electrolytes are

continually absorbed through the gallbladder mucosa, concentrating the remaining bile constituents that contain the bile salts, cholesterol, lecithin, and bilirubin.

Most of this gallbladder absorption is caused by active transport of sodium through the gallbladder epithelium, and this is followed by secondary absorption of chloride ions, water, and most other diffusible constituents. Bile is normally concentrated in this way about 5-fold, but it can be concentrated up to a maximum of 20-fold.

Comparison of Hepatic Duct Bile and Gallbladder Bile.

	Hepatic Duct Bile	**Gallbladder Bile**
Percentage of solids	2–4	10–12
Bile acids (mmol/L)	10–20	50–200
pH	7.8–8.6	7.0–7.4

This table shows that gall bladder bile has more solutes which are mainly the bile salts. Also secreted or excreted in large concentrations are bilirubin, cholesterol, lecithin, and the usual electrolytes of plasma. In the concentrating process in the gallbladder, water and large portions of the electrolytes (except calcium ions) are reabsorbed by the gallbladder mucosa; essentially all other constituents, especially the bile salts and the lipid substances cholesterol" and lecithin, do not get reabsorbed and, therefore; become highly concentrated in the GB bile.

HORMONAL CONTROL OF BILE SECRETION:

1. CHOLECYSTOKININ

When food begins to be digested in the upper gastrointestinal tract, the gallbladder begins to empty, especially when fatty foods reach the duodenum about 30 minutes after a meal. The mechanism of gallbladder emptying is rhythmical contractions of the wall of the gallbladder, but effective emptying also requires simultaneous relaxation of the sphincter of Oddi, which guards the exit of the common bile duct into the duodenum. By far the most potent stimulus for causing the gallbladder contractions is the hormone cholecystokinin. This is the same cholecystokinin discussed earlier that causes increased secretion of digestive enzymes by the acinar cells of the pancreas. The stimulus for cholecystokinin entry into the blood from the duodenal mucosa is mainly the presence of fatty foods in the duodenum. In addition to cholecystokinin, the gallbladder is stimulated less strongly by acetylcholine-secreting nerve fibers from both the vagi and the intestinal enteric nervous system. They are the same nerves that promote motility and secretion in other parts of the upper gastrointestinal tract. In summary, the gallbladder empties its store of concentrated bile into the duodenum mainly in response to the cholecystokinin stimulus that itself is initiated mainly by fatty foods. When fat is not in the food, the gallbladder empties poorly, but when significant quantities of fat are present, the gallbladder normally empties completely in about 1 hour.

1. SECRETIN

In addition to the strong stimulating effect of bile acids to cause bile secretion, the hormone secretin that also stimulates pancreatic secretion increases bile secretion, sometimes more than doubling its secretion for several hours after a meal. This increase in secretion is almost entirely secretion of a sodium bicarbonate-rich watery solution by the epithelial cells of the bile ductules and ducts, and not increased secretion by the liver parenchymal cells themselves. The bicarbonate in turn passes into the small intestine and joins the bicarbonate from the pancreas in neutralizing the hydrochloric acid from the stomach. Thus, the secretin feedback mechanism for neutralizing duodenal acid operates not only through its effects on pancreatic secretion but also to a lesser extent through its effect on secretion by the liver ductules and ducts.

ENTEROHEPATIC CIRCULATION:

About 94% of "the bile salts are reabsorbed into the blood from the small intestine, about one half of this by diffusion through the mucosa in the early portions of the small intestine and the remainder by an active transport process through the intestinal mucosa in the distal ileum. They then enter the portal blood and pass back to the liver. On reaching the liver, on first passage through the venous sinusoids these salts are absorbed almost entirely back into the hepatic cells and then are resecreted into the bile. In this way, about 94 per cent of all the bile salts are recirculated into the bile, so that on the average these salts make the entire circuit

some 17 times before being carried out in the feces. The small quantities of bile salts lost into the feces are replaced by new amounts formed continually by the liver cells. This recirculation of the bile salts is called the enterohepatic circulation of bile salts.

The quantity of bile secreted by the liver each day is highly dependent on the availability of bile salts—the greater the quantity of bile salts in the enterohepatic circulation (usually a total of only about 2.5 grams), the greater the rate of bile secretion. Indeed, ingestion of supplemental bile salts can increase bile secretion by several hundred milliliters per day. If a bile fistula empties the bile salts to the exterior for several days to several weeks so that they cannot be reabsorbed from the ileum, the liver increases its production of bile salts 6- to 10-fold, which increases the rate of bile secretion most of the way back to normal. This demonstrates that the daily rate of liver bile salt secretion is actively controlled by the availability (or lack of availability) of bile salts in the" enterohepatic circulation.

2.3 GALLSTONES- PATHOPHISIOLOGY:

The major organic contents in bile are cholesterol; bilirubin; bile salts and phospholipids. Gallstones "are classified as cholesterol and pigment stones based on their cholesterol content. In general the incidence of cholesterol ctones is higher than pigment" stones in Asia.

Cholesterol Stones:

Pure cholesterol stones "are uncommon and account for <10% of all stones. They usually occur as single large stones with smooth surfaces. Most other cholesterol stones contain variable amounts of bile pigments and calcium, but are always >70% cholesterol by weight. These stones are usually multiple, of variable size, and may be hard and faceted or irregular, mulberry-shaped, and soft. Colors range from whitish yellow and green to black. Most cholesterol stones are radiolucent; <10% are radiopaque. Whether pure or of mixed nature, the common primary event in the formation of cholesterol stones is supersaturation of bile with cholesterol. Therefore, high bile cholesterol levels and cholesterol gallstones are considered as one disease. Cholesterol is highly nonpolar and insoluble in water and bile. Cholesterol solubility depends on the relative concentration of cholesterol, bile salts, and lecithin (the main phospholipid in bile). Supersaturation almost always is caused by cholesterol hypersecretion rather than by a reduced secretion of phospholipid or bile salts. Cholesterol is secreted into bile as cholesterol-phospholipid vesicles. Cholesterol is held in solution by micelles, a conjugated bile salt-phospholipid-cholesterol complex, as well as by the cholesterol-phospholipid vesicles. The presence of vesicles and micelles in the same aqueous compartment allows the movement of lipids between the two. Vesicular maturation occurs when vesicular lipids are incorporated into micelles. Vesicular phospholipids are incorporated into micelles more readily than vesicular cholesterol. Therefore, vesicles may become enriched in cholesterol, become unstable, and then nucleate cholesterol crystals." In unsaturated bile, cholesterol enrichment of vesicles is inconsequential. In the supersaturated bile,

cholesteroldense “zones develop on the surface of the cholesterol-enriched vesicles, leading to the appearance of cholesterol crystals. About one third of biliary cholesterol is transported in micelles, but the cholesterol-phospholipid vesicles” carry the majority of biliary cholesterol.

Pigment Stones:

Pigment stones contain <20% cholesterol and “are dark because of the presence of calcium bilirubinate. Otherwise, black and brown pigment stones have little in common and should be considered as separate entities. Black pigment stones are usually small, brittle, black, and sometimes spiculated. They are formed by supersaturation of calcium bilirubinate, carbonate, and phosphate, most often secondary to hemolytic disorders such as hereditary spherocytosis and sickle cell disease, and in those with cirrhosis. Like cholesterol stones, they almost always form in the gallbladder. Unconjugated bilirubin is much less soluble than conjugated bilirubin in bile. Deconjugation of bilirubin occurs normally in bile at a slow rate. Excessive levels of conjugated bilirubin, as in hemolytic states, lead to an increased rate of production of unconjugated bilirubin. Cirrhosis may lead to increased secretion of unconjugated bilirubin. When altered conditions lead to increased levels of deconjugated bilirubin in bile, precipitation with calcium occurs.

In Asian countries such as Japan, black stones account for a much higher percentage of gallstones than in the Western hemisphere. Brown stones are usually <1 cm in diameter, brownish yellow, soft, and often mushy. They may

form either in the gallbladder or in the bile ducts, usually secondary to bacterial infection caused by bile stasis. Precipitated calcium bilirubinate and bacterial cell bodies compose the major part of the stone. Bacteria such as Escherichia coli secrete β-glucuronidase that enzymatically cleaves bilirubin glucuronide to produce the insoluble unconjugated bilirubin. It precipitates with calcium, and along with dead bacterial cell bodies, forms soft brown stones in the biliary tree. Brown stones are typically found in the biliary tree of Asian populations and are associated with stasis secondary to parasite infection. In Western populations, brown stones occur as primary bile duct stones in patients with biliary strictures or" other common bile duct stones that cause stasis and bacterial contamination.

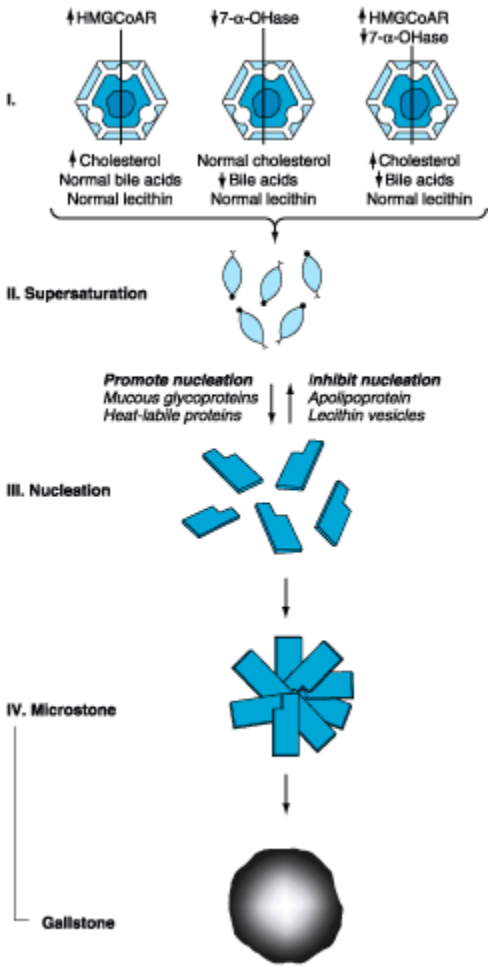


Fig 5: Mechanism of bile stone formation

Fig 6: Cholesterol and pigment stones

Choledocholithiasis:

Common "bile duct stones may be small or large and single or multiple, and are found in 6% to 12% of patients with stones in the gallbladder. The incidence increases with age. About 20% to 25% of patients above the age of 60 with symptomatic gallstones have stones in the common bile duct as well as in the gallbladder. The vast majority of ductal stones in Western countries are formed within the gallbladder and migrate down the cystic duct to the common bile duct. These are classified as secondary common bile duct stones, in contrast to the primary stones that form in the bile ducts. The secondary stones are usually cholesterol stones, whereas the primary stones are usually of the brown pigment type. The primary stones are associated with biliary stasis and infection and are more commonly seen in Asian populations.

The causes of biliary stasis that lead to the development of primary stones include biliary stricture," papillary stenosis, tumors, or other (secondary) stones.

Acute Cholecystitis:

Gall stones are the "initiating event in 90-95% of the cases. Tumour contributes to only 1% of the cases. Acalculous cholecytitis is found to occur as a part of systemic disease. Cystic duct gets obstructed by the gall stone, following which the gall bladder gets distended and the inflammatory process begin. Toxin lysolecithin, a product of lecithin, is released along with bile salts and platelet aggregating factor, these are the mediators invloved in the inflammatory process. This process gets amplified by increase in prostaglandin synthesis. Secondary bacterial infection occurs in 15% to 30% of patients. In acute cholecystitis, GB wall becomes thickened and subserosal haemorrhages are seen. The mucosa is hyperaemic and patchy necrosis of the mucosa occurs. The gall stone dislodges and the inflammatory process subsides in" most of the cases, but in few cases the inflammation will progress leading to the necrosis of the entire gall bladder wall.

Chronic Cholecystitis:

About two thirds of patients "with gallstone disease present with chronic cholecystitis characterized by recurrent attacks of pain, often inaccurately labeled biliary colic. The pain develops when a stone obstructs the cystic duct, resulting in a progressive increase of tension in the gallbladder wall. The

pathologic changes, which often do not correlate well with symptoms, vary from an apparently normal gallbladder with minor chronic inflammation in the mucosa, to a shrunken, nonfunctioning gallbladder with gross transmural fibrosis and adhesions to nearby structures. The mucosa is initially normal or hypertrophied, but later becomes atrophied, with the epithelium protruding into the muscle coat, leading to the formation of the" so-called Aschoff- Rokitansky sinuses.

2.4 Clinical Features

Gallstone disease is one of the most "common problems affecting the digestive tract. Autopsy reports have shown a prevalence of gallstones from 11% to 36%. The prevalence of gallstones is related to many factors, including age, gender, and ethnic background. Certain conditions predispose to the development of gallstones. Obesity, pregnancy, dietary factors, Crohn's disease, terminal ileal resection, gastric surgery, hereditary spherocytosis, sickle cell disease, and thalassemia are all associated with an increased risk of developing gallstones. Women are three times more likely to develop gallstones than men, and first-degree relatives of patients with gallstones have a" twofold greater prevalence.

