A Thesis in General Surgery

A STUDY OF PREVALENCE OF HYPOTHYROIDISM IN CHOLELITHIASIS

Submitted in partial fulfillment of the Requirements for the Degree of M.S General Surgery (Branch I)

Kilpauk Medical College
The Tamilnadu Dr. M.G.R Medical University Chennai

APRIL – 2015
DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation titled “A STUDY OF PREVALENCE OF HYPOTHYROIDISM IN CHOLELITHIASIS” is a bonafide and genuine research work carried out by me under the guidance of Dr. V. Chitra, M.S., Professor, Department of General Surgery, Kilpauk Medical College, Chennai.

This dissertation is submitted to THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY, CHENNAI in partial fulfillment of the requirements for the degree of M.S. General Surgery examination to be held in April 2015.

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The Institutional Ethical Committee of Govt. Kilpauk Medical College, Chennai reviewed and discussed the application for approval “A Study of Prevalence of hypothyroidism in cholelithiasis” – For Project Work submitted by Dr.V.P.B.Maharajan, MS (GS), PG Student, KMC, Chennai-10.

The Proposal is APPROVED.

The Institutional Ethical Committee expects to be informed about the progress of the study any Adverse Drug Reaction Occurring in the Course of the study any change in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

30 MAY 2014

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PREVALENCE OF HYPOTHYROIDISM IN CHOLELITHIASIS...

By 2212111557 mes General Surgery

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INTRODUCTION Among biliary pathology, gall bladder stones are the most common. Gall bladder Stone prevalence varies among different parts of the world. About 10% in western countries and around 4% in India. Gall stones are of three different types. Cholesterol, pigment or mixed type. In pigment stones, it could be either brown or black. In asian population, pigment stones accounts for about 80%, whereas among European population, cholesterol and mixed stones are more common. Gall stones may be single or multiple. Most of the Gallstones are asymptomatic, they are identified incidentally at the time of imaging for other reasons or at the time of laparotomy. Now in India, incidence of gall stones is increasing. Mainly due to factors like westernization in dietary habits, easy availability of investigations and also because of increased affordability. Gall stone formation depends upon various factors like Concentration, supersaturation, crystal nucleation and also abnormal gall bladder mobility. Biliary stones is an important factor in gall stone formation. Previous studies mainly focused on supersaturation of cholesterol in bile, which is a critical process in formation of gall stones. Many discussions going around for decades, whether thyroid dysfunction could cause cholelithiasis. Various explanations include altered lipid metabolism, imbalance of odd dysfunction and altered flow of bile in thyroid failure patients. AIM AND OBJECTIVE OF THE STUDY To know the prevalence of hypothyroidism in patients with cholelithiasis. REVIEW OF LITERATURE HISTORY The malady of biliary tract stones is by no means a modern times, it dates back to 21 Egyptian dynasty. Archeological evidence suggests that young Egyptian women had gallstones over 2600 years ago. During the time of Roman Empire, Pliny described the rare anomaly of double gallbladder. The well known physician, Seneca of Ephesus described jaundice and the associated signs of extra hepatic obstruction, including acholic stools, dark urine and pruritus. The description about biliary tract calculi was given in the 5 century AD by the Greek physician Aldandar Trallianus. The surgical relevance of biliary tract disease was made obvious by the Islamic physician Ibusina (980 - 1037), who proved that the biliary cutaneous fistula could result from drainage of abdominal wall abscess. Hoffmann in 1793 described the presence of asymptomatic gallstones. In 1790, Jean Louis Puff recognized that a gallbladder could become adherent to abdominal wall and proposed that it could be punctured by a trocar through the abdominal wall. It was Belzius in 1809 who recognized the bile acid fraction in bile. Later in 1863, Hoppe-Seyler postulated a continuous circulation of the bile acids in human system. Leberg in 1873 coined the term bile acid. In 1903 Buxom demonstrated the stones radiologically. The field had further developed by the performance of cholecystography by Graham and Cole in 1924. Cholecystography was developed later. Endoscopic retrograde routes were introduced in 1950s. Sonogram came into vogue in 1960s to confirm pregnancy. A decade later, high resolution converters were available to produce grey scale display of internal organs. Although abdominal sonogram infrequently demonstrated choledocholithiasis, it has
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LIST OF ABBREVIATIONS USED

AMP - Adenosine mono phosphate
CSI - Cholesterol saturation index
CBD - Common bile duct
DGB - Distended gall bladder
MC - Multiple calculi
RTH - Resistance to thyroid hormone
SC - Single calculus
TG - Thyroglobulin
TRH - Thyrotropin releasing hormone
TSH - Thyroid stimulating hormone
UDP - Uridine diphosphate
UDPGA - Uridine diphosphate glucuronic acid
USG - Ultrasonogram
ABSTRACT

BACKGROUND AND OBJECTIVE

For decades there has been discussion whether thyroid disorders could cause gall stone disease. This study attempts to know the prevalence of hypothyroidism in cholelithiasis.

METHODS

A cross sectional study was done between April 2014 to September 2014. 50 Patients diagnosed as cholelithiasis in department of general surgery, Govt. Royapettah Hospital were included in the study. Full history, clinical examination, ultrasound abdomen and laboratory blood test for free T3, free T4 and TSH were done for every patient.

RESULTS

Out of 50 patients of cholelithiasis, 29(58%) were females and 21(42%) were males. Thyroid disorder in form of hypothyroidism was found in 19 (38%) patients. In that 11(22%) patients presented with subclinical hypothyroidism and 8(16%) patients with clinical hypothyroidism.

CONCLUSION

There is an increase in prevalence of hypothyroidism in cholelithiasis in this study. The prevalence was more among >40 years age group. This increase
in prevalence could have an effect on the diagnostic and therapeutic workup of cholelithiasis patients.

Key words: cholelithiasis, hypothyroidism, thyroid hormone assay.
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INTRODUCTION

Among biliary pathology, gall bladder stones are the most common. Gall bladder Stone prevalence varies among different parts of the world. About 10% in western countries and around 4% in India. Gall stones are of three different types. Cholesterol, pigment or mixed type. In pigment stones, it could be either brown or black. In asian population, pigment stones accounts for about 80%, whereas among European population, cholesterol and mixed stones are more common. Gall stones may be single or multiple. Most of the Gallstones are asymptomatic, they are identified incidentally at the time of imaging for other reasons or at the time of laparotomy. Now in India, incidence of gall stones is increasing. Mainly due to factors like westernization in dietary habits, easy availability of investigations and also because of increased affordability.

Gall stone formation depends upon various factors like Concentration, supersaturation, crystal nucleation and also abnormal gall bladder motility. Biliary stasis is an important factor in gall stone formation. Previous studies mainly focused on supersaturation of cholesterol in bile, which is a critical process in formation of gall stones. Many discussions going around for decades, whether thyroid dysfunction could cause cholelithiasis. Various explanations include altered lipid metabolism, sphincter of Oddi dysfunction and altered flow of bile in thyroid failure patients.
AIM AND OBJECTIVE OF THE STUDY

To know the prevalence of hypothyroidism in patients with cholelithiasis.
REVIEW OF LITERATURE

HISTORY

The malady of biliary tract stones is not just modern times, it dates back to 21st Egyptian dynasty. Archeological evidence suggests that young Egyptian women had gallstones over 2000 years ago. During the time of Roman Empire\(^1\), Plimy described the rare anomaly of double gallbladder. The well known physician, Sonares of Ephesus described jaundice and the associated signs of extra hepatic obstruction, including acholic stools, dark urine and pruritis.

The description about biliary tract calculi was given in the 5th century AD by the Greek physician Altender Tralliamus. The surgical relevance of biliary tract disease was made obvious by the Islamic physician Ibusina (980 - 1037), who proved that the biliary cutaneous fistula could result from drainage of abdominal wall abscess. Hoffmann in 1793 described the presence of asymptomatic gallstones. In 1790, Jean Louis Peff recognized that a gallbladder could become adherent to abdominal wall and proposed that it could he punctured by a trochar through the abdominal wall.

It was Belzius in 1809 that recognized the bile acid fraction in bile. Later in 1863, Hoppe-Seyler postulated a continuous circulation of the bile acids in human system. Leberg in 1873 coined the term bile acid.
In 1903 Buxom demonstrated the stones radiologically. The field had further developed by the performance of cholecystogram by Graham and Cole in 1924. Cholescintigraphy was developed later. Endoscopic retrograde routes were introduced in 1950s. Sonogram came into vogue in 1960s to confirm pregnancy. A decade later, high resolution converters were available to produce grey scale display of internal organs. Although abdominal sonogram infrequently demonstrated choledocholithiasis, it has evolved as the primary screening modality due to its reliability to demonstrate gallstones.

As surgery and anaesthesia began to evolve, John Bobbs, an Indiana surgeon, performed the first intervention in biliary tree, a cholecystolithotomy. In 1882, Karl Langenbuck, a noted German surgeon, performed the first successful cholecystectomy. Innovations and new endeavors have resulted in the evolution of new surgical approach, called minimally invasive surgery. Mouret, recently, in 1987, pioneered the technique of laparoscopic cholecystectomy in Lyon, France, which has grown ever since.

In 1966 – Maki proposed that bacterial infection plays a key role in the pathogenesis of pigment gallstones.

In 1982 – National Institute of Health International Workshop classified most pigment gallstones as either black or brown.
In 1996 – Attila Csendes & Patricio Burdiles found out that no bacteria is seen in control groups in bile culture studies, when compared to bile culture study of patients with gallstone disease.

In 1867 – Ioenisus was the first person to extract gallstones from the gallbladder.

In 1891 – Calot described triangle of cholecystectomy and dissection of this area should show the anatomic structures and allow safe dissection.

In 1924 – Schoff – classification of GS. Classified as – Inflammatory gallstones, metabolic (cholesterol) gallstones, Mixed gallstones, Pigment gallstones.

In 1981 – Schoenfield and Lachin – Treated 144 patient including 92 men and 52 women with symptomatic gallstones by conservative management and about 50% has to undergo cholecystectomy as further management.

In 1985 – Muller et al – proposed that MTBE can be used for dissolution of gallstones (cholesterol stones) successfully in the presence of an occluded cystic duct.

In 1986 – Muhe in Boblingen (Germany) performed first laparoscopically assisted cholecystectomy.

In 1989 – Bushenne, Sackman – ESWL (extracorporeal shock wave lithotripsy) can be done with ultrasound guidance and requires no percutaneous cholecystectomy.

In 1991 – PA grace – Lap cholecystectomy.
In 1992 - IG Marton et al – operated 162 patients with gallstones.

In 1992 - Ajay K. Kripalani lap cholecystectomy has been a very safe procedure which reduces the morbidity and mortality associated with surgery for symptomatic gallstones.

In 1995 – Shyamal Kumar Gosh et al showed female preponderance for GS disease.

In 1996 - Carter De, Russel, Bismuth H – in there hepatobiliary and pancreatic surgery mentioned about congenital anomalies of GB.

In 1996 – J.R. Barton et al complications after lap cholecystectomy like bile leak is managed endoscopically by stunting or sphincterotomy.

In 1996 – Majeed and Assalia – done minilaparotomy cholecystectomies for patients with gallstones after ultrasound detection of gallstones with smaller abdominal incisions.