Natural History

Most patients will remain "asymptomatic from their gallstones throughout life. For unknown reasons, some patients progress to a symptomatic stage, with biliary colic caused by a stone obstructing the cystic duct. Symptomatic gallstone

disease may progress to complications related to the gallstones. These include acute cholecystitis, choledocholithiasis with or without cholangitis, gallstone pancreatitis, cholecystocholedochal fistula, cholecystoduodenal or cholecystoenteric fistula leading to gallstone ileus, and gallbladder carcinoma.

Rarely, complication of gallstones is the presenting picture. Gallstones in patients without biliary symptoms are commonly diagnosed incidentally on ultrasonography, CT scans, or abdominal radiography or at laparotomy. Several studies have examined the likelihood of developing biliary colic or developing significant complications of gallstone disease. Approximately 3% of asymptomatic individuals become symptomatic per year (i.e., develop biliary colic). Once symptomatic, patients tend to have recurring bouts of biliary colic. Complicated gallstone disease develops in 3% to 5% of symptomatic patients per year. Over a 20-year period, about two thirds of asymptomatic patients with gallstones remain symptom free. Because few patients develop complications without previous biliary symptoms, prophylactic cholecystectomy in asymptomatic persons with gallstones is rarely indicated. For elderly patients with diabetes, for individuals who will be isolated from medical care for extended periods of time, and in populations with increased risk of gallbladder cancer, a prophylactic cholecystectomy may be advisable. Porcelain gallbladder, a rare premalignant condition in which the wall of the gallbladder becomes calcified," is an absolute indication for cholecystectomy.

Acute Cholecystitis:

About 80% of patients with acute cholecystitis give a history compatible with chronic “cholecystitis. Acute cholecystitis begins as an attack of biliary colic, but in contrast to biliary colic, the pain does not subside; it is unremitting and may persist for several days. The pain is typically in the right upper quadrant or epigastrium and may radiate to the right upper part of the back or the interscapular area. It is usually more severe than the pain associated with uncomplicated biliary colic. The patient is often febrile, complains of anorexia, nausea,” and vomiting, and is reluctant to move, as the inflammatory process affects the parietal peritoneum.

On physical examination, focal tenderness and guarding are usually present in the right “upper quadrant. A mass, the gallbladder and adherent omentum, is occasionally palpable; however, guarding may prevent this. A Murphy’s sign, an inspiratory arrest with deep palpation in the right subcostal area, is characteristic of acute cholecystitis. A mild to moderate leukocytosis (12,000–15,000 cells/mm3) is usually present. However, some patients may have a normal WBC. A high WBC count (above 20,000) is suggestive of a complicated form of cholecystitis such as gangrenous cholecystitis, perforation, or associated cholangitis. Serum liver chemistries are usually normal, but a mild elevation of serum bilirubin, <4 mg/mL, may be present along with mild elevation of alkaline phosphatase, transaminases, and amylase. Severe jaundice is suggestive of common bile duct stones or obstruction of the bile ducts by severe pericholecystic inflammation secondary to impaction of a stone in the infundibulum of the gallbladder that mechanically obstructs the bile duct

(Mirizzi's syndrome). In elderly patients and in those with diabetes mellitus, acute cholecystitis may have a subtle presentation resulting in a delay in diagnosis. The incidence of complications is higher in these patients, who also have approximately 10-fold the mortality rate compared" to that of younger and healthier patients.

The differential "diagnosis for acute cholecystitis includes a peptic ulcer with or without perforation, pancreatitis, appendicitis, hepatitis, perihepatitis (Fitz-Hugh–Curtis syndrome), myocardial ischemia, pneumonia, pleuritis, and herpes" zoster involving the intercostal nerve.

Chronic Cholecystitis:

The chief "symptom associated with symptomatic gallstones is pain. The pain is constant and increases in severity over the first half hour or so and typically lasts 1 to 5 hours. It is located in the epigastrium or right upper quadrant and frequently radiates to the right upper back or between the scapulae. The pain is severe and comes on abruptly, typically during the night or after a fatty meal. It often is associated with nausea and sometimes vomiting. The pain is episodic. The patient suffers discrete attacks of pain, between which they feel well. Physical examination may reveal mild right upper quadrant tenderness during an episode of pain. If the patient is pain free, the physical examination" is usually unremarkable.

Laboratory values, such as WBC count and liver function tests, are usually normal in patients with uncomplicated "gallstones. Atypical presentation

of gallstone disease is common. Association with meals is present in only about 50% of patients. Some patients report milder attacks of pain, but relate it to meals. The pain may be located primarily in the back or the left upper or lower right quadrant. Bloating and belching may be present and associated with the attacks of pain. In patients with atypical presentation, other conditions with upper abdominal pain should be sought out, even in the presence of gallstones. These include peptic ulcer disease, gastroesophageal reflux disease, abdominal wall hernias, irritable bowel disease, diverticular disease, liver diseases, renal calculi, pleuritic pain, and myocardial pain. Many patients with other conditions have gallstones. When the pain lasts >24 hours, an impacted stone in the cystic duct or acute cholecystitis should be suspected. An impacted stone without cholecystitis will result in what is called hydrops of the gallbladder. The bile gets absorbed, but the gallbladder epithelium continues to secrete mucus, and the gallbladder becomes distended with mucinous material. The gallbladder may be palpable but usually is not tender. Hydrops of the gallbladder may result in edema of the gallbladder wall, inflammation, infection, and perforation. Although hydrops may persist" with few consequences, early cholecystectomy is generally indicated to avoid complications.

Essentials of Diagnosis:

✓ Episodic abdominal pain.

✓ Dyspepsia

✓ Gallstones on cholecystography or ultrasound scan.

Choledocholithiasis:

Choledochal stones may be silent and often are discovered incidentally. They may cause obstruction, complete or incomplete, or they may manifest with cholangitis or gallstone pancreatitis. The pain caused by a stone in the bile duct is very similar to that of biliary colic caused by impaction of a stone in the cystic duct. Nausea and vomiting are common.

Physical examination may be normal, but mild epigastric or right upper quadrant tenderness as well as mild icterus are common. The symptoms may also be intermittent, such as pain and transient jaundice caused by a stone that temporarily impacts the ampulla but subsequently moves away, acting as a ball valve. A small stone may pass through the ampulla spontaneously with resolution of symptoms. Finally, the stones may become completely impacted, causing severe progressive jaundice. Elevation of serum bilirubin, alkaline phosphatase, and transaminases are commonly seen in patients with bile duct stones. However, in about one third of patients with common bile duct stones, the liver chemistries are normal.

Commonly, the first test, ultrasonography, is useful for documenting "stones in the gallbladder (if still present), as well as determining the size of the common bile duct. As stones in the bile ducts tend to move down to the distal part of the common duct, bowel gas can preclude their demonstration on ultrasonography. A

dilated common bile duct (>8 mm in diameter) on ultrasonography in a patient with gallstones, jaundice, and biliary pain is highly suggestive of common bile duct stones. Magnetic resonance cholangiography (MRC) provides excellent anatomic detail and has a sensitivity and specificity of 95% and 89%, respectively, at detecting choledocholithiasis >5 mm in diameter. Endoscopic cholangiography is the gold standard for diagnosing common bile duct stones. It has the distinct advantage of providing a therapeutic option at the time of diagnosis. In experienced hands, cannulation of the ampulla of Vater and diagnostic cholangiography are achieved in >90% of cases, with associated morbidity of <5% (mainly cholangitis and pancreatitis). Endoscopic ultrasound has been demonstrated to be as good as ERCP for detecting common bile duct stones (sensitivity of 91% and specificity of 100%), but it lacks therapeutic intervention and requires expertise, making it less available. PTC is rarely needed in patients with secondary common bile duct stones but is frequently performed for both diagnostic and" therapeutic reasons in patients with primary bile duct stones.

2.5 Diagnostic Studies

Baseline Blood Investigations:

- Complete hemogram
- Differential Count
- Renal Function Test

• Liver Function Test including liver enzymes

• Fasting Lipid Profile

- Prothrombin time

When patients with "suspected diseases of the gallbladder or the extrahepatic biliary tree are evaluated, a complete blood count and liver function tests are routinely requested. An elevated white blood cell (WBC) count may indicate or raise suspicion of cholecystitis. If associated with an elevation of bilirubin, alkaline phosphatase, and aminotransferase, cholangitis should be suspected. Cholestasis, an obstruction to bile flow, is characterized by an elevation of bilirubin (i.e., the conjugated form) and a rise in alkaline phosphatase. Serum aminotransferases may be normal or mildly elevated. In patients with biliary colic or chronic cholecystitis, blood tests will typically be normal". A variety of diagnostic modalities; are available.

The diagnosis of gallstones was improved significantly by the introduction of " oral cholecystography by Graham and Cole". For several years, it remained the investigation for gallstones. In the 1950s, "biliary scintigraphy was developed, as well as intrahepatic and endoscopic retrograde cholangiography (ERC), allowing imaging of the biliary tract. Later ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI)" improved the ability to image the biliary tract.

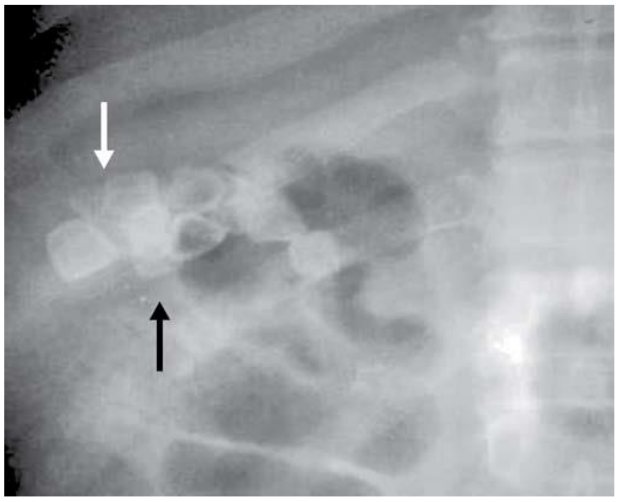


Fig7: *Multiple gallstones in a plain X- ray Abdomen showing radio-opaque shadow*

Ultrasonography:

An ultrasound is the initial investigation of any patient suspected of disease of the biliary tree. It is " non-invasive, painless, does not submit the patient to radiation, and can be performed on critically ill patients. It is dependent upon the skills and the experience of the operator, and it is dynamic (i.e., static images do not give the same information as those obtained during the ultrasound investigation itself). Adjacent organs can frequently be examined at the same time. Obese patients, patients with ascites, and patients with distended bowel may be difficult to examine satisfactorily with an ultrasound. Ultrasound will show stones in the gallbladder with sensitivity and specificity of >90%. Stones are acoustically dense and reflect the ultrasound waves back to the ultrasonic transducer. Because stones block the passage of sound waves to the region behind them, they also produce an acoustic shadow. Stones move with changes in position. Polyps may be calcified and reflect shadows, but do not move with change in posture. Some stones form a layer in the gallbladder; others a sediment or sludge. A thickened gallbladder wall and local tenderness

indicate cholecystitis. The patient has acute cholecystitis if a layer of edema is seen within the wall of the gallbladder or between the gallbladder and the liver in association with localized tenderness." When a stone obstructs the neck of the gallbladder, the gallbladder may become very large, but thin walled. A contracted, thick-walled gallbladder is indicative of chronic cholecystitis.

The extrahepatic bile ducts are also well visualized by ultrasound, except for the retroduodenal portion. Dilation of the ducts in a patient with jaundice establishes an extrahepatic obstruction as a cause for the jaundice. Frequently, the site and, sometimes, the cause of obstruction can be determined by ultrasound. Small stones in the common bile duct frequently get lodged at the distal end of it, behind the duodenum, and are, therefore, difficult to detect. A dilated common bile duct on ultrasound, small stones in the gallbladder, and the clinical presentation allow one to assume that a stone or stones are causing the obstruction. Periampullary tumors can be difficult to diagnose on ultrasound, but beyond the retroduodenal portion, the level of obstruction and the cause may be visualized quite well. Ultrasound can be helpful in evaluating tumor invasion and flow in the portal vein, an important guideline for resectability of periampullary and pancreatic head tumors.

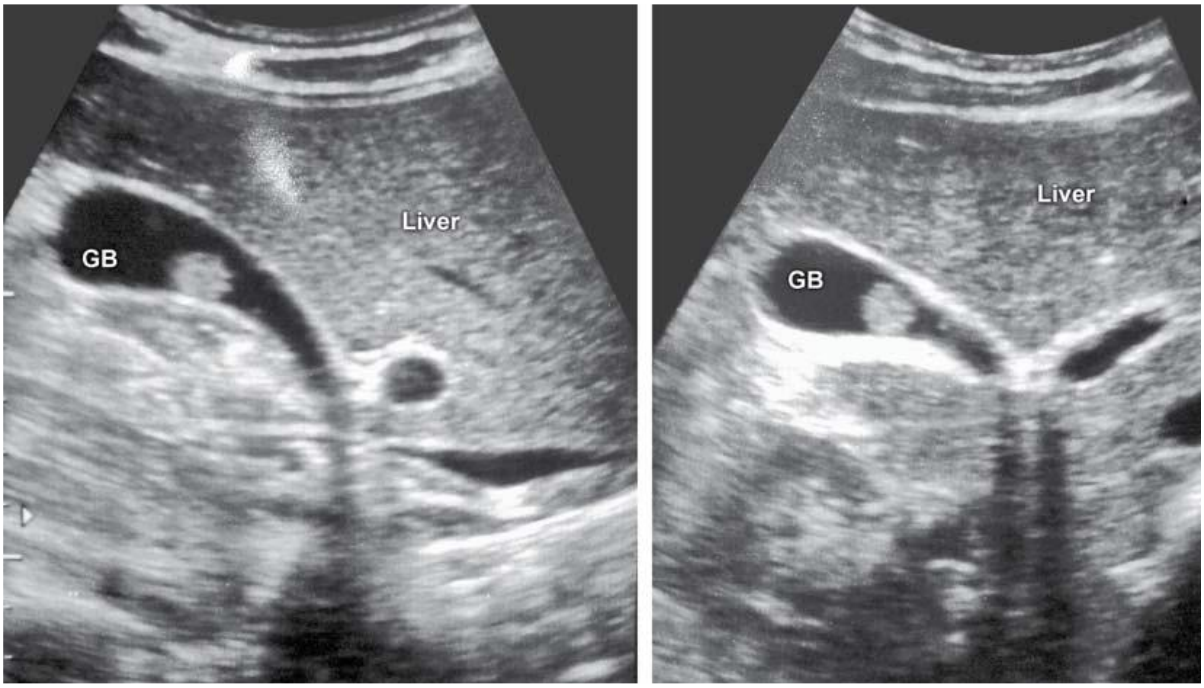


Fig 8: Ultrasound: gallbladder showing echogenic lesion. US should be done with change of position to find out movement of the lesion with posterior acoustic shadow to say it as gallstone. Otherwise it will be gallbladder polyp or sludge ball.

Oral Cholecystography:

Once considered the diagnostic procedure of choice for gallstones, "oral cholecystography has largely been replaced by ultrasonography. It involves oral administration of a radiopaque compound that is absorbed, excreted by the liver, and passed into the gallbladder. Stones are noted on a film as filling defects in a visualized, opacified gallbladder. Oral cholecystography is of no value in patients with intestinal malabsorption, vomiting, obstructive" jaundice, and hepatic failure.

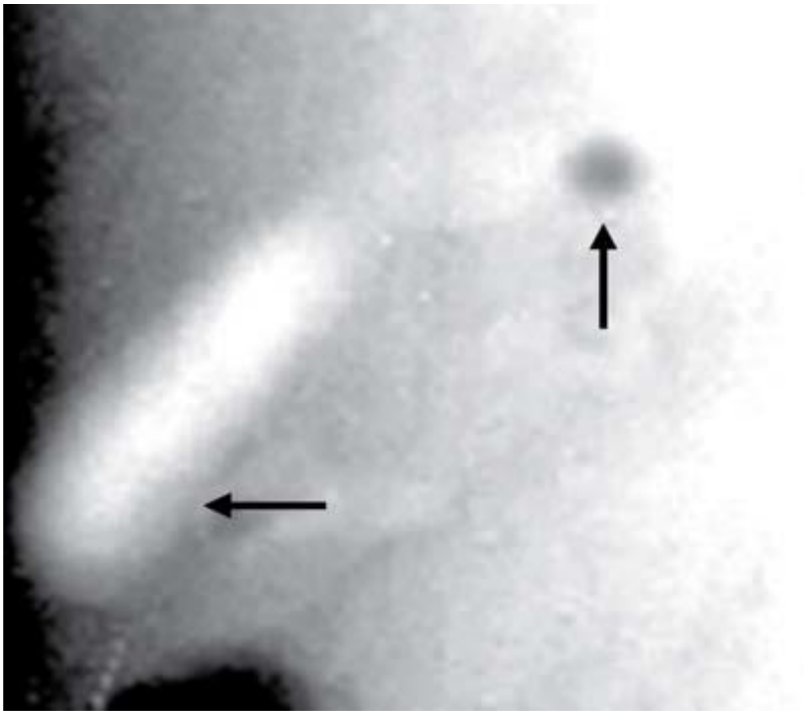


Fig 9: *Oral cholecystogram with smooth filling defect (Cystic duct stone).*

Biliary Radionuclide Scanning (HIDA Scan)

Biliary scintigraphy; provides a noninvasive evaluation of the liver, GB, ducts, and duodenum ; with anatomic and functional information. "99mTechnetium-labeled derivatives of dimethyl iminodiacetic acid (HIDA) are injected intravenously, cleared by the Kupffer cells in the liver, and excreted in the bile. Uptake by the liver is detected within 10 minutes, and the gallbladder, the bile ducts, and the duodenum are visualized within 60 minutes in fasting subjects. The primary use of biliary scintigraphy is in the diagnosis of acute cholecystitis, which appears as a nonvisualized gallbladder, with prompt filling of the common bile duct and duodenum. Evidence of cystic duct obstruction on biliary scintigraphy is highly diagnostic for acute cholecystitis. The sensitivity and specificity for the diagnosis are about 95% each. False-positive results are increased in patients with gallbladder stasis,

as in critically ill patients and in patients receiving parenteral nutrition. Filling of the gallbladder and common bile duct with delayed or absent filling of the duodenum indicates an obstruction at the ampulla. Biliary leaks as a complication of surgery of the gallbladder or the biliary" tree can be confirmed and frequently localized by biliary scintigraphy.

Computed Tomography:

Abdominal CT scans are inferior to ultrasonography in diagnosing gallstones. The major application of CT scans is to define the course and status of the extrahepatic biliary tree and adjacent structures. It is the test of choice in evaluating the patient with suspected malignancy of the gallbladder, the extrahepatic biliary system, or nearby organs, in particular, the head of the pancreas. Use of CT scan is an integral part of the differential diagnosis of obstructive jaundice. Spiral CT scanning provides additional staging information, including vascular involvement in patients with periampullary tumors.

Percutaneous Transhepatic Cholangiography:

Intrahepatic bile ducts are accessed percutaneously "with a small needle under fluoroscopic guidance. Once the position in a bile duct has been confirmed, a guidewire is passed, and subsequently, a catheter is passed over the wire through the catheter, a cholangiogram can be performed and therapeutic interventions done, such as biliary drain insertions and stent placements. Percutaneous transhepatic

cholangiography (PTC) has little role in the management of patients with uncomplicated gallstone disease but is particularly useful in patients with bile duct strictures and tumors, as it defines the anatomy of the biliary tree proximal to the affected segment. As with any invasive procedure, there are potential risks. For PTC, these are mainly bleeding, cholangitis, bile leak", and other catheter-related problems

.

Magnetic Resonance Imaging

Available since the mid-1990s, MRI provides anatomic details of the liver, gallbladder, and pancreas similar to those obtained from CT. Many MRI techniques (i.e., heavily T2-weighted sequences, pulse sequences with or without contrast materials) can generate high-resolution anatomic images of the biliary tree and the pancreatic duct. It has a sensitivity and specificity of 95% and 89%, respectively, at detecting choledocholithiasis. MRCP offers a single noninvasive test for the diagnosis of biliary tract and pancreatic disease. In many centers, MRCP is first performed for diagnosis of biliary and pancreatic duct pathology, reserving endoscopic retrograde cholangiopancreatography (ERCP) for therapeutic purposes only.

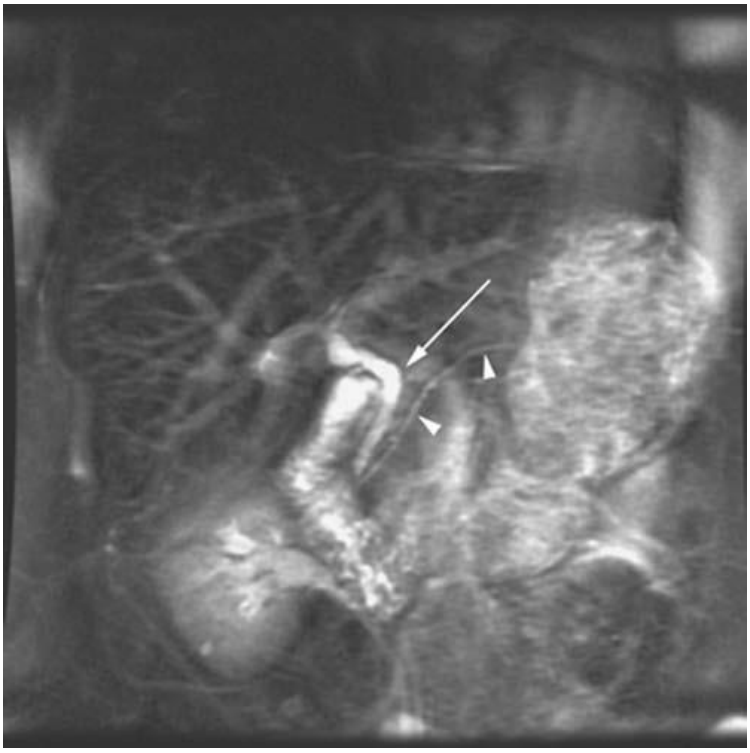


Fig 10: MRCP- This view shows the course of the extra- hepatic biliary tree marked by the arrow heads.

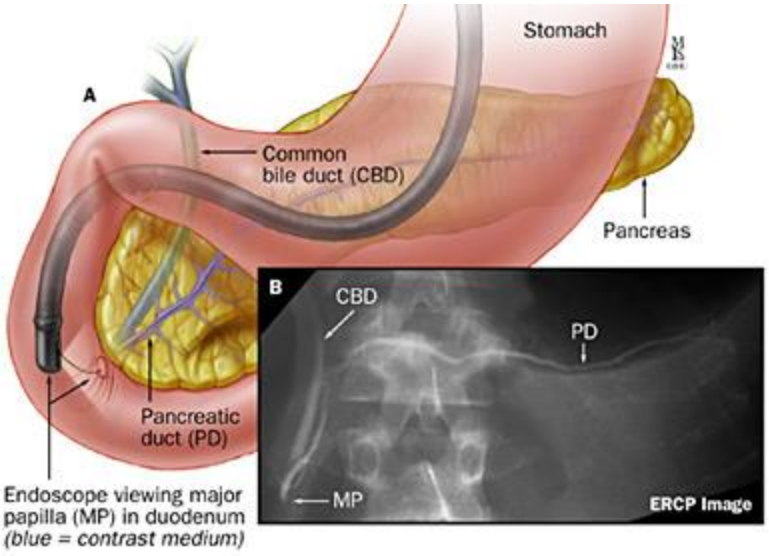


Fig 11A: *Endoscopic retrograde cholangiography. A schematic picture showing the side-viewing endoscope in the duodenum.*

B: An endoscopic cholangiography image showing Pancreatic duct, CBD, ampulla.

Endoscopic Retrograde Cholangiopancreatography :

Using a side-viewing endoscope, the common bile duct can be cannulated and a cholangiogram performed using fluoroscopy. The procedure requires intravenous (IV) sedation for the patient. The advantages of ERC include direct visualization of the ampullary region and direct access to the distal common bile duct, with the possibility of therapeutic intervention. The test is rarely needed for uncomplicated gallstone disease, but for stones in the common bile duct, in particular, when associated with obstructive jaundice, cholangitis, or gallstone pancreatitis, ERC is the diagnostic and often therapeutic procedure of choice. Once the endoscopic cholangiogram has shown ductal stones, sphincterotomy and stone extraction can be performed, and the common bile duct cleared of stones. In the hands of experts, the success rate of common bile duct cannulation and cholangiography is >90%.

Complications of diagnostic ERC include pancreatitis and cholangitis and occur in up to 5% of patients. Intraductal endoscopy has been shown to have therapeutic applications that include biliary stone lithotripsy and extraction in high-risk surgical patients. As with most endoscopic procedures, intraductal endoscopy generally is considered safe, but there are no large trials that specifically address this issue. Typical complications such as bile duct perforation, minor bleeding from sphincterotomy or lithotripsy, and cholangitis have been described. Further refinement of this technology will enhance ERCP as a diagnostic and therapeutic tool.

Endoscopic Ultrasound

Endoscopic ultrasound "requires a special endoscope with an ultrasound transducer at its tip. The results are operator dependent, but offer noninvasive imaging of the bile ducts and adjacent structures. It is of particular value in the evaluation of tumors and their resectability. The ultrasound endoscope has a biopsy channel, allowing needle biopsies of a tumor under ultrasonic guidance. Endoscopic ultrasound also has been used to identify bile duct stones, and although it is less sensitive than ERC, the technique is less invasive as cannulation of the sphincter of Oddi is not necessary" for diagnosis of choledocholithiasis.

2.6 Management

Symptomatic Gallstones

Patients with symptomatic gallstones should be advised to have "elective laparoscopic cholecystectomy." While waiting for surgery; or if surgery has to be postpone; the patient should be advised to avoid dietary fats and large meals. Diabetic patients with symptomatic gallstones; should have a cholecystectomy promptly; as they are more prone to develop acute severe cholecystitis .