In 1998 – GPH, GUI, CVN Chruvu et al, operated 92 patients with symptomatic gallstones and cholecystectomy has improved the symptoms suggesting surgery remains the gold standard for symptomatic treatment for gallstones.

In 2000 – UL Wills et al, laparoscopy is useful in the management of minor bile leak after laparoscopic cholecystectomy.

In 2002 – Michael Rosen et al, Laparoscopic cholecystectomy were performed.
In 1347 patients. Out of this 71 patients required conversion to open surgery. Obese patients with cholelithiasis have increased chance of conversion of laparoscopic cholecystectomy to open surgery. Patients with multiple comorbid disease have again more chance of failure of laparoscopic cholecystectomy.

In 2002 – Nakeeb and co-workers established that genetic factors were responsible for at least 30% symptomatic gallstone disease.

In 2002 – Schiffman and associates studied that there is decrease in gallstone formation in obese persons who is on low calorie diet for long periods. They also stated that previous gastric bypass surgery increases the incidence of gallstone formation.
ANATOMY, PHYSIOLOGY AND EMBRYOLOGY OF GALLBLADDER

EMBRYOLOGY

At 3rd week when the embryo is 3mm in length an endodermal bud arises from the ventral aspect of the gut at the point between for foregut and midgut. This endodermal bud enlarges and divides into pars hepatica and pars cystica. It passes through the septum transversum and grows into ventral mesogastrium. Cranial portion that is pass hepatica and caudal portion pass cystica.

- Pars cystica develops into gall bladder and cystic duct\(^\text{19}\).
- Pars hepatica cells grows into the transverse septum\(^\text{16}\).
- At 12th week of gestation liver function starts and cystic duct joins the hepatic duct and forms common bile duct (CBD).

ANATOMY

Gallbladder is pear shaped organ (pyriform shaped), sac like, hollow organ measuring 7.5 to 12 cm in length with capacity of about 50ml. It is capable of distension of about 50 times. It lies in the gallbladder bed of the inferior surface of liver. It extends slightly below the inferior margin of the liver. Extrahepatic portion of the gallbladder is covered by peritoneum\(^\text{16}\).
Gall bladder has got four parts –

1. Fundus

2. Corpus or body

3. Infundibulum

4. Neck

**Figure 1:** Anatomy of gall bladder – inferior view
Cystic duct

It starts from gallbladder and drains into common hepatic duct at an acute angle. Average length is 4 cm. Cystic duct have spiral valve of heister. Cystic duct joins common hepatic duct to become common bile duct which enters the 2nd part of duodenum in its medial aspect at the summit of ampulla of vater\textsuperscript{19}.

Right, left and common hepatic duct

Right hepatic duct is about 1cm long and it courses more vertically. In 25\% of individuals, posterior segment duct crosses the segmental fosse to join the left hepatic duct or one or its tributaries. The left hepatic duct drains from lateral & medial branches of II, III & IV segments. It is longer than the right hepatic duct, measures 1-3 cm in length & is partially extraperitoneal, which therefore dilates readily in the presence of distal obstructive disease. The extrahepatic portion of the left hepatic duct and its segment III branch can be accessed through the round ligament for bilioenteric bypass in common hepatic strictures and inoperable cholangiocarcinoma\textsuperscript{8}.

Common bile duct

The common bile duct (ductus choledochus) extends from the junction of the cystic duct and common hepatic duct to the papilla of Vater in the second part of duodenum. It varies in length from 5-15 cm and an average diameter of 7mm, ranges from 4-10 mm. It serves as a conduit for bile from the liver & gallbladder to the duodenum.\textsuperscript{3,11,14}
Four segments of CBD.

1. Supraduodenal

2. Retroduodenal

3. Infraduodenal (intrapancreatie) &

4. Intraduodenal

Figure 2: Anatomy of the gallbladder, biliary radicals.
The supraduodenal portion measures 2-5 cm in length, average of 2.5 cm. It is important surgically because it is the area which is commonly explored. The retroduodenal portion is between the superior margin of the 1st part of duodenum to the head of the pancreas. It measures about 2.5 cm long, ranges 1-3.5 cm.

The infraduodenal part runs in the substance of pancreas towards the duodenum. In 20% of cases it has a partial or a complete extraperitoneal course. It measures about 2.5 cm in length, range of 1.5-3.5 cm.

The intramural portion traverses obliquely through the duodenal wall & measures around 1 cm in length. It usually joins the pancreatic duct. A localized dilatation of the common channel is called as Ampulla of Vater which is present in 10-20% of cases. In 10% of cases these two ducts open separately in to the duodenum. This vaterian segment includes distal 2.5-3.0 cm of CBD, terminal part of the pancreatic duct, ampulla of vater and the major duodenal papilla. These structures are surrounded by a condensation of circular & longitudinal smooth muscle fibers often referred to as Sphincter of Oddi. The inferior sphincter is the strongest component which is known as the papillary muscular ball.
HISTOLOGY OF GALL BLADDER

Gall bladder has three layers-

- The Serous layer
- Fibromuscular layer
- Mucous layer

Mucous membrane is elicited into minute rogue which give honey comb appearance. It is yellowish brown in colour. Epithelium consist of a single layer of columnar cells of varying size. Apical surface contains microvilli which helps in absorption of water and solutes from bile to make it more concentrated. Mucus granules are present in the apical half of some cells which secretes mucus into the lumen.

Figure 3: Histology of gall bladder
SURGICAL IMPORTANCE OF GALL BLADDER

• Fundus of the gallbladder is least vascular and it may undergo ischaemic changes and perforation is common.\textsuperscript{29}

• Gallstones may get impacted in the cystic duct and obstruct the flow of bile. Gallstones are commonly become impacted in Hartman’s pouch.\textsuperscript{29}

ARTERIAL SUPPLY OF GALLBLADDER

Major blood supply is from cystic artery which is branch of right hepatic artery. It runs in Calot’s triangle closed to cystic duct. At the superior border of the neck of the gallbladder it divides into superficial and deep branches. Occasionally cystic artery may arise from hepatic artery proper or rarely from gastroduodenal artery. Cystic artery also supplies branches to hepatic ducts and upper part of common bile duct.\textsuperscript{29} Venous drainage is carried out by small veins which enter directly liver.

LYMPHATIC DRAINAGE OF GALLBLADDER

Proximally the lymphatic channels of the gallbladder communicate with those of Glisson’s capsule of the liver which in turn drain into the thoracic duct through several channels. Distally the lymphatics from gallbladder and extrahepatic bile duct drain into the cystic lymph node, which is situated near the cystic artery origin from the right hepatic artery.\textsuperscript{33}
NERVE SUPPLY

Parasympathetic fibres of hepatic branch of anterior vagal trunk stimulate contraction of gallbladder and relax ampullary sphincter. Sympathetic fibres from cell bodies of coeliac ganglion inhibit contraction of gallbladder. The hormonal activity is much more important than neural function.

Afferent pain fibres pass mainly through the right sympathetic fibres into the spinal segments T₇-T₉. This causes referred pain over the right infraspinacular region. Some fibres may pass through the right phrenic nerve, C₃-C₅.

Fibers from the right phrenic nerve travel by way of the phrenic, celiac, and hepatic plexuses to reach the gallbladder. Many of these fibers are afferent and may account for the pain referred to the right hypochondrium and radiating the back between the shoulder blades in some patients with gallbladder diseases.

Burnett and associates demonstrated three nerve plexuses: subserous, muscular, and mucosal. The ganglion cells in each nerve plexus decrease in number from subserous to mucosal levels. In comparison with the myenteric plexus of the gut, the subserous plexus ganglia are larger and spaced farther apart.
COMMON ANOMALIES AND VARIATIONS

- Absent gallbladder.
- Bilobed gallbladder.
- Fundal diverticulum.
- Phrygian cap.
- Hour glass gallbladder.
- Left sided gallbladder, floating gallbladder.
- Double gallbladder.
- Persistent intrahepatic gallbladder
- Diverticulum of body or neck of gallbladder
- Accessory peritoneal fold due to congenital adhesions.

PHYSIOLOGY OF GALLBLADDER

Bile secretion by liver is an active and continuous process. Its expulsion into duodenum, which is its site of action, is intermittent. Hence, it is necessary for bile to be stored and to be released when needed. Gallbladder serves this main function. Strictly bile is not a digestive secretion, because it doesn't possess any digestive enzymes. Liver secretes bile at the rate of 40ml/hr. The sphincter of Oddi dictates the flow of bile.4
The functions of gallbladder are –

- Reservoir of bile
- Concentration of bile
- Pressure regulation
- Secretion of bile

**Figure 4:** Circulation of bile salts
MECHANISM OF STORAGE

The CBD is shut off from duodenum by sphincter of Oddi when pressure exceeds \( >70 \text{ mm H}_2\text{O} \), bile is directed from CBD into gallbladder. Because of inherent capacity of gallbladder to absorb water and inorganic constituents, bile is concentrated 4-10 times.

MOVEMENTS OF GALLBLADDER

- Tonic contractions begin 5-30 minutes after food intake, intermittently till the gallbladder is empty. Normal emptying time varies between 2-5 hours.
- Rhythmic contractions, which are weak, not exceeding \( 50\text{mmH}_2\text{O} \) are not able to expel bile into duodenum. Since this pressure is less than the secretory pressure of liver, filling and evacuation is entirely dependant upon reciprocal sphincter of Oddi contraction and relaxation.

MECHANISM IN EXPULSION OF BILE

Expulsion of bile requires 2 factors

- increased pressure of bile
- relaxation of sphincter of Oddi.

Pressure of bile is increased and secretion of bile is stimulated by bile acids and fatty meal. Gallbladder contraction is brought about by stimulation of right vagus, which is motor to gallbladder and inhibitory to sphincter. The second mechanism is hormonal which is more important than neural reflex.
Cholecystokinin is secreted by duodenal mucosa, in response to food and low pH. The hormone has potent stimulative action on gallbladder and inhibitory action on sphincter of Oddi.

**BILE SALTS AND BILE ACIDS**

These are steroid molecules, formed from cholesterol by hepatocytes and are major pathway of cholesterol excretion by body. To enhance their solubility in bile, bile acids are conjugated with glycine and taurine before excretion as sodium salts.

Bile acids - primary - cholic acid / cheno acid

- secondary - deoxycholic / lithocholic / 7 ketolithocholic acid

- tertiary -ursodeoxycholic acid

**BILE PIGMENTS**

Bilirubin is the chief bile pigment, produced by the breakdown of senescent RBCs in reticuloendothelial system. Biliverdin is produced from bilirubin.²⁷
GALLSTONES CLASSIFICATION\textsuperscript{17}

1) Pure gallstones

- Cholesterol gallstones 70%
- Pigment gallstones 30%
- Calcium carbonate gallstones

2) Mixed and combined stones

**Cholesterol gallstones**

10% gallstones are cholesterol stones. They are usually solitary with smooth surface, oval or round in shape, pale yellow in colour. They are thought to be formed in aseptic static bile and commonly found in Hartman’s pouch. On section they shows radiating lines crossing the circular strata. In combined
gallstone, the stone starts as pure cholesterol stones but ultimately receives mixed covering of pigment and cholesterol.

**Pigment stones**

May be pure or contain Calcium bilirubinate. They constitute about 80% of all gallstones. They are Dark or black brown in colour, found exclusively in the gallbladder associated with excessive haemolysis like hereditary spherocytosis, sickle cell disease, thalassemia etc. Excessive breakdown of hemoglobin resulting in increase bilirubin which are excreted in bile and forms pigment stones in the gallbladder. Stones are usually appear as small soft fatty like masses.

Calcium bilirubinate stones are brown to orange in colour and soft in consistency. These stones are more often seen in bile ducts. These stones are often caused by infection (E.Coli and parasites).9

**Calcium carbonate stones**

Calcium carbonate stones are rarest type of stone they are grayish white in colour with smooth surface or articulated surface. Increase alkalinity of the bile favours this stone formation.3
**Mixed or combined stones**

Mixed stones have varying proportion of all three of the stone forming constituents of the bile eg. cholesterol, bile pigment and calcium. They constitute about 10% of gallstones.

Combined stones are those in which central core or external layers are pure and the reminder of the stone is mixture of constituents. Combined stones may be solitary but mixed gallstones are invariably multiple with faceted surface. Stones may vary in size few cm in diameter. Colour of the stone depends on constituents of stones.\(^7\)

Pale yellow - Cholesterol

Black - Calcium bilirubinate

Grayish white - Calcium carbonate.

On section of laminated central nucleus may contain epithelial debris and bacteria. This suggests inflammatory origin of stones. Chemical inflammatory changes prepare the soil for bacterial invasion.\(^9\)
EPIDEMIOLOGY OF GALLSTONES

It provides information about the prevalence and incidence of the disease.

a. True incidence: 5 year incidence in women aged 30, 40, 50, and 60 are (4%), (3.6%), (3%) and (3.7%) years and the same incidence rate in men were 0.3%, 2.9%, 2.5% and 3.3% at the same age. This shows that the incidence is more in women.

b. Prevalence and incidence: Gallstones are two times more common in women than in men.

c. Ethnic predisposition: Several genes that are associated with gallstone formation and resistance are identified in mice. The importance of these genes in human gallstone formation has not been established. Pima Indians in southern Arizona are an example of an extremely high risk population in which 70% of women less than 25 years are affected by the disease.39 Populations at the lowest risk are sub Saharan Africans and Asians.

d. Risk factors: Gallstone disease is multifactorial in origin and occur sporadically. Specific risk factors predisposing gallstones have been identified.

1) Age and gender

    Gallstone disease increases with age. Hence bile become more lithogenic with increasing age.1 Most studies report that incidence and prevalence of gallstones is three to four fold higher in female. But after 50 years the incidence
may become equal in male and females. This may be due to increase oestrogen in young women lead to increased secretion of cholesterol into bile.\textsuperscript{27}

2) Pathophysiology of gallstone formation with aging

Changes in bile composition with aging accounts for an increase risk of cholesterol gallstone formation. Biliary cholesterol saturation index (CSI) rises with age in both men and women. An inverse relation was seen between the age and hepatic bile salt synthesis and activity of enzyme 7 $\alpha$-hydroxylase (rate limiting enzyme for bile salt synthesis).\textsuperscript{3}

Factors that change with the age like change in contraction of gallbladder, ability to concentrate bile are also incriminated in gallstone formation including pigment or mixed stones.\textsuperscript{2}

3) Rapid weight loss

The physiological alterations that lead to gallstone formation as a result of rapid weight loss are multiple.

i. Hepatic cholesterol secretion increase during caloric restriction.

ii. Increase secretion of mucin which is potent stimulator of cholesterol crystal formation.

iii. Decrease gall bladder motility leading to biliary sludge formation.
Gallstone formation can be prevented by administration of ursodeoxycholic acid in these patients. It is also found that there is decrease in gallstone formation in obese persons who are taking low caloric diet.40

4) Pathophysiology of gallstone formation in obese persons

In obese persons hepatic cholesterol synthesis is increased and cholesterol saturation index (CSI) more.10 Gallbladder bile is supersaturated with cholesterol. Secretion of bile salts and phospholipids is either normal or increased. Gallbladder contractility may be decreased in the obese persons. So gallbladder stasis with supersaturated bile lead to gallstone formation.38

5) Pregnancy and parity

Due to increase eostrogen level bile became more lithogenic due to increase in cholesterol secretion and supersaturation of bile. Gallbladder volume will be doubled and stasis develops with formation of biliary sludge. Higher progesterone levels also impairs gallbladder motility.21

Both biliary sludge and stones are silent in nature but it may become symptomatic. After delivery in 60-70% pregnant woman biliary sludge disappears and gallstones disappears in 20-30%.

6) Drugs

Drugs which increases the gallstone formation are oestrogens, oral contraceptives, clofibrate octreotide ceftriaxone (third generation cephalosporin).
Oestrogen: The observations that gallstones are seen more in reproductive age group lead to initial hypothesis that oestrogen may promote gallstone formation. Exogenous estrogen increase biliary cholesterol secretion by 40% causing cholesterol supersaturation of bile. Estrogen therapy also decrease plasma LDL and increase plasma HDL. There is increase LDL receptor expression by liver in estrogen therapy results in increased secretion of cholesterol into bile.\textsuperscript{1,21}

Octreotide, a somatostatin analogue increase the gallstone formation. Decreased gallbladder motility and bile stasis are associated with octreotide treatment and leads to gallstone formation.

Ceftriaxone is generally excreted in the urine but upto 40% secreted unmetabolised in the bile and reaches 100-200 times the concentration in serum. Once it exceeds the saturation level it combines with calcium and form insoluble salt. In 43% children who receive ceftriaxone in high doses (20 – 100 mg/kg/day) biliary symptoms are reported.

7) Systemic diseases

Gallstone formation is common in diabetic persons and its complications are also more. Insulin resistant diabetes mellitus is associated with hypertriglyceridemia, obesity, hypomotility of gallbladder leading to biliary sludge formation which inturn may lead to gallstone formation. The prevalence of gallstones in persons who had spinal cord injury is about 31% and biliary
complications occur in 2.2% Hence biliary stasis is likely the cause of gallstone formation.38

8) Cirrhosis of liver

Gallstone formation is 2-3 times greater in cirrhotic patients than a non cirrhotic population at all ages. In advanced cirrhosis there is marked reduction in bile salt secretion. It is stated that decrease in bile salt is matched by diminished biliary lecithin and cholesterol and bile is not lithogenic. Gallstone in cirrhosis and other chronic liver disease is usually due to chronic haemolysis and majority of the stones are pigment type. Jaundice in cirrhosis is more likely to be due to hepatic decompensation than a stone in the CBD.26

9) Ileal disease or resection :

In crohn’s disease with extensive involvement of ileum and major resection of ileum lead to malabsorption of bile salts. This inturn leads to increased cholesterol and supersaturated bile. Therefore gallstone formation is more. Gallstone are usually cholesterol type.40,26

10) Gastric surgery

Gastric bypass surgery for peptic ulcers and for gross obesity is complicated with increase prevalence in gallstone formation. Truncal vagotomy will adversely affect gallbladder emptying or bile lipid composition.40
11) Haemolytic anaemia

Patients with haemolytic anaemia and hereditary spherocytosis is associated with increased incidence of pigment gallstone formation due to haemolysis.¹

Prevalence rate:

- In hereditary spherocytosis is about 43.66%
- In sickle cell anaemia 37%.
- Thalassaemia 10%

Saudiarabs with sickle cell anaemia have milder haemolysis due to increase alkali resistant Hb and has get low rate of gallstone formation.¹

12) Other conditions

Children with cystic fibrosis have increased incidence of gallstones. Association with peptic ulcer and hyperparathyroidism – a firm evidence is not available.²⁶
PATHOGENESIS OF FORMATION OF GALLSTONES

Pathogenesis of gallstone is multifactorial. There are significant difference in etiology of cholesterol and pigment gallstone. This understanding of this factor is important to prevent the disease and for treatment modalities. Gallstones are concretions and aggregations that are formed as a result of imbalance between bile acids and cholesterol in the ratio 1:10.1,2

STAGES OF GALLSTONE FORMATION

Cholesterol saturation – Cholesterol is not soluble in bile. Bile acids are emphipathic compounds with one end being hydrophilic and polar and other end being hydrophobic and nonpolar. These ionized molecules form micelles in dilute solutions with hydrophobic end inwards and hydrophilic end outwards. Incorporation of lecithin into the micelle allows H2O to penetrate the structure causing swelling. This process increase the ability of the micelle to transport greater amount of cholesterol. Recent information indicates that no more than 30% of cholesterol is transported in micelles.2

The relative amounts of cholesterol transported by vesicles and micelles is related to the degree of bile saturation and crystal precipitation and stone formation. Cholesterol supersaturation can occur secondary to secretion of hepatic bile with increased amounts of cholesterol or increased amounts of bile acids or lecithin.
Sequence of events in cholesterol stone synthesis includes -

**Nucleation** – Aggregation of cholesterol crystals with in a supersaturated bile solution. Cholesterol monohydrate crystals form and agglomerate to become macroscopic stones. Mucin is a pronucleating factor and act as a matrix on which crystals can conglomerate and clusterise.⁹

**Stone growth** – It is natural consequence of cholesterol precipitation and conglomeration.

**GALLBLADDER FACTORS**

Gallbladder contributes in gallstone formation by a complex interaction of muscular and mucosal events.

**a) Stasis**

Gallbladder’s ability to empty is more slow and incomplete in cholelithiais. This muscle abnormality precedes gallstone formation and persists after the gallstone have been removed by dissolution therapy. This stasis is a feature of both cholesterol and pigment stones. Other factors are like sequestration of bile acids within the gallbladder reducing the amount of bile salts available for cholesterol solubalisation, alterations in the secretory or absorptive function of gallbladder leading to biliary stasis.²³
b) Phospholipids in bile

Studies indicate that gallstone formation is accompanied by an increase in arachidonic acid containing phospholipids. Increased hydrolysis of arachidonyl lecithin provides the substrate for formation of prostanoids in the gallbladder wall. This activation of the prostanoid synthetic cascade is accompanied by reduced gallbladder motility and increase in mucin production by the gallbladder mucosa.\textsuperscript{12}

c) Bile mucus glycoproteins

The excessive production of glycoproteins by gallbladder mucosa precedes stone formation. Mucin gel interferes with gallbladder contractility and emptying and acts as a nucleating matrix for cholesterol crystals to form cholesterol phospholipids vesicles.

d) Calcium

Role of calcium is indicated by the presence of calcium salts in majority of gallstones. Preliminary results suggest that gallbladder bile from patients with cholesterol gallstones contain high levels of calcium. Exact mechanism by which biliary calcium increases the formation gallstones remains unknown but possible explanation includes enhanced absorption of water and solutes by the gallbladder and increase gallbladder secretion of calcium, or decrease absorption of calcium. Crystalline structures of calcium carbonate and cholesterol monohydrate crystals provide frame work for gallstone formation. In
addition to the structural role, data suggests that calcium promotes fusion of vesicles and evaluates cholesterol crystal growth.\textsuperscript{8}

**EPITAXY**

This is the phenomenon of the growth of one compound in one or more particular orientation on the substrate of another with near geometrical fit between respective networks which are in contact. Studies have shown that expitaxial role plays a significant part in almost all cases.
Sequence of events in cholesterol lithogenesis

1. Secretion of cholesterol
2. Secretion of bile
3. Lithogenic bile
4. Multilocular vesicles
5. Cholesterol crystals
6. Nucleation promoting
7. Aggregation of cholesterol crystals
CLINICAL MANIFESTATIONS

Majority of patients with gallstone are asymptomatic some will have atypical or nonspecific symptoms. Others will manifest with clinically significant symptoms of gallstones.