Pregnant women with symptomatic gallstones; who cannot be managed expectantly with diet modifications can safely undergo laparoscopic cholecystectomy; during the 2nd trimester. "Laparoscopic cholecystectomy is safe and

effective in children as well as in the elderly. Cholecystectomy, open or laparoscopic, for patients with symptomatic gallstones offers excellent long-term results." About 90% of patients with "typical biliary symptoms and stones are rendered symptom free after cholecystectomy. For patients with atypical symptoms or dyspepsia (flatulence, belching, bloating, and dietary fat intolerance) the results are not" as favorable.

Acute Cholecystitis

Patients who present with acute cholecystitis will need IV fluids, antibiotics, and analgesia. "The antibiotics should cover gram-negative aerobes as well as anaerobes. A third generation cephalosporin with good anaerobic coverage or a second-generation; cephalosporin combined with metronidazole is a typical regimen. Cholecystectomy is the definitive treatment for acute cholecystitis. In the past, the timing of cholecystectomy has been a matter of debate. Early cholecystectomy performed within 2 to 3 days of the illness is preferred over interval or delayed cholecystectomy that is performed 6 to 10 weeks after initial medical treatment and recuperation. Several studies have shown that unless the patient is unfit for surgery, early cholecystectomy should be recommended, as it offers the patient a definitive solution in one hospital admission, quicker recovery times, and an earlier return to work. Laparoscopic cholecystectomy is the procedure of choice for acute cholecystitis. The conversion rate to an open cholecystectomy is higher (10%– 15%) in the setting of acute cholecystitis than with chronic cholecystitis. When patients present late, after 3 to 4 days of illness, or if they are unfit for surgery, they can be treated with antibiotics with laparoscopic cholecystectomy scheduled for

approximately 2 months later. Approximately 20% of patients will fail to respond to initial medical therapy and require an intervention. For those unfit for surgery, a percutaneous cholecystostomy or an open cholecystostomy under local analgesia can be performed. Failure to improve after cholecystostomy usually is due to gangrene of the gallbladder or perforation. For these patients, surgery is unavoidable. For those who respond after cholecystostomy, the tube can be removed once cholangiography through it shows a patent ductus cysticus. Laparoscopic cholecystectomy may then be scheduled in the near future. For the rare patients who can't tolerate surgery, the stones can be extracted" via the cholecystostomy tube before its removal.

Choledocholithiasis

For patients with; symptomatic gallstones and suspected common bile duct stones; either preoperative "endoscopic cholangiography or an intraoperative cholangiogram will document the bile duct stones. If an endoscopic cholangiogram reveals stones, sphincterotomy and ductal clearance of the stones is appropriate, followed by a laparoscopic cholecystectomy. An intraoperative cholangiogram at the time of cholecystectomy will also document the presence or absence of bile duct stones. Laparoscopic common bile duct exploration via the cystic duct or with formal choledochotomy allows the stones to be retrieved in the same setting. An open common bile duct exploration is an option if the endoscopic method has already been tried or is, for some reason, not feasible. If a choledochotomy is performed, a T tube is left in place. Patients >70 years old presenting with bile duct stones should have their ductal stones cleared endoscopically. Studies comparing

surgery to endoscopic treatment have documented less morbidity and mortality for endoscopic treatment in this group of patients. They do not need to be submitted for a cholecystectomy, as only about 15% will become symptomatic from their gallbladder stones, and such patients can be treated as the need arises" by a cholecystectomy.

Surgical Interventions in Biliary Disease:

Cholecystostomy:

This procedure is performed in patients who are unfit for anaesthesia. In this procedure under ultrasound guidance the distended gall bladder is decompressed by percutaneous drainage. Initially a guide- wire is inserted through the abdominal wall, liver and the gall bladder, then a catheter is passed over it. Once the patient's condition has improved the catheter is removed and cholecystectomy can be done at a later date. This procedure is rarely performed nowadays.

Laparoscopic Cholecystectomy:

Philippe Mouret from France was the one who introduced Lap Cholecystectomy in the year 1987 which has revolutionised the treatment of gallstones. Most of laparoscopic cholecysyectomies are done for the purpose of biliary colic, but it can also be safely caried out in acute settings, except that the conversion rates to open are higher. It is perfomed under general anaesthesia. Because of the smaller incisions, less pain and shorter hospital stay increasing number of laparoscopic cholecystectomies are being performed.

Open Cholecystectomy:

Due to the advent of laparoscopic technique the number of open procedures has drastically come down. It is now performed under two settings, one following conversion of the laparoscopic approach and two as a step during another surgery like pancreaticoduodenectomy.

Common Bile Duct Exploration:

Laparoscopic techniques have been improvised in the recent years which have paved the way for laparoscopic clearance of the bile duct is being practised. First the CBD is visualised fluroscopically, the duct is irrigated. Glucagon is instilled which relaxes the sphincter of Oddi. If the attempt fails a flexible choledochoscope is used. In both open and laparoscopic methods, stay sutures are made, and a choledochotomy is performed in the supraduodenal portion of the CBD. Usually a longitudinal incision is made and the stone is retrieved. At the end of the procedure a T- tube is placed via the choledochotomy site and the duct is closed with absorbable sutures.

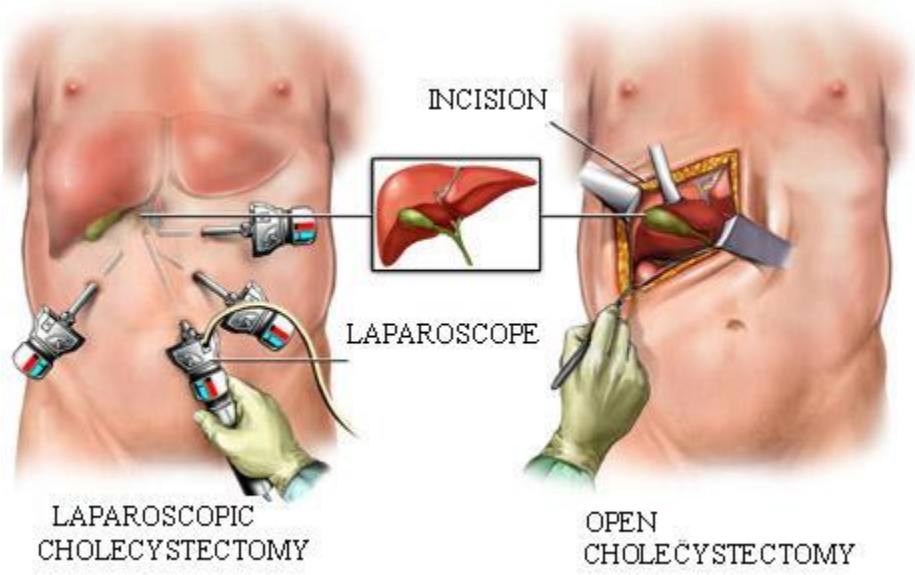


Fig 12: Lap and open techniques

2.7 Thyroid Function

Hypothyroidism:

Hypothyroidism is a common disorder; again especially in women, the incidence being about 350/100 000 women yearly. The prevalence of subclinical hypothyroidism among women over 60 years of age is as high as 20%. Hypothyroidism; is defined as " in any state which results in a deficiency of TH, including hypothalamic or pituitary diseases, generalized tissue resistance to TH, and disorders directly affecting the thyroid gland. Thyroid deficiency in adults is characterized by a slowing of all metabolic processes." The clinical symptoms of the condition include "weakness, lethargy and fatigue, memory impairment, dementia, cold intolerance, weight gain, constipation, loss of hair, hoarseness, deafness, dyspnea, myalgia and arthralgia, paraesthesias, precordial pain and menstrual

irregularity. When THs are lacking in early childhood, the result is severe bodily and mental retardation. Clinical signs of hypothyroidism may be dry, coarse and cold skin, periorbital and peripheral oedema, coarse and thin hair, pallor of skin, thick tongue, slow speech, decreased reflexes, hypertension, bradycardia, pleural and pericardial effusions, ascites and vitiligo. In laboratory tests, e.g. hypercholesterolaemia and anaemia are associated findings." The laboratory hallmark of primary hypothyroidism and the most sensitive test for detecting early thyroid failure is an "increased serum TSH concentration. The serum FT4 level is decreased in clinical hypothyroidism. In the subclinical form an increased serum TSH level is accompanied by a normal serum FT4 level, and the patient is asymptomatic." The presence of thyroperoxidase antibody confirms chronic autoimmune thyroiditis as the cause of hypothyroidism. The treatment of hypothyroidism with levothyroxine is usually lifelong.

The effects of thyroid hormones:

The thyroid gland secretes both T4 and triiodothyronine (T3) into the circulation. "In extrathyroidal tissues, T4 is converted to T3, assumed to be the major active TH. Characteristic of THs is the multiplicity of the cellular functions they regulate in virtually every type of vertebrate tissue. The diverse responses to TH can be divided into two major categories:

- Regulation of metabolic activity, energy consumption and muscular activity in adult mammals, and
- Regulation of postembryonic or perinatal growth and development.

Most actions of THs can be explained by their interaction with nuclear receptors. THs bind to specific intranuclear TH receptors (TR), TR1, TR1 or TR2. This ligand-receptor complex binds to TH response elements in the target genes to regulate the rate of synthesis of specific messenger RNAs. This results in a change in the amount or activity of the cognate proteins, which in turn alter the rate of the metabolic process. The TRs are expressed in a tissue- and development-stage-specific fashion. For example, TR1 is known to be highly expressed in brain, muscle and fat, and has been identified in frog, chicken, rat, mouse and humans; TR1 is highly expressed in liver and kidney, and has been demonstrated in frog, chicken, rat, mouse and humans. TR2, again, is highly expressed in the pituitary, and has been demonstrated in rat and mouse. The expression of TRs in the SO has not been studied. The genomic effects of THs necessarily require a finite period of time for protein synthesis and for the biological response. Acute response of a cell to THs is unlikely to involve a transcriptional mechanism but is rather a result of nongenomic mechanisms involving extranuclear sites of action. Extranuclear sites of TH action include the cell membrane, the cytoskeleton, the sarcoplasmic reticulum, the cytoplasm, the mitochondria, and in vascular smooth-muscle cells presumably the contractile elements." For example, THs mediate sugar uptake, adenylate cyclase, and Ca2+-ATPase activity directly at the level of the plasma membrane of various tissues. The second messengers associated with the extranuclear actions of the THs are not yet known.

Thyroid hormones and cholesterol metabolism:

The elevation of serum cholesterol levels is a clinically important accompaniment of hypothyroidism. Patients with overt hypothyroidism have approximately 50% higher serum cholesterol levels than euthyroid patients; 90% of all hypothyroid patients have elevated cholesterol levels, triglyceride levels, or both. This is primarily due to elevations in low-density lipoprotein (LDL) rather than high-density lipoprotein (HDL) levels. Treatment of hypothyroid patients who also have hyperlipidaemia will have beneficial effects on serum cholesterol levels. The aetiology of the hypercholesterolaemia in hypothyroid patients is probably multifactorial.

THs have been shown to have a number of effects on cholesterol metabolism. LDL "receptor activity is increased (Ness et al. 1990) because of increased expression of the LDL receptor gene, and the expression may be decreased in hypothyroidism, leading to reduced removal of cholesterol from the serum. THs increase the synthesis of cholesterol by regulating the expression of HMG-CoA reductase, and the regulation is reduced in hypothyroid patients, leading to decreased cholesterol synthesis. Also the synthesis of bile salts is increased by THs by the effect on cholesterol-7-hydroxylase, and a decrease in biliary bile salt concentration in hypothyroidism has been reported. Absorbtion of cholesterol is decreased by THs. Hypothyroidism lowers biliary cholesterol secretion in the rat, while T4 replacement in hypothyroid animals markedly increases cholesterol secretion. However, in the cholesterol-fed hypothyroid rat, biliary cholesterol content

is significantly increased and the rate of bile secretion decreased. Biliary secretion of cholesterol is reduced in hypothyroidism compared to euthyroidism. However, when serum cholesterol values rise, bile may also become supersaturated with cholesterol and thus result in gallstone formation. An association has been reported between cholesterol gallstones and treated hypothyroidism in women." It has also been reported that gallbladder stones may have been dissolved after T4 treatment.

2.8 Prevalence of Clinical Hypothyroidism in Gall Stone Patients

Several recent studies report an association between hypothyroidism, and subclinical hypothyroidism, and gall stones. In a retrospective study on patients over 60 years of age, it was noted for the first time that CBD stone "p"atients have significantly more diagnosed hypothyroidism (11%), not only when compared to "control patients from whom gallstones had been excluded (2%), but also when compared to gallbladder stone patients without CBD stones (6%). In this study, there was no difference between groups in the frequency of other diseases. This finding suggested that factors other than merely those affecting cholesterol metabolism, for example, specific effects on bile flow, might be behind the association between CBD stones and hypothyroidism. A prospective study showed that even subclinical hypothyroidism is more common among gall stone patients. This study investigated the prevalence of previously undiagnosed subclinical hypothyroidism in clinically euthyroid CBD stone patients compared to nongallstone controls. It was found that 5.3% of the gall stone patients had subclinical hypothyroidism, defined as serum thyrotropin above the normal upper limit (6.0

mU/L), compared to only 1.4% in the control group. In women over 60 years, the prevalence of subclinical hypothyroidism was as high as 11.4% in the gall stone group" compared to 1.8% among" the control patients.

Finally in 2010, "a large, medical registry-based study from Finland confirmed that hypothyroid patients did indeed seem to have a higher likelihood for gall stone treatment. In this study, the prevalence of gall stone treatments was investigated in patients with diagnosed hypothyroidism and compared to age, sex, and area of residence adjusted glaucoma (control) patients. Patients with other diseases were excluded to create a "purely" hypothyroid (or glaucoma) cohort of patients. Out of 14,334 patients in each group who met the inclusion criteria, 0.23% in the hypothyroid cohort and 0.16% in the control cohort had been treated for gall stones. The groups did not differ in the number of gall stone treatments before the diagnosis of hypothyroidism or glaucoma, but after these diagnoses there were 56% more gall stone treated individuals in the hypothyroid cohort than in the control cohort. This may suggest that the higher risk for gall stones in hypothyroid patients may increase after taking medication for hypothyroidism. As the process of bile stone formation takes time, stone formation may have started during the untreated period of hypothyroidism and have been completed regardless of thyroxine replacement therapy. This hypothesis is supported by the findings that both subclinical and clinical hypothyroidism are more common in gall stone patients. However, the question remains whether thyroxine replacement therapy is sufficient to cause the physiological effects of thyroxine, as it seems that even though thyroxine replacement therapy has

been initiated, the gall stones do indeed form or continue to grow. Earlier studies with subclinical hypothyroid patients have demonstrated that a positive effect on changes in the cholesterol level, cardiovascular effects, or neuromuscular symptoms may be achieved with early replacement treatment with thyroxine. It has also been reported that gallstones have dissolved after initiation of thyroxine therapy. It is possible that thyroxine replacement therapy is not sufficient at all times of the day, in all patients to maintain normal sphincter of Oddi function, causing the formation of gall stones. These interesting findings raise a question" about the mechanisms underlying the association, which is stronger between hypothyroidism and CBD stones than between hypothyroidism and gallbladder stones.

Mechanism of Formation of Gallstones in Hypothyroidism:

In general, the pathogenesis of gallstones is a complex process involving mechanisms affecting bile content and bile flow. There are several factors that may contribute to the formation of gall stones in hypothyroid patients. Based on the investigations currently available, it cannot be concluded whether hypothyroid individuals develop isolated gall stones or present with CBD stones in addition to gallbladder stones. "*However, based on what is known about the effects of hypothyroidism on the formation of gallbladder and CBD stones, it seems likely that in hypothyroidism both the risk for gallbladder-originated as well as for de novo CBD stones is increased*."

In hypothyroidism, the lack of thyroxine

➢ decreases liver cholesterol metabolism resulting in bile cholesterol supersaturation, which in turn impairs the motility, contractility, and filling of the gallbladder, contributing to the retention of cholesterol crystals and to the nucleation and growth of gallstones.

➢ diminishes bile secretion from hepatocytes resulting in impaired clearance of precipitates from the bile ducts.

➢reduces SO relaxation resulting in delayed bile flow and thus the formation and accumulation of CBD stones.

THs regulate multiple functions in virtually every type of vertebrate tissue. Most actions of THs can be explained by their interaction with nuclear receptors, which are expressed in a tissue- and development stage-specific fashion. In human, the SO expresses both TR β1 and β2. Any acute-type response of a cell to THs is unlikely to involve a transcriptional mechanism but is rather a result of nongenomic mechanisms involving extranuclear sites of action. In general, thyroid hormone actions are largely intracellular events that require transport across the plasma membrane. Recently, several active and specific thyroid hormone transporters have been identified, including monocarboxylate transporter 8 (MCT8), MCT10, and organic anion transporting polypeptide 1C1 (OATP1C1).

Hypothyroidism May Reduce Hepatic Bile Secretion:

In a prospective study in humans, the dynamic Tc99m HIDA biligraphy performed in the acute hypothyroid stage after thyroidectomy showed that the hepatic maximal uptake and appearance of radioactivity in the large bile ducts at the hepatic hilum was similar to the euthyreotic stage in the same patients. This suggested that hepatocytic bile secretion may not be significantly reduced in humans in the early phase of hypothyroidism. However, in rats, where bile secretion rate can be measured by cannulating bile ducts proximal to the SO (to block out the SO effect), decreased bile secretion in prolonged hypothyroidism has been reported, whereas hyperthyroidism seems to have no effect. Thus decreased bile hepatic secretion may have at least some impact on the delayed bile flow in prolonged hypothyroidism.

Hypothyroidism Reduces Bile Flow into the Duodenum:

In a "rat study where the effect of SO was not excluded by cannulation, hypothyroidism reduced and hyperthyroidism increased the bile flow into the duodenum. Similarly, in a prospective human study, hepatic clearance was significantly decreased and the hilum-duodenum transit time had a tendency to increase in the hypothyroid stage after thyroidectomy, when compared to the euthyroid stage in the same patients. As the hepatic maximal uptake and the appearance of radioactivity in the large bile ducts at the hepatic hilum were similar in the hypothyroid and euthyreotic stages of this study, the findings are hardly attributable to different hepatic secretion but strongly suggest that bile flow into the

duodenum is reduced in the hypothyroid stage. This could be due to changes in bile composition and gallbladder motility, and because of changes" in the resistance to flow, that is, in the SO motility.

Hypothyroidism Leads to Impaired SO Relaxation:

The existence "of gastrointestinal hypoactivity in hypothyroidism has been well known for decades. For example, the effect of thyroxine has been documented in anal canal pressure and in lower esophageal sphincter pressure. The effect of THs on smooth muscle contraction depends on the smooth muscle type and the species studied. THs have a direct, relaxing effect on vascular smooth muscle contractility. This effect is mediated by intranuclear binding of TH to the TR, and partly by nongenomic mechanisms involving extranuclear sites of action. The potassium (K+) channel blocker glibenclamide attenuates triiodothyronine-induced vasodilatation in rat skeletal muscle arteries, and triiodothyronine-induced vasodilatation may thus be mediated by ATP-sensitive K+-channels. Since Sandblom et al. first demonstrated the hormonal action of cholecystokinin (CCK) on the SO in 1935; several other hormones have been shown to affect SO activity. *In 2001, it was shown for the first time that thyroxine has a direct effect on SO contractility in physiological concentrations in pig experiments."* Triiodothyronine had a similar effect on thyroxine, whereas cortisone, estrogen and testosterone had no effect. Thus the effect of THs is not an unspecific effect of any hormone. Progesterone, which is thought to be involved in the smooth muscle

relaxation seen in pregnancy, reduced not only the ACh- and Hist-induced but also KCl-induced SO contractions. Thus, its effect on SO relaxation differs from the more specific effect of thyroxine. Thyroxine reduced receptor-mediated acetylcholine and histamine-induced SO contraction, but had no effect on unspecific, KCl-induced SO contraction, which suggests a direct effect of thyroxine on the control mechanisms of SO motility. Since the effect of thyroxine on the precontracted SO is relaxing, the absence/insufficient concentration of thyroxine may result in increased tension of the SO in hypothyroidism. A similar relaxant effect of thyroxine was also shown in human SO specimens, indicating that the finding may also be of clinical significance.

Mechanisms by Which Thyroxine Mediates SO Relaxation:

Several "examinations were performed to determine how the relaxant effect of thyroxine on SO is mediated. The experiments with α- and β-adrenoceptor antagonists, NO synthesis inhibitor, and the elimination of nerve function with tetrodotoxin showed that the thyroxine-induced relaxation of SO is not mediated via neural effects. Human SO was shown to express TR β1 and β2. The presence of TRs in the SO is necessary but not sufficient evidence that thyroxine exerts its prorelaxant effect via a hormone-receptor complex action. However, the experiments with different incubation times of thyroxine showed that the underlying cellular mechanisms involved do not act immediately but require a certain time lag, supporting the theory that at least part of the action of thyroxine is TH-TR mediated.

The passage of TH through cell membrane, cytoplasm, and nuclear membrane and binding to a nuclear protein (TR) is a relatively fast event, whereas the resulting transcriptional and translational regulation is time consuming, and probably explains why the relaxant effect is not immediate. Thus, the effect of thyroxine could be mediated by regulatory proteins partly synthesized as a result of thyroxine-induced gene expression. The prorelaxant effect of thyroxine is probably partly mediated via transporter proteins, and partly via binding to nuclear receptors, subsequently leading to the activation of K+ channels." The opening of K+ channels is followed by hyperpolarisation, which closes cell membrane Ca2+ channels, reduces Ca2+ influx, and results in reduced contraction of the SO smooth-muscle cell in response to any specific stimulus.

Conclusions and Clinical Implications:

In summary, several recent studies "report an association between hypothyroidism, or subclinical hypothyroidism, and gall stones. The higher prevalence of hypothyroidism in gall stone patients compared to gallbladder stone patients suggests that not only changes in the cholesterol metabolism, or bile excretion rate, but particularly changes in the function of the SO that may underline the association between gall stones and hypothyroidism. It remains to be investigated whether hypothyroid individuals who have had their gallbladder removed are at an increased risk to develop CBD stones when compared to euthyroid individuals in the same situation. It seems likely that the lack of thyroxine in hypothyroidism gives rise to a reduction in bile flow in many ways. In addition to the increased cholesterol load

in bile and the reduced bile secretion rate, the deficiency of the pro relaxant effect of thyroxine on the SO appears to be a crucial factor leading to the reduced bile flow in hypothyroidism. The initial formation of bile cholesterol crystals may begin during the untreated period of hypothyroidism, and the stones may continue to develop or mature even after the thyroxine replacement therapy has begun. It is possible that thyroxine replacement therapy is not sufficient in all patients to maintain normal SO function, causing increased risk of CBD stone formation. Studies with subclinical hypothyroid patients have demonstrated that a positive effect on the changes in the serum cholesterol level, on cardiovascular effects, or on neuromuscular symptoms may be achieved with early replacement treatment with thyroxine, and it can be assumed that patients at risk of forming gall stones due to subclinical hypothyroidism may also benefit from such early treatment. *In conclusion patients presenting with gallstones, especially females clinicians should be aware of the hypothyroid backround and perform a thyroid profile."*

CHAPTER 2

MATERIALS AND METHOS

MATERIALS AND METHODS

3.1 Type of study: Prospective and observational study

3.2 Approval : Prior to conducting the study approval was obtained from the ethical committee of Thanjavur Medical College, Thanjavur.

3.3 Study Place: Thanjavur Medical College & Hospital, Thanjavur – 613004.

3.4 Study Period : 2014 June to 2015 August

3.5 Sample size:

3.6 Inclusion Criteria:

1. Patients in age group of 18-70 yrs and
2. Patients with USG proven cholelithiasis/ choledocholithiasis

3.7 Investigation

1. USG abdomen
2. T3, T4, TSH

3.7 Study procedure:

Method of sampling was non-random, purposive. After admission short historywas taken and physical examination was conducted on each

patient admitted in surgery department with features suggestive of extrahepatic biliary lithiasis. Baseline investigations, as routinely required, were done, followed by imaging studies. Patients were then explained about their disease process and the possible line of management. All the necessary information regarding the study was explained to the patients or their valid guardian. Informed written consent was taken from the patients or their guardian willing to participate in the study. Detailed history was taken from the study group to establish proper diagnosis. Thorough physical examination was done in each case. Data collection sheets were filled in by the investigator himself. All of the preoperative factors related to the patient were noted down in the data sheet. After proper evaluation and preparation, patients who required surgical management were taken up for surgery. Strict aseptic precautions were followed during the operation. Meticulous techniques were practiced as far as possible. The operation procedure and related per operative factors were observed directly and recorded in the data collection sheet instantly. After completing the collection of data it was compiled in a systematic way.

3.8 Operational definitions:

Cholelithiasis: a condition marked by presence of calculi in the gallbladder

Choledocholithiasis: a condition marked by presence of calculi in the common bile duct

Hypothyroidism: abnormally low activity of the thyroid gland develops when the thyroid gland fails to produce or secrete as much thyroxine as the body needs.

ERCP: (short for endoscopic retrograde cholangiopancreatography) is a procedure used to diagnose and treat diseases of the gallbladder, biliary system, pancreas, and liver.

3.9 Variables Studied:

Dependent variable: Hypothyroidism

Independent variable:

1. Age
2. Sex
3. Co- morbidities: Diabetes, obesity.
4. USG findings
5. Surgeries performed

3.10 Ethical consideration

All the patients/ legal guardians were given an explanation of the study and about the investigative and operative procedures with their merits and demerits, expected results, and possible complications. If he/she agreed then the case had been selected for this study. The study did not involve any additional investigation or any significant risk. It did not cause economic burden to the patients. The study was approved by the institutional review board prior to commencement of data collection. Informed consent was taken from each patient/guardian. Data were collected by approved data collection form.

3.11 Data collection

Data were collected by pre-tested structured questionnaire. Data were collected from all the respondents by direct interview after getting informed written consent from them or from their legal guardian.