Gallstone disease symptoms may be acute, chronic or totally absent. The differentiation between silent and symptomatic gallstones is important since this affects the management in individual case.32

1) Asymptomatic or silent stones

About 85-90% of patient with gallstones remains asymptomatic. The probability of a patient with silent gallstones developing biliary related pain is 1-2% per year and risk of developing complication like perforation and emphysema is even less (0.1% per year). The yearly risk of biliary pain decrease with time and gallstones in females are more likely to become symptomatic. In 90% of cases of carcinoma - gallbladder, gallstones are present.18

2) Flatulent dyspepsia

Its more commonly qualitative dyspepsia – for fatty food. This symptom occurs irregularly and lacks the periodicity of peptic ulcer.30 Other conditions like hiatus hernia, peptic ulcer and chronic pancreatitis should be ruled out before the diagnosis of cholelithiasis is made.
3) Right hypochondriac pain

In some it may be more discomfort and in some it may be excruciating pain. Pain radiates to interscapular region or right intra scapular area. Patient may complain of aching pain over the tip of the right shoulder. Due to distension of the gallbladder diffuse epigastric pain may be complained off. Localized pain may be due to inflammation of parietal peritoneum.36

4) Biliary colic

It is a misnomer as the biliary symptoms are usually gradual in onset and pain is localized to right upper quadrant (right hypochondrium) or epigastrium and not a colicky pain. Episodes of biliary colic are typically seen after meals and often associated with nausea and vomiting. Pain lasts for minute to hours and may radiate to the back or tip of the right scapula, pain resolves spontaneously or diminishes with analgesics.26

5) Jaundice

Cholestatic jaundice due to complete obstruction of common bile duct (CBD).

6) Fever

Occurs in 1/3 of patients and may be raised during an attack of colic. Fever may seen without cholangitis, and may be associated with rigors.
PHYSICAL SIGNS

1. Enlarged gallbladder may be palpable if there is mucocele or emphysema. Enlarged gallbladder is seen cholelithiasis when there is double impaction of stones i.e. one in cystic duct and other in CBD. Enlarged gallbladder palpable below tip of ninth rib. It moves with respiration and side wards.30

2. Tenderness and rigidity in right hypochondrium.

3. Murphy’s sign (Moynihan’s method) – patient is asked to deep breath in and pressure is exerted with the fingers to palpate the fundus of the gallbladder. The gallbladder descends and hits the finger, the patient wince with pain and with a catch in the breath. This examination can be done in sitting posture. This is present in acute cholecystitis.

4. Bao’s sign : Hyperasthesia between 9th to 11th rib posteriorly on the right side. It suggests acute cholecystitis.

COMPLICATIONS OF GALLSTONES

In the gall bladder:

☐ Acute cholecystitis

☐ Chronic cholecystitis

☐ Gangrenous cholecystitis

☐ Perforation

☐ Empyema
Mucocele (hydrops)

Carcinoma

**In the bile ducts:**

- Obstructive jaundice
- Cholangitis
- Acute pancreatitis

**In the intestine:**

- Acute intestinal obstruction (gallstone ileus)

**ACUTE CHOLECYSTITIS**

Most of the acute cholecystitis is due to gallstones obstructing the cystic duct, in 90 – 95% of cases. Following this, if the cystic duct remains obstructed, the gallbladder distends and the wall becomes inflammed and edematous. In most of the cases, stone dislodges and the inflammation gradually subsides, but in 5 – 10% of cases, this process causes necrosis of gall bladder. Initial inflammation is chemically induced and not by bacterial origin. Gallstone impaction leads to mucosal damage, which inturn leads to release of phospholipase. Phospholipase acts on lecithin converts into toxic lysolecithin, which further damages mucosa. In the first few hours/days, the bile appears macroscopically normal and sterile, but within a few hours/days of supervening infection, frank pus is formed. If the inflammation progresses without the
infection, absorption of pigments and bile salts takes place and mucosa secretes lot of mucin to form mucocele (hydrops). Inflammation resolves in some 80% of cases with conservative treatment. Tension within the gallbladder lifts the stone impacted in the Hartmann’s pouch leading to decompression and resolution of the inflammation.

Sequence of events following acute cholecystitis -

- Resolution (80%) with scary, abnormal function or nonfunction of gallbladder.
- Persistence of infection: the gall bladder becomes distended with pus (empyema of gallbladder).
- Resolution of the inflammatory process within the gallbladder with persistence of the cystic duct obstruction – mucocele of the gallbladder.
- Gangrene and perforation leading to localized abscess or frank biliary peritonitis.
- Chronic perforation with development of bilioenteric and biliobiliary fistulas.

Jaundice may be seen in cholecystitis but common bile duct stones were detected only in 10 – 12% of these patients. In the absence of ductal calculi, jaundice has been ascribed to reactive hepatitis or edema of the common bile duct. Tender palpable mass in the subcostal region found in 25% of cases may
be due to empyema, omental phlemon, abscess due to localized perforation and
carcinoma of the gallbladder. The differential diagnosis of this acute condition
are perforated peptic ulcer, acute pancreatitis, retrocaecal appendicitis, viral
hepatitis, right sided pyelonephritis, right sided lobar pneumonia and
myocardial infarction. Half the patients have positive bile culture with E.coli.
Occasionally there is secondary infection with gas forming organisms and gas
may be identified within the gallbladder on plain radiography. Severe pain in
the right hypochondrium is made worse with movement. Signs include pyrexia,
tachycardia and local peritonitis with guarding and rigidity. A plain radiograph
may reveal stones but unfortunately only 10 - 20% of calculi are radio opaque.
The WBC count is usually high and liver functions are mildly altered. USG and
radionucleide scans are confirmatory. Treatment is with emergency
cholecystectomy.

**CHRONIC CHOLECYSTITIS**

Chronic inflammation of the gall bladder is most commonly due to stones
(> 90%) and the term cholecystitis should be restricted to gallbladder containing
gallstones with varying degree of inflammation from mild mucosal /
submucosal to gross transmural fibrosis leading to a contracted fibrous
encasement of the biliary calculi. Patient may have recurrent attack of epigastric
or right hypochondrial often radiating to the right side of the back, less
commonly, to the shoulder blade. The pain generally increases over 30 to 60 minutes, plateaus over approximately 1 hour and gradually subsides.

**EMPHYSEMATOUS CHOLECYSTITIS**

Anaerobic infection, particularly with Clostridia and anaerobic Streptococci, is recognized by gas within the gallbladder wall. Gallstones are not always present. The infection tends to progress rapidly and a high proportion of cases go on to perforation. The infection may be blood-borne with biliary colonization.

**MUCOCOELE OF GALLBLADDER**

It occurs in 1 – 4% of symptomatic gall disease. A typical attack of biliary colic may be followed by pain in the right hypochondrium secondary to the development of a mucocoele. Examination reveals large, tense gallbladder. Bile pigments are absorbed but mucus secretion continues. The gallbladder may become enormous and cholecystectomy is then the treatment of choice.74

**GANGRENOUS CHOLECYSTITIS**

The diagnosis of gangrenous cholecystitis is made using clinical criteria of fever, leukocytosis, persistent pain, abdominal tenderness or guarding, with sonographic findings and intraoperative findings. Clinically this cannot be differentiated from empyematosus cholecystitis.
PERFORATION OF GALLBLADDER

Perforation of gallbladder has been documented to occur more frequently in elder patients. The presentation may be one of generalized peritonitis of unknown cause. Urgent surgery is essential. Ischaemia and infection can lead to patchy gangrene which may be walled off by the omentum, duodenum and small bowel or this may progress to a pericholecystic abscess. These patients are very toxic and again surgery is essential.

CHOLECYSTENTERIC FISTULA

A cholecystenteric fistula follows adherence of an inflammed gallbladder to the stomach, duodenum or colon with subsequent pressure necrosis. Fistula formation therefore follows an episode of acute cholecystitis. It is diagnosed commonly during an elective cholecystectomy.

Cholelolecystocolic fistula presents with diarrhoea, due to discharge of bile into the colon. The diagnosis may be confirmed by.

1. A plain X-ray showing air in the biliary tree.
2. Barium studies demonstrating reflux of contrast into gallbladder.
3. A percutaneous transhepatic cholangiogram or endoscopic retrograde cholangiopancreatogram.
CARCINOMA GALLBLADDER

Malignant change in the gallbladder is the fifth commonest cause of carcinoma in the gastrointestinal tract. Majority of cases are associated with gallstones\textsuperscript{31} and the malignant change is found in approximately 0.9\% of cholecystectomies. Untreated, chronic symptomatic gallstones are the major risk factor. \textsuperscript{32} The 5-year survival is only 1-3\%.

CHOLANGITIS

Acute cholangitis, which usually presents as a combination of fever, rigors and jaundice (Charcot's triad), is a serious and potentially lethal condition. It is produced by obstruction of biliary tract in combination with ascending infection of the biliary tree. It in turn may lead to septicemia and multiple hepatic abscesses. It is important to be aware that serious infections may not always present with the full Charcot's triad and so attention to the clinical state of the patient, the use of serial blood cultures and early parenteral administration of antibiotics are important in order to prevent the development of serious complications. Acute suppurative cholangitis is a rare subgroup in which pus is under tension within the biliary tree, causing a profound illness with Gram-negative septicemia. It requires high-dose antibiotics and urgent decompression of the bile ducts.\textsuperscript{36}
BILIARY PANCREATITIS

Small gallstones are particularly liable to cause this complication and there is now evidence that an attack is due to the impaction or passage of a stone through the ampulla of Vater - the data have been obtained from routine examination of feces or from endoscopic appearances. Diagnosis is based on an elevated serum amylase, the ultrasonic demonstration of gallbladder stones and the absence of alcohol ingestion.

INVESTIGATIONS

To date there are no serum or other lab tests that are absolutely specific for the presence of gallstones. In acute cholecystitis due to gallstones patient will have leucocytosis. There may be mild elevation of transaminases and alkaline phosphatase. In CBD stones serum alkaline phosphatase will be elevated along with serum gamma glutamyl transpeptidase.

Abdominal x-ray

Only 10% gallstones are radioopaque and can be visualized.

Oral cholecystography

For years this test was the mainstay and gold standard for the diagnosis of gallstone though now it has been replaced by USG except where function of the gallbladder has to be assessed. Cholecystography is more accurate than USG in terms of quantification of the number of stones and their sizes. The sensitivity
for detection of radiolucent stones exceeds 90% but visualization of the ductal stones is obtained in only 20%.\textsuperscript{25}

**Abdominal USG**

This is the preferred investigation for suspected cholelithiasis or cholecystitis. Examination should be performed after overnight fast of 8 to 12 hours. Two types of transducers are used, 3.5 MHZ for most of the patients. 5 MHZ provides superior imaging resolution and can be used in obese patients. Major signs of diagnosis of acute cholecystitis are demonstration of gallstones or edema or gas in the gallbladder wall. Non visualization of the gallbladder is also a major sign. Simple wall thickening is a minor sign as is local tenderness, a round shaped or dilatation. Pericholecystitic fluid is also a minor sign. The demonstration of major and minor sign together gives an overall accuracy of over 90%. When the gallbladder is normal, ultrasound often indicates other pathologies.