3.12 Data analysis

Data analysis was done both manually and by using computer. Calculated data were arranged in systemic manner, presented in various table and figures and statistical analysis was made to evaluate the objectives of this study with the help of Statistical Package for Social Science (SPSS).

CHAPTER 3

RESULTS

RESULTS

A prospective study was performed to determine the incidence of hypothyroidism in patients having cholelithiasis and choledocolthiasis. 68 patients were studied who fulfilled the inclusion criteria. All these patients were taken from the surgery department of Thanjavur Medical College, from 2014 June to 2015 August. All patients were evaluated clinically and only essential investigatons were performed before surgery, in addition patients underwent the thyroid function test. The results obtained are as follows.

TABLE 1: Age distribution of patients with gall stone

AGE/ SEX yrs	MALE	FEMALE	TOTAL
20-29	2	4	6
30-39	3	13	16
40-49	6	11	17
50-59	5	7	12
60-70	6	11	17
TOTAL	22(32.35%)	46(67.64%)	68

The mean age of patients with gall stones is 47.14 yrs. Male to female ratio is 1: 2.2.

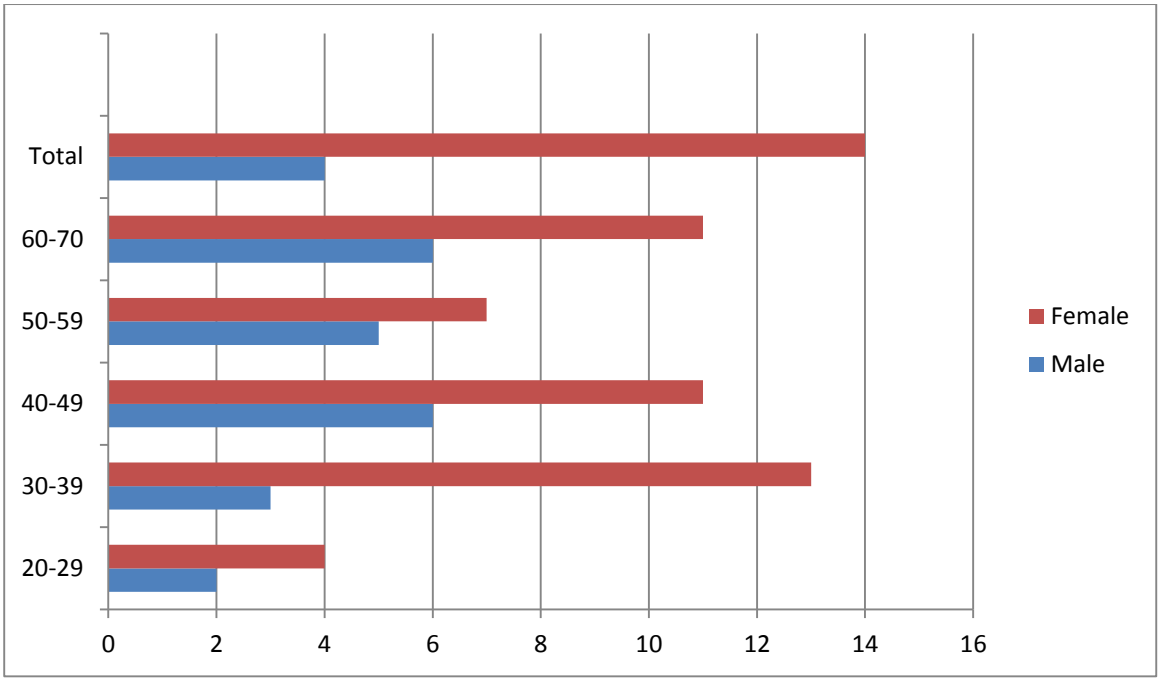


Table 2: Percentage of patient with co- morbidities

Co- Morbidity	Number	Percentage
Diabetes Mellitus	11	16
Hypertension	14	20.5
Both DM and HT	6	8
No co morbidity	49	72.05

Hypertension was the predominant co- morbidity in this study- in 20% of the patients.

Table 3: USG / CT findings of patients

USG / CT Findings	Number	Percentage
GB- Single stone	20	29.4
GB- Multiple stones	46	67.64
CBD Stones	5	27.3
Both GB and CBD stone	3	4.4

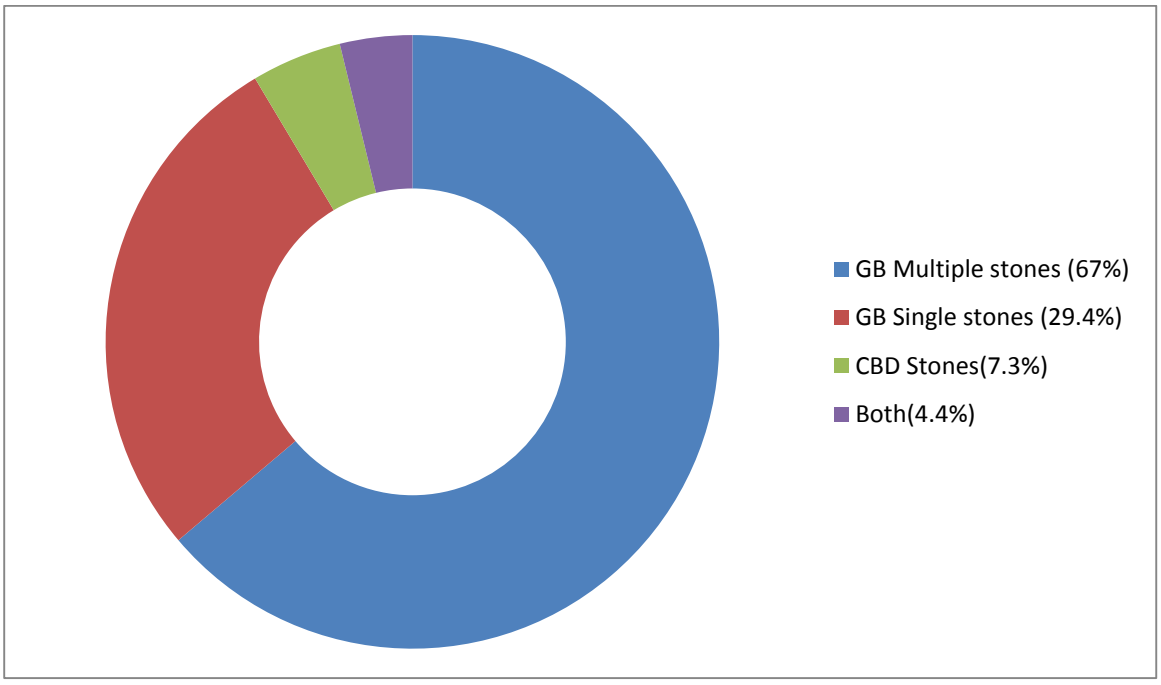
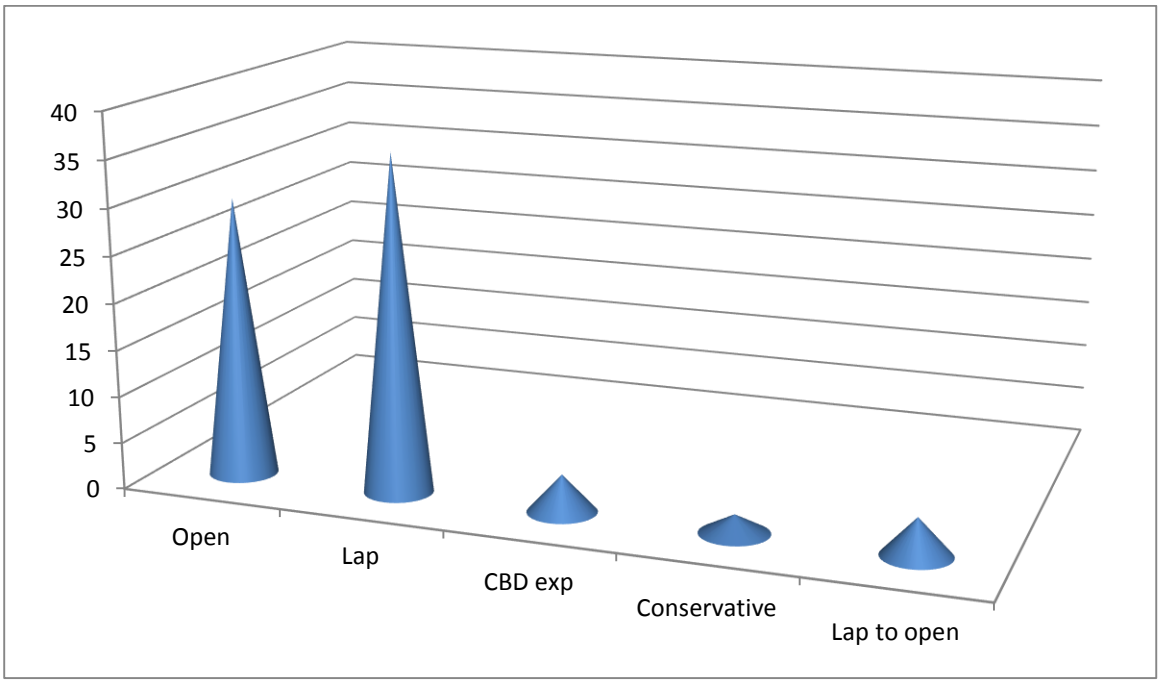


Table 4: Management profile of gall stones

Surgery Performed	Numbers	Percentage
Open cholecystectomy	30	44.11
Lap Cholecystectomy	36	52.94
CBD exploration	4	5.8
Conservative	2	2.9
Lap Converted to open	4	5.8



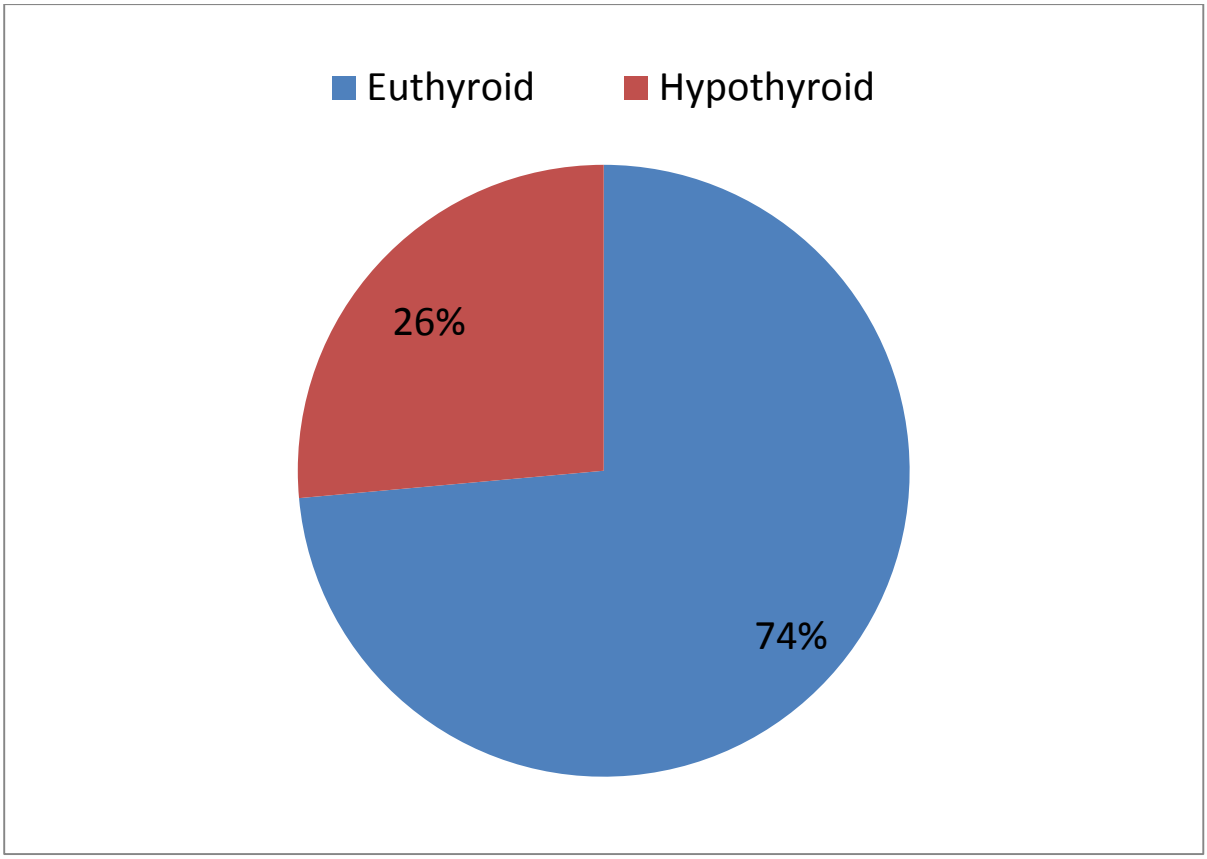
36 Patients underwent laparoscopic cholecystectomy out of which 4 patients were converted from lap to open procedure.

Table 5: Thyroid Profile of the patients

	Numbers	Percentage
Hypothyroid	18	26.47
Euthyroid	50	73.52

p value <0.05 and it is statiscally significant.