In chronic cholecystitis the wall is also thickened but lacks the echo poor halo and there is no local tenderness. The gallbladder fails to empty after a meal or CCK Challenge. Stones are usually present. A mucocele appears as a large, sometimes enormous gallbladder which is non tender and thin walled. The contents are usually echo free, apart from stones, though debris may form.
When there is no visualization of the gallbladder consider the following.

1. Technical error.
2. Physiological contraction.
3. Contraction from acute, severe hepatitis.
4. Sludge, isoechoic to liver.
5. Obliterated gallbladder lumen.
6. Unusual position of gallbladder.

In general ultrasonography has distinct advantages over conventional oral cholecystography. These include absence of radiation exposure, independent of patient compliance and the lack of requirement for an intact digestive and hepatic system. In addition to identifying stones within the gallbladder or bile duct, abdominal ultrasonography provides important ancillary information regarding the anatomy of bile ducts, pancreas, and other structures in the upper abdomen. The newer techniques of sonography include the endoscopic ultrasonography. It is more sensitive in identifying small gallstones and also common bile duct stone. Endoscopic ultrasonography is useful for detecting small gallbladder stones missed on transabdominal imaging, especially those located in the neck of the gallbladder, where duodenal gas can obscure the image when scanning percutaneously.
Sensitivity of USG to detect cholelithiasis is 95-99%. They are seen as echogenic foci with accousting shadowing and move with change in posture. This can detected the gallstones of about 1mm in size. The difficulty in USG is its limitation in measuring large gallstones and quantifying multiple gallstones.\textsuperscript{19}

**CT scan**

This test provides more useful information than USG when there is extrahepatic obstruction avoiding to causes other than choledocholithiasis.\textsuperscript{25}

**ERCP**

ERCP is very accurate in the diagnosis of ductal calculi but is less accurate than USG and oral cholecystography in the diagnosis of gallbladder disease and gallstones.

**Cholangiogram**

For common bile duct stones.

**Operative biliary endoscopy**

**ORAL CHOLECYSTOGRAPHY\textsuperscript{25}**

Visualization of gallbladder by giving radioopaque dye. This test is useful in patients in whom USG is unsatisfactory. Contrast media is given which is excreted by liver into the bile after its absorption in the intestine. (Contrast media – iodine containing preparation like telepaque or bioptin).
**Uses**

Accuracy of gallstone detection is 80-95%, number, size of stones, patency of the cystic duct, ability of the gallbladder wall to concentrate the bile and contraction of the gallbladder wall.

**Contraindications**

1. Conjugated bilirubin level above 2mg/100ml
2. Failure of gallbladder filling with in 12 hour
3. Poor LFT
4. Previous cholecystectomy
5. In the presence of renal disease.

**Technique**

- Initial control x-ray is taken prior to cholecystography.
- A fatty meal is given to the patient in the previous day.
- 6 tablets of telepaque is are given orally at 9-00 pm. The next day (after 12-16 hours) x-ray of abdomen is taken in erect and supine position. If gallbladder is visualized a fatty meal is given and one hour later another x-ray of the abdomen is taken to see the gallbladder contraction. If gallbladder is not visualized, double dose of the contrast is given.
• Gallstones are seen as filling defects in the form of translucent areas in opaque shade of gallbladder.

• If the gallbladder does not contract to 1/3 of its size in response to fatty meal it indicates malfunction and often associated with stones.

**Failure to visualize the gallbladder stones**

1. Failure of the patient to take telepaque tablets.

2. Excessive diarrhea and vomiting due to contrast

3. Liver disease

4. Gastric surgeries and small intestinal anastomosis.

5. Small intestine diseases

6. Previous cholecystectomy

7. Blocked cystic duct

8. Poor preparation

9. Cholestasis.
CHOLANGIOGRAPHY

When IV route is used the entire biliary tree can be visualized. Biligrafin is the contrast media used (20ml of 20% biligrafin). After doing a sensitivity test, it is used in whom oral cholecystography is unsuccessful. It is also used with oral cholecystography to visualize gallbladder and intra and extra hepatic biliary apparatus. 25

PTC37

It can be done in jaundiced patients. It is done by using chiba needle under fluoroscopy. Clotting time and platelet count should be done before PTC. Antibiotic cover is given before and after the procedure. Vitamin K infection is given if coagulation studies are abnormal. In supine position patient is sedated and under lumbar aspiration (LA) needle inserted in 8th intercostal space (ICS) in mid axillary line. Contrast media injected until it enters the biliary radicle to see intrahepatic pathology and biliary calculus. Complications are haemorrhage and sepsis.

LFT25

Alterations in LFT may be due to long standing obstruction of CBD due to gallstone or due to repeated attacks of ascending cholangitis and hepatitis.

It includes –

1. Serum bilirubin
2. Van Den Berg’s reaction

3. Serum alkalinephosphatase

4. SGOT, SGPT

5. Serum proteins

6. Serum albumin

7. PT (prothrombin time)

Investigations other associated pathological states:

- Urine routine

- RBS, RFT

- Serum cholesterol

- Upper GI endoscopy

- Serum amylase and urinary amylase for pancreatitis.

**TREATMENT**

There are various treatments available for treatment of gallstones but cholecystectomy still remains the gold standard.
NON INVASIVE TREATMENT OF GALLSTONES

1. Oral dissolution therapy

2. Extracorporeal shock wave lithotripsy. (ESWL)

MINIMALLY INVASIVE GALLBLADDER PROCEDURE

1. Percutaneous cholecystostomy

2. Contact dissolution therapy

3. Percutaneous cholecystolithotomy

4. Laparoscopic cholecystectomy

INVASIVE PROCEDURE

1. Open cholecystectomy.
THYROID AND THYROID DYSFUNCTION

The thyroid gland, which is a butterfly shaped organ, is one of the largest endocrine glands in the body. This gland is situated in the neck below the thyroid cartilage, and anterior to cricoid cartilage. The thyroid is controlled by the hypothalamus and pituitary. It has two lobes or wings: lobus dexter (right lobe) and lobus sinister (left lobe), connected by a horizontal part, isthmus. The gland lies in the anterior part of the neck, lying anterior to and around the larynx and trachea, extending posteriorly up to the esophagus and carotid sheath.

Hormones produced by the thyroid gland are

- thyroxine (T4)
- triiodo-thyronine (T3)
- calcitonin.

In the peripheral organs like liver, kidney, spleen, 80% of the thyroxine gets converted into triiodo-thyronine which is about ten times more active than T4\(^5\).

PHYSIOLOGY OF THE THYROID GLAND

The thyroid gland weighs 10 to 20 g in normal adults and is responsible for the production of two families of metabolic hormones: the thyroid hormones thyroxine (T4) and triiodothyronine (T3) and the calcium-regulating hormone calcitonin. The spherical thyroid follicular unit is the important site of thyroid
hormone production. The thyroid follicle is made up of a single layer of cuboidal follicular cells that encompass a central depository of colloid filled mostly with thyroglobulin (TG), the protein within which T4 and T3 are synthesized and stored. Each follicle is surrounded by a rich network of capillaries that interdigitate among the multiple follicular units contained within normal thyroid matrix. Iodine is essential for normal thyroid function. It can be efficiently absorbed from the gastrointestinal tract in the form of inorganic iodide and rapidly enters the extracellular iodide pool. The thyroid gland is responsible for storing 90% of total body iodide at any given time, with less than 10% existing in the extracellular pool. The extracellular pool consists of freshly absorbed iodide, as well as the total derived from the breakdown of previously formed thyroid hormone.

Within the thyroid, iodide is stored either as preformed thyroid hormone or as iodinated amino acids. Iodide is transported from the extracellular space into the follicular cells against a chemical and electrical gradient. The transporter is an intrinsic transmembrane protein located in the basolateral membrane of the thyroid follicular cells. Once inside the cells, iodide rapidly diffuses to the apical surface, where it is quickly moved to exocytic vesicles. Here it is rapidly oxidized and bound to TG. Transport of iodide into follicular cells is regulated by thyroid-stimulating hormone (TSH) from the pituitary gland, as well as by the follicular content of iodide. C cells, derived from the
neural crest, migrate into the thyroid during embryologic development. These cells rest in a parafollicular position, predominantly in the upper lobe of each thyroid. C cells are responsible for production of the hormone calcitonin, which has important regulatory properties on calcium metabolism.

**Thyroid Hormone Synthesis**

Once organic iodide is efficiently oxidized and bound, it couples to TG with tyrosine moieties to form iodotyrosines in either a single conformation (monoiodotyrosine [MIT]) or a coupled conformation (diiodotyrosine [DIT]). The formation of DIT and MIT is dependent on an important intracellular catalytic agent, thyroid peroxidase, which has been well characterized and is an integral part of the initial process of organification and storage of inorganic iodide. This enzyme is localized to the apical portion of the follicular cell, where it reacts at the cell-colloid interface.53

MIT and DIT are biologically inert. Coupling of these two residues gives rise to the two biologically active thyroid hormones T4 and T3. T4 is formed by coupling of two molecules of DIT, whereas T3 is formed by coupling of a molecule of MIT with a molecule of DIT. In normal circumstances, formation of T4 is the major pathway. Both T3 and T4 are bound to TG and stored within the colloid in the center of the follicular unit, which allows quicker secretion of the hormones than if they had to be synthesized. This rapid and metabolically
active process results in the storage of about 2 weeks' worth of thyroid hormone within the organism under normal circumstances. The majority of thyroid hormone released from the thyroid gland is T4, which is deiodinated in peripheral extrathyroidal tissues and converted to T3. Release of T4 and T3 is regulated by the apical membrane of the follicular cell via lysosomal hydrolysis of the colloid that contains the TG-bound hormones.

The apical membrane of the thyroid cell forms multiple pseudopodia and incorporates TG into small vesicles, which are then brought within the cell apparatus. Within the vesicles, lysosomal hydrolysis results in reduction of the disulfide bonds, and both T3 and T4 are then free to pass through the basement membrane and be absorbed into the circulation, where more than 99% of each of the hormones is bound to serum proteins.54
Figure 5: Regulation of Thyroid Hormone Synthesis
Regulation of Thyroid Hormone Secretion

Triiodothyronine and Thyroxine

The hypothalamic-pituitary-thyroid axis regulates thyroid hormone production and release in a classic endocrine feedback system. The major regulator of thyroid gland activity is the glycoprotein TSH, which is a major growth factor for the thyroid. TSH stimulates thyroid cell growth and differentiation, as well as iodine uptake and organification and release of T3 and T4 from TG. TSH is a 28-kd glycoprotein that is secreted in a pulsatile fashion by the anterior pituitary gland. It has two components. The α subunit is common to other anterior pituitary hormones. However, the β subunit is unique to TSH and determines the hormone's biologic specificity. TSH has specific activity through a receptor on the surface of the thyroid cell. Once the receptor is activated, it interacts with a guanine nucleotide–binding protein (G protein). This interaction stimulates the production of cyclic adenosine monophosphate (AMP). It is through this cyclic AMP pathway that the synthesis of thyroid hormones is mediated. Negative feedback through increased peripheral levels of T3 and T4 can affect TSH secretion. Peripheral T4 is locally deiodinated in the pituitary and converted to T3, which then directly inhibits the release and synthesis of TSH. Excessively large doses of iodide have interesting and complex effects, including an initial increase in organification followed by
suppressive effects, a syndrome known as the Wolff-Chaikoff effect.

**THYROID STIMULATING HORMONE (TSH)**

TSH is a glycoprotein with a molecular weight of 30KD, it increases thyroid growth and general metabolic activity such as:

- Glucose oxidation
- Oxygen consumption
- Synthesis of phospholipids and RNA
- Iodine uptake and thyroxine metabolism

TSH is composed of α and β sub unit. The α sub unit is common to TSH, LH, FSH and HCG but the β sub unit is unique and confers specificity of action.\(^5^9\)

The α subunit is the earliest hormone gene expressed embryonically; activation of the β subunit gene occurs later under the influence of GATA-2 & pit-II. The 13.5kb α subunit gene is located on chromosomes 6 and comprises four exons and three introns. Although the α sub unit gene is expressed in thyrotroph, gonadotroph and the placental cells, its regulation is uniquely cell specific. The α sub unit transcription is inhibited by T3 at regions close to the transcriptional initiation site, in concert with other nuclear co-repressors. The 4.9kb TSH β-subunit gene located on chromosome comprises three exons and two introns. Intrapituitary TSH is stored in secretory granules and the nature hormone (28 KD) is released into the venous circulation primarily in response
to hypothalamic TRH. The predicted structural model of the TSH molecule is that of a cystine knot growth factor. The tertiary TSH structure comprises 3 hairpin loops separated by central disulphide bonds, with longer loop straddling one side. Production of the mature heterodimeric TSH molecule requires complex cotranslation glycosylation and folding of nascent α & β subunits. After subunit translation and signal peptide cleavage, glycosylation occurs at asparagine 23 on the β subunit and at two asparagine residues, 52 and 78, on the α subunit. Appropriate glycosylation is required for accurate molecular folding and subsequent combination of α and β subunits within the rough endoplasmic reticulum and golgi apparatus. Both TRH (Thyrotropin releasing hormone) and T3 regulate TSH glycosylation in opposite directions. TRH administration or T3 deprivation, resistance, enhance oligosaccharides addition to the TSH molecule. TSH binds to specific receptor and thyroid cells and so stimulates the synthesis and secretion of thyroid hormones. Secretion of TSH is stimulated by the hypothalamic tripeptide TRH. The thyroid hormones synthesis is regulated by a negative feedback system. If plasma concentration of thyroid hormones decreases, TSH secretion increases stimulating thyroid hormone synthesis, if thyroid hormones level increase TSH secretion is suppressed.
CAUSES OF HYPOTHYROIDISM

Hypothyroidism and hyperthyroidism are the two primary pathological condition that involve the thyroid glands.\textsuperscript{48} Hypothyroidism is a common disorder that occurs in mild to severe forms in 2-15% of the population.\textsuperscript{49}

Classification

Goitrous

- Acquired causes

Hashimoto’s thyroiditis

Also called as autoimmune thyroiditis type 2A. It is the most common cause of goitrous hypothyroidism in areas of iodine sufficiency.

Pathophysiology

Impairment of hormone synthesis is due to apoptotic destruction of thyroid cells leading to follicular destruction. Although both antibodies to thyroid peroxidase(TPOAb) and thyroglobulin(TgAb) maybe complement-fixing and cytotoxic, the thyroid gland is infiltrated by both B and T cells; the latter are armed with Fas ligand capable of destroying thyroid cells. Fas expression on thyroid cells is secondary to elaboration of a variety of cytokines from T cells that undergo blast transformation when exposed to thyroid antigens (Thyrotropin receptor, TPO and thyroglobulin) suggesting a cell mediated autoimmune mechanism.
**Histopathology**

The thyroid gland is pale and firm. There is diffuse lymphocytic infiltration\textsuperscript{52} with germinal center formation, obliteration of thyroid follicles by widespread apoptosis and fibrosis.

Histologically two variants are present:

1. Oxyphilic and

2. Fibrotic

**Risk factors**

1. Genetic susceptibility

   There is significant association between Hashimoto's disease and HLA-DR3, -DR4 & -DR5\textsuperscript{(22,23)} and certain DQ alleles. Hashimoto's disease occurs with increased frequency in Downs syndrome\textsuperscript{(22,23)} and gonadal dysgenesis.

2. Non-genetic

   i. Pregnancy- Transient post-partum thyroiditis develops in some patients and thyroid failure developing permanently or in early years after pregnancy in a significant proportion

   ii. Iodine and drugs- Iodine and iodine containing drugs (amiodarone) precipitate autoimmune thyroiditis in susceptible populations

   iii. Cytokines- Treatment of patients with interleukin-2 or interferon \( \alpha \) may precipitate the appearance of autoimmune thyroid disease.
iv. Irradiation – Thyroid autoantibodies are more prevalent after exposure low 
doses of radioiodine 
v. Age- Prevalence increases with age. Infection - Congenital Rubella 
syndrome.

Iodine deficiency (Endemic Goiter)

Endemic goiter denotes any goiter occurring in the region where goiter is 
prevalent. It almost always occurs in areas of environmental iodine deficiency, 
it could be aggravated by dietary minerals or naturally occurring goitrogens or 
pollution of water supplies. It is estimated to affect more than 200 million 
people throughout the world, more than 10% of the population and is more 
common in mountainous areas like the Himalayas. It is more common in 
children. The incidence has greatly reduced with the introduction of iodized salt.

Iodide excess

Goiter and hypothyroidism are sometimes induced by chronic 
administration of large doses of iodine in either organic or inorganic form. It is 
seen in only in some patients who have a background of underlying 
autoimmune thyroiditis, especially after treatment with radioiodine, cystic 
fibrosis, patients who have undergone hemithyroidectomy for solitary nodule, 
newborn infants born to women given large doses of iodine during pregnancy. 
Large doses of iodine causes an acute inhibition of organic binding that abates 
in normal individuals despite continued Iodine administration (Wolff Chaikoff
effect and escape). In iodide goiter there is more pronounced inhibition of organic binding and a failure of escape. This in turn leads to enhanced iodide transport. Decreased hormone synthesis leads to increased TSH which in turn tries to increase organic binding and a vicious cycle results. Free T4 Iodine level is low, TSH is increased and 24-hr urinary iodine excretion and serum inorganic iodide concentration is increased.

**Drugs Blocking Thyroid Hormone synthesis & release**

Apart from drugs used in the treatment of hyperthyroidism, anti thyroid agents may be countered either as drugs for the treatment of disorders unrelated to the thyroid gland or as natural agents in foodstuffs. Goiter with or without hypothyroidism can occur in patients given Lithium, usually for Bipolar Manic-Depressive psychosis. Lithium inhibits the release of thyroid hormones. Autoimmune thyroiditis maybe one factor precipitating Lithium induced hypothyroidism. Other drugs that occasionally produce hypothyroidism include para-aminosalicylic acid, phenylbutazone, aminogluthethemide and ethionamide. They interfere with both the organic binding of iodine and the later steps in hormone biosynthesis. Cigarette smoking increases the risk of hypothyroidism in patients with underlying autoimmune hypothyroidism.

**Goitrogens in foodstuffs or as Endemic Substances or Pollutants**

Antithyroid agents in food stuffs are widely distributed in the family Cruciferae or Brassicaceae. They include cabbages, turnips, kale, kohlrabi,
mustard etc. It is likely that some thiocyanate is present in such plants or they may yield thiocyanates on metabolism. Cassava meal contains Linamarin which yields thiocyanate on metabolism.

A number of synthetic chemical pollutants have been implicated in causing goitrous hypothyroidism, including polychlorinated biphenyls and resorcinol derivatives.

Cytokines

Patients with chronic hepatitis C or various malignancies may be given interferon α or interleukin-2 and they may experience transient hypothyroidism but sometimes persists. These agents activate the immune system and can induce a clinical picture suggesting an exacerbation of underlying autoimmune disease. Autoimmune hypothyroidism may also occur after successful treatment of Cushing’s disease, presumably as a result of the release of glucocorticoid induced immunosupression.

Congenital causes

It is usually an autosomal recessive trait, affects females only slightly more than males. Five specific defects in the hormone synthesis pathways have been identified
a. Iodide transport defect

It is characterized by impaired iodide transport mechanism and a low RAIU. Administration of iodide permits the synthesis of normal quantities of hormone.

b. Defects in expression or function of thyroid peroxidase.

c. Pendreds Syndrome

Characterised by a defect in iodine organification accompanied by sensory nerve deafness.

d. Defects in thyroglobulin synthesis

e. Iodotyrosine dehalogenase defect

There is an impairment of both intrathyroidal and peripheral deiodination of iodotyrosines. Labeled MIT and DIT present in the blood and together with their deaminated derivatives in the urine.

**Thyroid infiltration**

Riedel’s struma, amyloidosis, hemochromatosis or scleroderma may cause hypothyroidism with/without goiter.

**Atrophic Hypothyroidism**

Here, the patient has manifestations of hypothyroidism but there is no obvious thyroid enlargement. It could be due to congenital or acquired causes.
Nongoitrous hypothyroidism

- Acquired causes

Hypothyroidism in the absence of classic Hashimoto’s goiter is primary hypothyroidism.

The most commonest cause is Autoimmune Thyroiditis Type 2B which probably represents the end stage of an autoimmune thyroiditis. It could also be due to TSH receptor antibodies that block the response of thyroid cells to endogenous TSH.

Post- ablative hypothyroidism

The most common cause is subtotal resection of diffuse goiter of Grave’s disease or multinodular goiter. It could also occur following total thyroidectomy usually for thyroid carcinoma. The frequency depends on the amount of tissue remaining, but continued autoimmune destruction of the thyroid in patients with Grave’s disease may lead to an increase in incidence. Hypothyroidism following destruction of thyroid tissue with radioiodine is common and is the only established disadvantage of this form of treatment. Its frequency is determined in large part by the dose of radioiodine and also by variations in individual susceptibility, including autoimmune factors.
The incidence keeps increasing with time to approach 100% in all the above cases. Primary atrophic thyroid failure may also occur in patients with Hodgkin’s disease after treatment with mantle irradiation or after high-dose neck irradiation for other forms of lymphoma or carcinoma

- **Congenital causes**

Thyroid agenesis or dysplasia

Thyroid aplasia due to thyrotropin receptor unresponsiveness

**Transient Hypothyroidism**

Transient hypothyroidism is defined as a period of reduced free T4 Iodine with suppressed, normal or elevated TSH levels that are eventually followed by a euthyroid state. It usually occurs in patients with subacute(post-viral), lymphocytic (painless), autoimmune or postpartum thyroiditis, in the first 3-4 months of radioiodine treatment.