26% of patients with cholelithiasis/ choledocolitiasis had hypothyroidism.

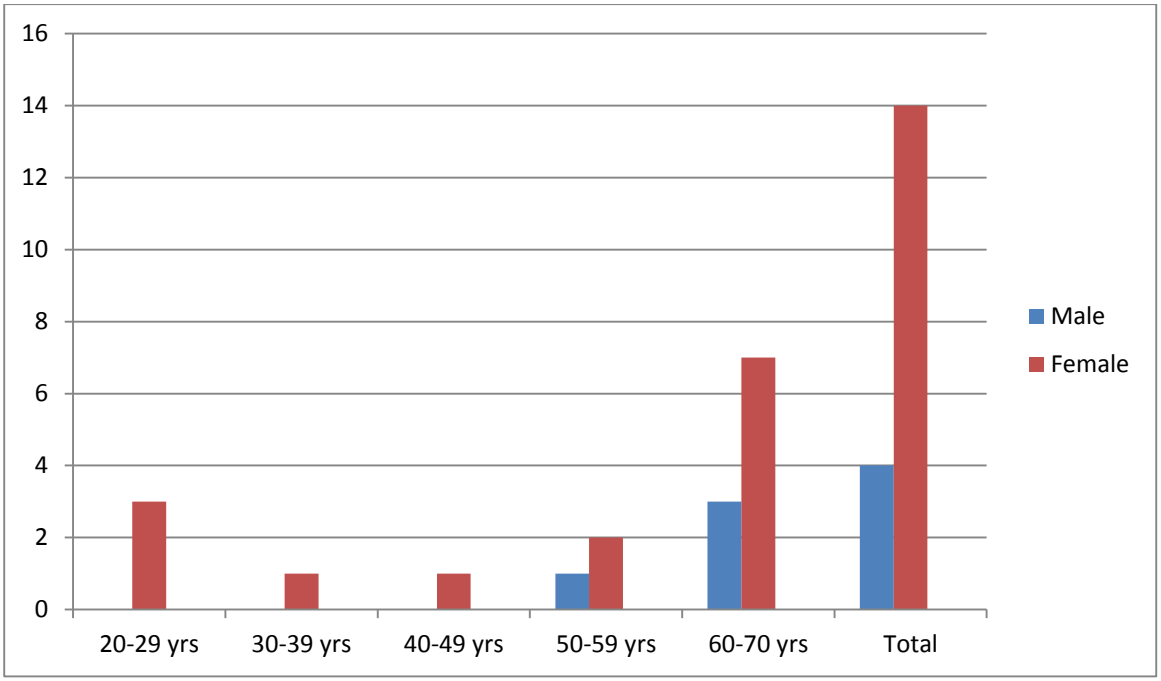


p value is < 0.05 and it is statistically significant.

Table 6: Age and sex distribution of patients **with hypothyroidism** and gallstones/ CBD stones

AGE/ SEX yrs	MALE	FEMALE
20-29	0	3(4.4%)
30-39	0	1(1.4%)
40-49	0	1(1.4%)
50-59	1(1.4%)	2(2.9%)
60-70	3(4.4%)	7(10.2%)
TOTAL	4(5.8%)	14(20.5%)

(Figures in parentheses indicates percentages)



Female sex and 50-70 yrs were the predominant group. More than 70% of the patients with hypothyroidism belong to this group.

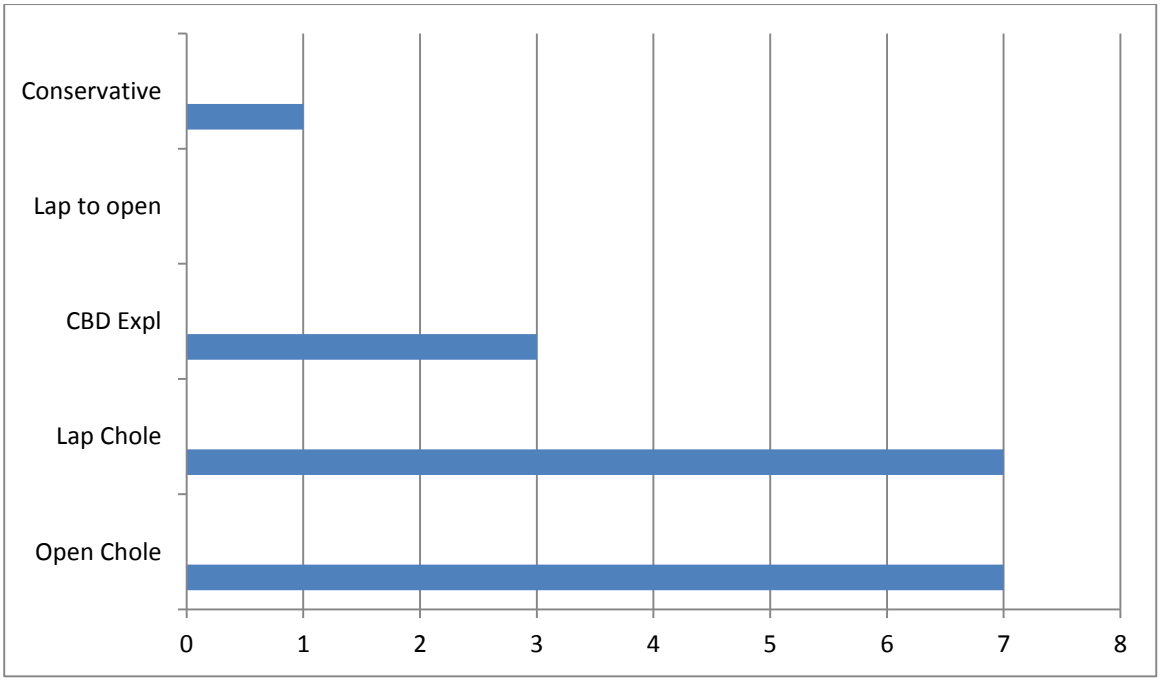
Table 7: Image findings of patients with hypothyroidism

USG Findings	Numbers	Percentage
GB- Single stone	2	11.11
GB- Multiple stones	14	77.77
CBD stone	3	16.6
Both	1	5.5
Total	18	26.47

Table 8: Management profile in gallstone patients with hypothyroidism

Surgeries Performed	Numbers	Percentage
Open Cholecystectomy	7	38.88
Lap Cholecysyecyomy	7	38.88
CBD exploration	3	16.66
Lap to Open	0	0
Conservative	1	5.5

Both laparoscopic and open procedures were performed in hypothyroid patients.


Conservative
Lap to open
CBD Expl
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8

CHAPTER 4

DISCUSSION

DISCUSSION

This prospective study was conducted 68 selected patients with evidence of cholelithiasis or choledocholithiasis in Department of General Surgery, Thanjavur Medical College. The study was carried out with a view to determine the prevalence of hypothyroidism in patients with extra hepatic biliary lithiasis in view of determining its importance as a causative factor and to include thyroid function tests as part of routine workup in gallstone patients.

Age of these selected patients ranged from 20- 70 yrs, with mean age being 47.14 yrs. 32% were male patients and 68% were female patients. The male to female ratio is 1: 2. Females were the predominant group. On analysing the co- morbid factors HT was the predominant co- morbid factor followed by Diabetes. HT was found to be a co- morbid factor in 14 patients (20%). DM was found to be a co- morbid factor in 11 (16%). 6 patients had both DM and HT.

On evaluation of patients with USG and CT, 46 patients (67.4%) had multiple stones, and 20 patients (29.4%) had single stone. 5 patients had CBD stones and 3 patients had both CBD and GB stones. The size of the stones ranged from 4-18mm.

Patients were managed with both laparoscopic and open procedures. 36 patients underwent laparoscopic cholecystectomy out of which 4 patients were converted from lap to open procedure. The reasons for conversion were bleeding, adhesions and technical difficulties. Open procedure was done in 30 patients and 4 patients underwent CBD exploration in addition to cholecystectomy.

Thyroid function test was performed in all 68 patients out of which, 18 patients (26.4%) were found to have hypothyroidism and the rest i.e. 50 patients were euthyroid. Of these 18 patients only 2 were known hypothyroid, rest 16 patients were newly diagnosed hypothyroid patients.

Of these 18 patients, 16 patients were females rest were males. 50-70 yrs were the predominant group. More than 70% of the patients with hypothyroidism belong to this group.

Of all the hypothyroid patients, 14 had multiple stones and 4 had single stone, one patient had CBD stone and one patient had both CBD and GB stone. 7 patients underwent open cholecystectomy and 7 underwent laparoscopic cholecystectomy. In 3 patients CBD exploration was done. Post operative and intraoperative periods were uneventful in all these patients.

LIMITATIONS OF THE STUDY

As this study has been carried out over a limited period of time with a limited number of patients and there was lack of financial and infrastructural support, it could not have been large enough to be of reasonable precision. The follow up period was not long enough to comment about recurrence in patients with hypothyroidism and the response of the patients to thyroid medications.. All the facts and figures mentioned here may considerably vary from those of large series covering wide range of time, but still then, as the cases of this study were collected from a tertiary level hospital in our country, this study has some credentials in reflecting the facts regarding prevalence of hypothyroidism in gallstone patients and its possible correlation with the natural progression of the disease process.

SUMMARY

Cholelithiasis and Choledocholithiasis are one of the commonly encountered diseases in a general surgery department. Multiple risk factors have been attributed to the development of gallstones which include age, female gender, obesity, high fat diet, family history etc. Patients usually present with right hypochondrial pain, dyspepsia, vomiting and occasionally fever or jaundice. Management includes diagnostic imaging studies followed by surgery, if indicated. Hypothyroidism is not an accepted or proven risk factor for gallstones as of yet. Several studies have postulated the possible pathophysiology behind the role of thyroxine in the normal physiology of the biliary system. No concurrence has been established

Age and Sex Distribution:

The most commonly involved age group in patients with gall stones was 50 - 70, with incidence increasing with age. This correlates with the general literature that gallstones is a disease of the elderly. Female sex, is in itself a risk factor for developing gallstones with more than seventy five percent of the involved patients belonging to the female gender.

Co Morbid Factors:

Hypertension and Diabetes Mellitus were the prevalent comorbid factors as cholelithiasis like previously told is a disease of the elderly. None of these seemed to have a significant correlation with the disease process.

Diagnostic Studies:

USG was sensitive in detecting stones in nearly all patients with CECT abdomen and MRCP required only in few cases.

Management:

Laparoscopic and open Cholecystectomy were both perfomed. Conversion to open was seen in 4 patients. This can be attributed to technical problems and as the study was done in a teaching institute and a good percentage of surgeries was done by trainees.

Hypothyroidism and gallstones:

Eighteen patients in our study had gallstones showing a prevalence of nearly one fourth of the patients being affected. All these indicated a pathophysiological role of thyroxine in gallstone formation, apart from the supposed lipid metabolism abnormalities. This has been substantiated by physiological studies in animal models by Johanna Laukkarinen et al.

CONCLUSION

This prospective ocservational type of study was conducted in Department of General Surgery, Thanjavur Medical College. It can be concluded from the findings of the study that hypothyroidism is a highly probable risk factor for development of hypothyroidism especially for middle aged females. Undetected and untreated hypothyroidism in such patients will result in persistence of the basic pathophysiology responsible for the initial disease process resulting in recurrence and complications. So, it can be assumed that patients at risk of forming gall stones due to hypothyroidism will benefit from early treatment. Most importantly, when treating patients with cholelithiasis or choledocholithiasis, clinicians should be aware of the possible hypothyroid background and consider examining the thyroid function, at least in female patients over 40 years of age, in which group the prevalence of clinical and subclinical hypothyroidism is the highest.

RECOMMENDATIONS

On the basis of the findings of the study, the following recommendations can be made:

1. Evaluation of thyroid profile should be a part of general workup in patients with both cholelithiasis and choledocholithiasis especially in female patients.

2. Proper evaluation and preoperative preparation in patients with hypothyroidism, anticipating complications.

3. The patients with clinical hypothyroidism should be started with appropriate thyroid medications.

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DATA COLLECTION CHART

QUESTIONAIRE

PATIENT DETAILS:

Name: Age: Sex:

IP No. :

ON ADMISSION:

Main Complaints :

Symptoms of Gallstone/CBD stones :

H/o right upper quadrant pain :

H/o vomiting :

H/o dyspepsia :

H/o fever :

H/o jaundice :

Symptoms of Hypothyroidism :

H/o weight gain :

H/o weakness/ lethargy :

H/o intolerance to cold :

H/o constipation :

H/o swelling of face or limbs :

H/o loss of hair / dry skin :

Co – Morbid Illness :

Significant Past History :

CLINICAL EXAMINATION:

Pulse: BP: RR: Temp:

Pallor: Icterus:

CVS: RS:

P/A:

Thyroid examination:

INVESTIGATIONS:

Hemogram: Renal Function Test:

Liver Function Test:

BT/CT: Blood Grouping: Fasting Lipid Profile:

ECG: CXR:

USG Abdomen:

Thyroid profile: T3 -- T4 -- TSH —

Operative Procedure:

FOLLOW UP:

S.No	Name	Age	Sex	Ip No.	Symptoms related to hypothyroidism	Co Morbid illness	Thyroid Examination	LFT	TFT			USG Abdomen/ CT			Procedure	Remarks
								T.Bil/Dir.Bil	TSH	T3 (pg/ml)	T4 (mcg/dl)	No. of calculi	Size largest	CBD stone		
1	Chinnathambi	50	Male	33790	No	DM	Normal	1.2/0.7	4.5	2.5	2	Multiple	6mm	Normal	Open Chole	
2	Krishnamoorthy	35	Male	34023	No	-	Normal	0.9/0.3	3.5	1.6	4	Multiple	5mm	Normal	Open Chole	
3	Segappi	65	Female	33560	No	-	Normal	1.1/0.4	5	2.8	5.5	Single	9mm	Normal	Lap Chole	
4	Krishnaveni	30	Female	34034	No	-	Normal	1.2/0.5	4.6	3.9	6.5	Multiple	5mm	Normal	Lap to open	
5	Govindasamy	70	Male	40756	No	-	Normal	2.5/1.2	1.5	2.7	9	Multiple		Normal	Conservative	
6	Shanthi	36	Female	40371	No	-	Normal	0.9/0.4	8.5	2.4	4	Multiple	7mm	Normal	Open Chole	
7	Jothika	20	Female	38909	No	-	Normal	1.2/0.5	> 16	0.4	0.9	Multiple	6mm	Normal	Lap Chole	Hypothyroid
8	Bangaru	55	Female	41027	No	DM	Normal	1.4/0.5	5.5	2.6	5	Single	8mm	Normal	Lap Chole	
9	Thilagavathy	30	Female	39123	No		Normal	1.2/0.6	3	3.8	5.5	Single	7mm	Normal	Lap Chole	
10	Shenbagavalli	55	Female	39563	No	-	Normal	1.1/0.6	1.5	4.5	8	Multiple	18mm	Normal	Lap to open	
11	Pichaiammal	68	Female	39845	No	DM	Normal	1.1/0.5	>12	3.4	4.5	Multiple	8mm	Normal	Open Chole	Hypothyroid
12	Chitra	43	Female	35421	No	-	Normal	1.2/0.5	4.5	2.5	3	Multiple	5mm	Normal	Open Chole	
13	Subramani	45	Male	37019	No	-	Normal	1.1/0.4	4	3.3	5.5	Single	8mm	Normal	Open Chole	
14	Anbumani	64	Female	37131	No	-	Normal	1.4/0.6	>20	0.6	4.2	Multiple	4mm	Normal	Lap Chole	Hypothyroid
15	Venmathy	48	Female	38939	No	HT	Normal	1.2/0.6	4	2.7	8	Single	7mm	Normal	Lap Chole	
16	Ganesh	63	Male	38741	No	-	Normal	1.2/0.6	5.5	3.6	7	Single	5mm	Normal	Lap to open	
17	Pankajavalli	50	Female	38666	No	-	Normal	1.8/0.8	>16	1.6	0.8	Multiple	8mm	Normal	Lap Chole	Hypothyroid
18	Saraswathy	70	Female	38995	No	HT/DM	Normal	2.0/0.8	>18	1.8	2	Multiple	12mm	Normal	Open Chole	Hypothyroid
19	Thanapal	45	Male	35415	No	HT	Normal	1.2/0.5	4	3.2	5.8	Multiple	5mm	Normal	Lap Chole	
20	Murali	24	Male	36422	No	-	Normal	1.4/0.5	5.5	4.1	8	Single	5mm	Normal	Lap Chole	
21	Krishnamoorthy	35	Male	34545	No	HT	Normal	2.0/1	5	3.7	7.8	Multiple	6mm	Normal	Open Chole	
22	Mani	45	Female	37845	No	-	Normal	1.5/0.6	4	2.5	9.2	Single	8mm	Normal	Lap Chole	
23	Selvi	35	Female	36261	No	-	Normal	1.4/0.5	5.2	3.6	8	Multiple	7mm	Normal	Lap chole	
24	Saralmary	20	Female	37121	No	-	Normal	1.0/0.4	>12	0.2	0.6	Multiple	6mm	Normal	Lap Chole	Hypothyroid
25	Mary	50	Female	32151	No		Normal	1.2/0.6	>80	1.2	0.4	Multiple	8mm	6mm	Conservative	Hypothyroid
26	Rajendran	52	Male	35020	No		Normal	1.6/0.5	>20	0.5	0.3	Multiple	8mm	Normal	Open Chole	Hypothyroid
27	Vennila	56	Female	34102	No	DM	Normal	1.5/0.6	4.5	3.2	6	Multiple	6mm	Normal	Lap Chole	
28	Vaduvambaal	45	Female	34523	No	-	Normal	1.2/0.6	4.2	3.2	7	Single	5mm	Normal	Lap Chole	
29	Indrani	60	Female	32012	Yes	-	Normal	2.6/1.2	>15	2.4	0.8			8mm	Open, CBD exploration	Hypothyroid
30	Chitra	34	Female	42587	No	-	Normal	1.2/0.5	4.2	2.2	9	Multiple	7mm	Normal	Lap Chole	
31	Nageshwaran	55	Male	42310	No	HT	Normal	1.0/0.3	5	2.6	7	Single	8mm	Normal	Lap Chole	
32	Nandhini	35	Female	42014	No	-	Normal	0.9/0.4	3.5	3.4	8.6	Single	8mm	Normal	Lap chole	
33	Kamalam	60	Female	32003	No	DM/HT	Normal	1.2/0.6	3	2.4	8.2	Multiple	5mm	Normal	Open Chole	
34	Hansiya	28	Female	45110	No	-	Goitre	1.1/0.6	>20	2.2	1.2	Multiple	6mm	Normal	Lap Chole	Hypothyroid
35	Sudha	36	Female	42201	No	-	Normal	2.0/1.0	5	3.5	7.9	Multiple	5mm	Normal	Lap Chole	
36	Sumathy	38	Female	35023	No	-	Normal	1.6/0.6	4.5	4.2	7.4			5mm	Open, CBD exploration	
37	Arul Mary	40	Female	34152	No	-	Normal	1.2/0.6	4.6	3.2	8.8	Multiple	7mm	Normal	Open Chole	
38	Thilagavathy	30	Female	48574	No	-	Normal	1.5/0.6	4.6	2.4	10	Multiple	8mm	Normal	Lap Chole	
39	Veerasamy	65	Male	47152	No	DM/HT	Normal	1.8/0.8	>20	3.5	2	Multiple	6mm	Normal	Open Chole	Hypothyroid
40	Vasuki	43	Female	35022	No	-	Normal	1.0/0.3	2.5	4.2	8.8	Single	8mm	Normal	Lap Chole	
41	Saraswathy	60	Female	35102	No	-	Normal	1.6/0.6	>30	0.6	2	Multiple	6mm	Normal	Open Chole	Hypothyroid
42	Mala	35	Female	36201	No	-	Normal	1.2/0.6	4.5	2.6	11	Multiple	8mm	Normal	Lap Chole	
43	Kaliammal	53	Female	35016	No	-	Normal	1.6/0.4	5.5	3.6	9.6	Multiple	7mm	Normal	Lap Chole	
44	Balasubramanian	49	Male	36001	No	-	Normal	2/0.8	4.5	3.4	7.4	Multiple	6mm	Normal	Lap Chole	
45	Pitchai	66	Male	45006	No	DM/HT	Normal	1.6/0.5	>15	0.4	2	Multiple	7mm	Normal	Open Chole	Hypothyroid
46	Amutha	40	Female	35465	No	-	Normal	1.6/0.4	4.5	2.5	9.4	Multiple	9mm	Normal	Lap Chole	
47	Raja	44	Male	45102	No	-	Normal	1.8/0.6	5	3	7.3	Single	6mm	Normal	Lap Chole	
48	Krishnaleela	35	Female	45181	No	-	Normal	2.4/0.8	4.5	2	8.4	Multiple	8mm	Normal	Lap Chole	
49	Pichaiammal	65	Female	38695	No	-	Normal	1.8/0.6	5	2.2	9.4	Multiple	7mm	Normal	Lap Chole	
50	Malar	34	Female	36558	No	-	Normal	1.3/0.6	4.6	2	7	Multiple	5mm	Normal	Lap to open	
51	Vellaiyammal	21	Female	38891	No	-	Normal	1.6/0.6	5.5	2.1	8.4	Single	8mm	Normal	Lap Chole	
52	Peter	52	Male	33161	No	HT	Normal	1.6/0.5	5.5	3.6	8.2	Multiple	5mm	Normal	Lap Chole	
53	Hyarunisha	60	Female	33406	No	HT	Normal	2.5/1.2	>30	3.2	2.6	Multiple	6mm	6mm	Open, CBD exploration	Hypothyroid
54	Ponnusamy	62	Male	45545	No		Normal	2.6/0.6	5.5	3	8.8	Multiple	5mm	Normal	Open Chole	
55	Sivakumar	38	Male	46335	No	HT	Normal	1.6/0.6	2.5	2.8	7.8	Multiple	4mm	Normal	Open Chole	
56	Manikandan	21	Male	49987	No	-	Normal	3.2/0.7	3.5	2.6	8.8	Single	7mm	Normal	Lap to open	
57	Kannan	45	Male	50024	No	-	Normal	1.8/0.5	5.5	3.7	8.9	Single	6mm	Normal	Lap Chole	
58	Abdul Latif	60	Male	33387	No	DM/HT	Normal	2.0/0.8	>20	1.2	3.8	Single	7mm	Normal	Lap Chole	Hypothyroid
59	Shanmugavalli	42	Female	38845	No	-	Normal	2.6/0.8	5	41	9	Multiple	8mm	Normal	Lap Chole	
60	Bhuvaneshwari	45	Female	58168	No	-	Normal	2.2/1.6	20.5	0.6	2.2	Multiple	10mm	Normal	Lap Chole	Hypothyroid
61	Malarkodi	45	Female	45012	No	-	Normal	1.6/0.4	4.2	0.8	8	Single	6mm	Normal	Lap Chole	
62	Manimegam	56	Male	58774	No		Normal	2/0.9	5	2.2	9.5	Multiple	5mm	Normal	Open Chole	
63	Kumaresan	47	Male	47587	No		Normal	1.2/0.6	4	2.6	7.4	Multiple	7mm	Normal	Lap Chole	
64	Muthulakshmi	36	Female	45645	No	-	Normal	3.5/1.2	>20	0.6	1.2	Multiple	6mm	5mm	Open, CBD exploration	Hypothyroid
65	Umarani	45	Female	36521	No	DM	Normal	1.2/0.6	4.5	4.2	7.4	Multiple	4mm	Normal	Lap Chole	
66	Seetha	56	Female	25412	No	HT	Normal	1/0.4	1.5	2.6	8.8	Single	7mm	Normal	Open Chole	
67	Govindaraj	70	Female	48725	No	HT,DM	Normal	2.5/1.2	13.5	2.6	3.3	Single	8mm	Normal	Open Chole	Hypothyroid
68	Munniyammal	66	Female	36586	No	-	Normal	1/0.3	1.8	2.9	9.8	Multiple	6mm	Normal	Lap chole	

ABSTRACT

TITLE: Association of Cholelithiasis, Choledocholithiasis And Hypothyroidism

INTRODUCTION:Thyroid disorder is a prevalent condition among adult population; however, it is frequently over looked**.** Hypothyroidism causes low bile flow and sphincter of Oddi dysfunction and hence promotes gall stone formation. This study was done to substantiate the need for evaluating the thyroid status in patients presenting with cholelithiasis/ choledocholithiasis.

AIMS: To study the prevalence of hypothyroidism in patients presenting with CHOLELITHIASIS/ CHOLEDHOCOLITHIASIS.To assess if thyroid profile is indicated in patients with biliary lithiasis.

MATERIALS AND METHODS: This is an observational and prospective study. Method of sampling was non-random, purposive. 68 patients with USG evidence of cholelithiasis/ choledocholilithiasis, were evaluated with basic investigations and additionally thyroid function test was performed. The operation procedure and related per operative factors were observed directly and recorded.

RESULTS: The operation procedure and related per operative factors were observed directly and recorded in the data collection sheet instantly. Age of these selected patients ranged from 20- 70 yrs, with mean age being 47.14 yrs. 32% were male patients and 68% were female patients. The male to female ratio is 1: 2. Females were the predominant group. Thyroid function test was performed in all 68 patients out of which, 18 patients (26.4%) were found to have hypothyroidism and the rest i.e. 50 patients were euthyroid. Of these 18 patients only 2 were known hypothyroid, rest 16 patients were newly diagnosed hypothyroid patients .Of these 18 patients, 16 patients were females rest were males. 50-70 yrs were the predominant group. More than 70% of the patients with hypothyroidism belong to this group.

CONCLUSION: Evaluation of thyroid profile should be a part of general workup in patients with both cholelithiasis and choledocholithiasis especially in females above the age of 40yrs and patient should be treated with appropriate thyroid medications.

KEY WORDS: Hypothyroidism, Cholelithiasis, Choledocholithiasis