**Consumptive Hypothyroidism**

Consumptive hypothyroidism is the term given to an unusual cause of hypothyroidism that has been identified in infants with visceral hemangiomas or related tumors. The TSH is markedly elevated with undetectable T3 and T4 levels. The cause is an accelerated degradation of thyroid hormones by the increased D3 activity in the tumor. Because a significant fraction of hemangiomas remit with glucocorticoid and interferon α therapy, it is important
to treat such patients with adequate doses of thyroid hormones to prevent permanent neurological damage.

Central hypothyroidism

Central hypothyroidism is due to TSH deficiency caused by either acquired or congenital hypothalamic or pituitary disorders. It is further classified as those of pituitary (secondary hypothyroidism) and hypothalamic (tertiary hypothyroidism) In many cases, hyposecretion of TSH is accompanied by decreased secretion of other pituitary hormones, and there is evidence of somatotroph, gonadotroph and corticotroph failure as well. Because a small but significant fraction of thyroid gland function is independent of TSH, hypothyroidism due to central causes is less severe than primary hypothyroidism.

Resistance to Thyroid hormones

Patients with resistance to thyroid hormone may have features of hypothyroidism if the resistance is more severe and affects all tissues, also called as generalized resistance to thyroid hormone. Alternatively, patients with RTH may have hyperthyroidism if the resistance is more severe in the hypothalamic-pituitary axis than in the remainder of the tissues, also called as pituitary resistance to thyroid hormones. Patients with both forms almost always have mutations in one allele of TR-22 beta (TR-β) gene that interfere with the capacity of that receptor to respond normally to T3 usually by reducing its
binding affinity. The mutant TR-β complex can interfere with the functioning of the three normal TR-expressing genes, producing a pattern termed Dominant Negative Inhibition with an autosomal dominant pattern of inheritance.

Two-thirds of the patients with RTH present with thyroid enlargement and usually present with a mixture of symptoms of hyperthyroidism and hypothyroidism. Abnormalities in neuropsychological development exist, with an increased prevalence of attention deficit hyperactivity disorder. The tests show the unusual combination of an increased FT4 accompanied by normal or slightly increased TSH levels.

**SUB CLINICAL HYPOTHYROIDISM**

Subclinical hypothyroidism is a condition in which the patient has no clinical symptoms and has a normal free T3 and free T4 levels with increased TSH level.

**Clinical presentation of hypothyroidism**

1. **Skin and Appendages**

   Accumulation of hyaluronic acid in the ground substance of dermis and other tissues. It absorbs water leading to boggy, non-pitting edema (Myxedema) around the eyes, dorsa of the hands and feet, tongue, pharyngeal and laryngeal mucous membranes\(^ {49,52}\). Skin is pale and cool due to cutaneous vasoconstriction and anaemia. Hyperkeratonemia gives a yellow tint to the skin. Wounds tend to heal slowly. Secretions of sebaceous and sweat glands is reduced leading to dry
skin and hair. Hair becomes brittle and falls off\textsuperscript{49,50}. Easy bruising occurs due to capillary fragility. The changes are less striking in secondary hypothyroidism.

2. Cardiovascular System

There is decreased cardiac output due to decreased stroke volume and bradycardia. Cardiac output and peripheral vascular resistance responds normally to exercise. In 30\% patients, there is pericardial effusion\textsuperscript{52} by fluid rich in protein and glycosaminoglycans.

There is considerable controversy over whether hypothyroidism is a risk factor for atherosclerosis. The Wickham’s study showed no increase in cardiovascular mortality in patients with subclinical hypothyroidism over 20 years, whereas the Rotterdam study suggested that there is a two-fold increase in risk.

Electrocardiography shows sinus bradycardia, prolongation of PR interval, low amplitude of P wave and QRS complex, alterations in the ST segment and flattened or inverted T waves. The serum levels of homocysteine, creatine kinase, aspartate transaminase and lactate dehydrogenase\textsuperscript{54} maybe increased, but the isoenzyme pattern suggests that the source of increased CK and LDH is skeletal muscle. The combination of large heart, hemodynamic and ECG alterations and the serum enzyme patterns has been termed as myxedema heart. Treatment of hypothyroidism corrects the changes.
3. **Respiratory system**

Pulmonary function is generally normal, but dyspnea may be caused by pleural effusion, depression of both the hypoxic and hypercapnic ventilatory drive, impaired respiratory muscle function and obstructive sleep apnea, which may contribute to the development of myxedematous coma.\(^{60}\)

4. **Alimentary System**

Modest weight gain is present which is partly due to retention of fluid by hydrophilic glycoprotein deposits in the tissues. Appetite is decreased. Peristaltic activity is decreased. Both lead to constipation and this causes fecal impaction (myxedema megacolon). Gaseous distension of abdomen (myxedema ileus) is accompanied by colicky pain and vomiting. There is also elevation of carcino embryonic antigen. The condition therefore mimics a mechanical ileus. Ascites alone is unusual but it may occur along with pericardial and pleural effusion. Achlorhydria after maximal histamine stimulation is present. Circulating antibodies against gastric parietal cells is present in one third of the patients with hypothyroidism. There is co-existence of pernicious anaemia and other autoimmune diseases suggesting that autoimmunity plays a central role in the pathogenesis of hypothyroidism.

Rates of absorption is reduced, but the amount absorbed is normal or increased due to decreased bowel motility and increased gastro-intestinal transit.
time. Liver function tests are normal but AST and ALT are elevated. Gall bladder is distended and contracts sluggishly.

5. Central and peripheral Nervous System

Deficiency of thyroid hormones at or before birth causes retention of infantile characteristics of the brain, hypoplasia of the cortical neurons with poor development of cellular processes, retarded myelination and reduced vascularity. If the deficiency is not corrected early, the damage is irreversible. Changes in adult life are reversible with replacement therapy. All intellectual functions are slowed. There is loss of initiative, slow wittedness, memory defects, dementia in the elderly. There occurs lethargy, somnolence and slowness of body movements. Cerebellar ataxia may occur. Depression and paronia which induces agitation (myxedema madness). Headaches are frequent. Cerebral hypoxia due to circulatory alterations may predispose to confusional attacks or syncope, further leading to stupor or coma. Epileptic seizures are more common during myxedema coma. Night blindness may occur due to deficiency of synthesis of pigment required for dark adaptation. Hearing loss of the perceptive type is frequent. Thick slurred speech and hoarseness due to infiltration of the tongue and larynx respectively.62

Carpal tunnel syndrome due to myxedematous infiltration and compression of the median nerve at the wrist.
EEG changes include slow alpha wave activity and general loss of amplitude. The CSF protein concentration is increased but the CSF pressure is normal.

6. Muscular system

Stiffness and aching of muscles occur which increases in cold temperatures. Delayed muscle contraction and relaxation cause slowness of movement and delayed tendon jerks and pseudomyotonia. Rarely a profound increase in muscle masses with slowness of muscular activity maybe the predominant manifestation. (Kocher-Debre-Semelaigne or Hoffmann’s syndrome) Myoclonus may be present. The electromyogram may be normal or may exhibit disordered discharge, hyperirritability and polyphasic action potential.

7. Skeletal muscle

There is growth failure in hypothyroidism due to both impaired protein synthesis and reduction in IGF-I levels.12 Cartilage growth is unaffected. There is decreased bone formation and resorption. The bone density is increased. Levels of PTH is increased and therefore there is resistance to its action. Levels of 1,25-Dihydroxycholecalciferol is also increased.

8. Renal Function: Water & Electrolytes

Renal Blood flow, Glomerular filtration rate, tubular reabsorptive and secretory maxima are reduced. Blood urea nitrogen and serum creatinine are
normal, but uric acid levels may be increased. There is an increase in TBW even though plasma volume is reduced. This leads to hyponatremia. Potassium levels are usually normal, serum magnesium concentration is increased62.

9. Haematopoetic system

Due to decreased oxygen requirement and decreased erythropoietin, the RBC mass is decreased and leads to normocytic normochromic anaemia. Anemia could also be due to menorrhagia or defective iron absorption caused by achlorhydria. There is high incidence of pernicious anaemia associated with hypothyroidism. Anaemia could be macrocytic due to Vitamin B12 and folate deficiency which could be due to malabsorption or dietary deficiency. The total and differential leucocyte count are usually normal and platelets are adequate, but adhesiveness is impaired. 13 There is decreased concentration of Factor VIII and IX, leading to defective intrinsic clotting mechanism and this, along with increased capillary fragility and decreased platelet adhesiveness may account for the bleeding tendency.

10. Pituitary and adrenocortical function

Hyperplasia of thyrotropes may cause pituitary gland to be enlarged and this can be detected radiologically as enlarged pituitary fossa. This may compromise the function of the other pituitary cells or cause visual field defects. In severe primary hypothyroidism, the response of growth hormone to provocative stimuli is subnormal. As a result of the decreased rate of turnover of
cortisol, the 24-hr urinary excretion of cortisol and 17-hydroxy corticosteroids is decreased, the plasma levels are usually normal. Plasma rennin activity is decreased. The rate of turnover of aldosterone is decreased and sensitivity to ATII is increased.

11. Reproductive Function

Untreated hypothyroidism in infants leads to immature sexual development. Hypothyroidism in young children causes a delayed onset of puberty and anovulatory cycles. In adult women, severe untreated hypothyroidism may cause decreased libido and anovulation. There is also decreased secretion of progesterone and abnormal endometrial proliferation causing breakthrough bleeding and menorrhagia. These changes maybe due to decreased secretion of Luteinizing Hormone. Rarely, in primary hypothyroidism, secondary depression of pituitary function may lead to ovarian atrophy and amenorrhoea. Fertility is reduced and spontaneous abortions may occur. In men it leads to diminished libido, impotence and oligospermia. Plasma gonadotropin levels are usually normal, except in post-menopausal women in whom it may be slightly less than their euthyroid counterparts.61

12. Catecholamines

The plasma cAMP response to epinephrine is decreased suggesting a state of decreased adrenergic activity. The secretion rates and plasma epinephrine is normal, but the corresponding norepinephrine levels are increased. The response
of plasma cAMP to glucagon and plasma parathyroid hormone are also decreased suggesting that thyroid hormones have a general modulating effect on cAMP action.

13. Energy metabolism

The rate of absorption and the rate of uptake of glucose by tissues are reduced. There is increased sensitivity to exogenous insulin. This, along with reduced appetite accounts for decreased insulin requirements in diabetes mellitus with hypothyroidism.

There is an increase in total cholesterol and LDL cholesterol. HDL concentrations are reduced. There is an increase in the levels of serum phospholipids. Plasma free fatty acids are decreased and the mobilisation of free fatty acids in response to fasting, catecholamines and growth hormone is impaired. All the abnormalities are relieved by treatment.
METHODS FOR ESTIMATION OF THYROID PROFILE (T3, T4, TSH)

There are different methods for Estimation of Thyroid Profile: -

1. Radio immunoassay (RIA)
2. Enzyme Linked Immunosorbent Assay (ELISA)
3. Enzyme Linked Fluorescent Assay (ELFA)
4. Chemiluminescence (CLIA)

| Hormone                         | Reference Interval   |
|---------------------------------|----------------------|
| Thyroid stimulating Hormone(TSH)| 0.30 – 5.5µIU/ml     |
| Free thyroxine(FT4)             | 0.70 – 1.80 ng/dl    |
| Free Triiodothyronine(FT3)      | 1.7- 4.2 pg/ml       |

TABLE 1 : Reference value for thyroid hormone assay

The introduction of serum thyroxine and serum thyroid stimulating hormone (TSH) radioimmunoassays has increased the sensitivity and specificity of thyroid function testing. The serum TSH assay has been shown to be a sensitive indicator of diminished thyroid functional reserve, since TSH levels become elevated before circulating serum thyroxine levels fall below the normal range.
A decrease in thyroid hormone is common to all forms of hypothyroidism except consumptive hypothyroidism and resistance to thyroid hormones. In patients with primary hypothyroidism, there is a significant increase in basal serum TSH concentration.

In patients with central hypothyroidism, there is low or normal level of TSH. A low thyroid hormone level with a low or normal level of TSH should lead to an evaluation of the possibility of failure of other endocrine systems. The only exception to this is posthyperthyroid hypothyroidism where the TSH continues to be suppressed for several months even though hypothyroidism has been induced by 131I, surgery or antithyroid drugs.
**Hypothyroidism in formation of gall stones**

Formation of gall stones is a complex process involving various mechanisms affecting the flow of bile and bile content. There are many factors which can contribute to formation of gall stones in hypothyroidism.

1. Decrease in liver cholesterol metabolism.
2. Reduced hepatic bile secretion
3. Reduced flow of bile into duodenum
4. Impaired sphincter of Oddi relaxation

Hypothyroidism affects cholesterol metabolism at multiple levels. Hypothyroidism causes increased serum cholesterol levels and supersaturation of bile with cholesterol causing decreased motility, contractility and filling of gall bladder causing prolonged residence of bile. This leads to retention of cholesterol crystals, sufficient time for them to enucleate and grow into mature gall stones. Delayed hilum duodenum transit time impairs the clearance of precipitates from gall bladder and biliary tract.

Biliary stasis can be caused by many conditions like sphincter of Oddi dyskinesia, stenosis and strictures of the bile duct. Thyroxine has a β1 and β2 receptor mediated prorelaxing action on sphincter of Oddi motility at physiological levels of serum T4. So the decreased levels of serum thyroxine alter the normal motility of sphincter of Oddi resulting in its contractility. Reduced prorelaxing effect on sphincter of Oddi in addition to the biliary stasis,
increased cholesterol load and delayed clearance from the hepatocyte shift the balance towards formation of gall stones.

**MECHANISM OF ACTION OF THYROXINE HORMONE ON SPHINCTER OF ODDI**

Passage of thyroxine hormone through cell membrane, cytoplasm and nuclear membrane

- Binding to a nuclear protein (TR)
- Transcriptional and translational regulation
- Activation of potassium channels
- Opening of potassium channels
- Hyperpolarisation
- Closure of cell membrane calcium channels
- Reduced contraction of sphincter of oddi smooth muscle
- Pro relaxing effect of thyroxine
MATERIALS AND METHODOLOGY

The present study is a cross sectional study of 50 cases of cholelithiasis diagnosed in Government Royapettah hospital, Chennai during the study period of April 2014 to September 2014.

50 cases for the purpose of the study were selected on the basis of the non probability (purposive) sampling method.

Source of study:

Patients diagnosed as cholelithiasis in department of General Surgery, Government Royapettah hospital.

Method of collection of Data:

Details of cases, full history, clinical examination and symptoms of hypothyroidism (loss of appetite, gaining weight, tiredness, constipation, cold intolerance, menstrual disturbances etc). Investigations – USG abdomen and thyroid function test.

Inclusion criteria : Patients with cholelithiasis.

Exclusion criteria : Patients with previous history of hypothyroidism on treatment.
**Design of study :**

Patients are divided according to history, clinical examination and lab estimation of T3, T4 and TSH.

- **Subclinical hypothyroidism:** symptom free patient with TSH level above upper limit of normal and T3, T4 within normal limit.

- **Clinical hypothyroidism:** in which there are symptoms of hypothyroidism with TSH level above the upper limit and T3, T4 or both decrease below normal limit.

- **Euthyroid group:** where clinical and lab tests are within normal range.

Data was analysed statistically using SPSS version 19.0. Results expressed in percentages.
OBSERVATION AND RESULTS

The following are the tables from the data of the study to know the prevalence of hypothyroidism in cholelithiasis. And distribution of patients according to sub clinical and clinical hypothyroidism.

Table 2: Distribution of patients according to age

| Age   | No of patients | Percentage |
|-------|----------------|------------|
| ≤20   | 2              | 4.0        |
| 21-30 | 9              | 18.0       |
| 31-40 | 9              | 18.0       |
| ≥41   | 30             | 60.0       |
| Total | 50             | 100.0      |
Among the study group, 60% i.e., 30 patients were in the age group of > 41 yrs, 18% i.e., 9 patients each in age groups 21-30 yrs and 31-40 yrs and 4% below 20 yrs.

Table 3: Distribution of patients according to sex

| Age     | No of patients | Percentage |
|---------|----------------|------------|
| Female  | 29             | 58.0       |
| Male    | 21             | 42.0       |
| Total   | 50             | 100.0      |

Among the study group, 58.0% i.e., 29 patients are females and 42.0% i.e., 21 patients are males.
Table 4: Distribution of patients according to thyroid function

| Diagnosis    | No of patients | Percentage |
|--------------|----------------|------------|
| Euthyroid    | 31             | 62.0       |
| Hypothyroid  | 19             | 38.0       |

Among the study group, 38% i.e., 19 patients had hypothyroidism and 62% i.e., 31 patients were in euthyroid state.
Table 5: Distribution of patients according to subclinical and clinical hypothyroidism

| Diagnosis               | No of patients | Percentage |
|-------------------------|----------------|------------|
| Euthyroid               | 31             | 62.0       |
| Sub-clinical hypothyroid| 11             | 22.0       |
| Clinical hypothyroid    | 8              | 16.0       |
| Total                   | 50             | 100.0      |

Among the study group, 22% i.e., 11 patients had subclinical hypothyroidism, 16% i.e., 8 patients had clinical hypothyroidism and 62% i.e., 31 patients were in euthyroid state.
Table 6: Distribution according to age and thyroid function

| Age  | Euthyroid | Hypothyroid |
|------|-----------|-------------|
| ≤20  | 2(100%)   | 0(0)        |
| 21-30| 8(88.9%)  | 1(11.1%)    |
| 31-40| 5(55.6%)  | 4(44.4%)    |
| ≥41  | 16(53.3%) | 14(46.7%)   |
| Total| 31(62%)   | 19(38%)     |

The following table shows the prevalence of hypothyroidism in different age groups. Below 20 yrs of age, all patients 100% i.e., 2 patients were in euthyroid state. Between the age group of 21-30 yrs 11.1% i.e., one patient had thyroid dysfunction, 88.9% i.e., 8 patients were in euthyroid state. Between the age group of 31-40 yrs 44.4% i.e., 4 patients had thyroid dysfunction, 55.6% i.e., 5 patients were in euthyroid state. Above 41yrs 46.6% i.e., 14 patients had thyroid dysfunction, 53.3% i.e., 16 patients were in euthyroid state. Among 50 patients, 38% i.e., 19 patients had thyroid dysfunction and 62% i.e., 31 patients were in euthyroid state.
Table 7: Distribution according to age and subclinical, clinical hypothyroidism

| Age  | Euthyroid | Subclinical hypothyroid | Clinical hypothyroid |
|------|-----------|-------------------------|----------------------|
| ≤20  | 2(100%)   | 0(0)                    | 0(0)                 |
| 21-30| 8(88.9%)  | 1(11.1%)                | 0(0)                 |
| 31-40| 5(55.6%)  | 1(11.1%)                | 3(33.3%)             |
| ≥41  | 16(53.3%) | 9(30%)                  | 5(16.7%)             |
| Total| 31(62%)   | 11(22%)                 | 8(16%)               |

The following table shows the prevalence of subclinical hypothyroidism and clinical hypothyroidism in different age groups. Among the patients less than 20 yrs of age, subclinical hypothyroidism and clinical hypothyroidism was not found. All patients 100% i.e., 2 patients were in euthyroid state. Between the age group of 21-30 yrs 11.1% i.e., one patient had subclinical hypothyroidism. Clinical hypothyroidism was not found. 88.9% i.e., 8 patients were in euthyroid state.

Between the age group of 31-40 yrs 11.1% i.e., one patient had subclinical hypothyroidism, 33.3% i.e., 3 patients had clinical hypothyroidism, 55.6% i.e., 5 patients were in euthyroid state. Above 41 yrs, 30% i.e., 9 patients had subclinical hypothyroidism, 16.7% i.e., 5 patients had clinical hypothyroidism, 53.3% i.e., 16 patients were in euthyroid state. Among 50
patients 22% i.e., 11 patients had subclinical hypothyroidism, 16% i.e., 8 patients had clinical hypothyroidism, 62% i.e., 31 patients were in euthyroid state.

**Table 8: Distribution according to sex and thyroid function**

| Age     | Euthyroid | Hypothyroid |
|---------|-----------|-------------|
| Male    | 16(76.2%) | 5(23.8%)    |
| Female  | 15(51.7%) | 14(48.3%)   |
| **TOTAL** | 31(62.0%) | 19(38.0%)   |

The following table shows the relationship between thyroid status in males and females. Among males, 23.8% i.e., 5 pts are hypothyroid and 76.2% i.e., 16 patients are euthyroid. Among females, 48.3% i.e., 14 patients are hypothyroid and 51.7% i.e., 15 patients are euthyroid. Among 19 hypothyroid patients 5 are males and 14 are females.
Table 9: Distribution according to sex and subclinical, clinical hypothyroidism

| Age    | Euthyroid       | Subclinical Hypothyroid | Clinical hypothyroid |
|--------|-----------------|-------------------------|----------------------|
| Male   | 16(76.2%)       | 3(14.3%)                | 2(9.5%)              |
| Female | 15(51.7%)       | 8(27.6%)                | 6(20.7%)             |
| TOTAL  | 31(62.0%)       | 11(22.0%)               | 8(16.0%)             |

This table shows the prevalence of subclinical hypothyroidism and hypothyroidism in males and females. Among 50 patients 29 patients were males and 21 patients were females. Among 29 male patients 14.3% i.e., 3 patients had subclinical hypothyroidism, 9.5% i.e., 2 patients had clinical hypothyroidism and 76.2% i.e., 16 patients were in euthyroid state. Among 21 female patients 27.6% i.e., 8 patients had subclinical hypothyroidism, 2.7% i.e., 6 patients had clinical hypothyroidism and 51.7% i.e., 15 patients were in euthyroid state. Among 50 patients 22.0% i.e., 11 patients had subclinical hypothyroidism, 16.0% i.e., 8 patients had clinical hypothyroidism and 62.0% i.e., 31 patients were in euthyroid state. Among 11 subclinical hypothyroid patients, 3 are males and 8 are females. Among 8 hypothyroid patients, 2 are males and 6 are females.
Table 10: symptoms and signs of the patients in the study

| Symptoms & Signs                  | Yes     | No      |
|-----------------------------------|---------|---------|
| Abdominal pain                    | 17(34%) | 33(66%) |
| Vomiting                          | 9(18%)  | 41(82%) |
| Fatigue                           | 8(16%)  | 42(84%) |
| Weight gain                       | 7(14%)  | 43(86%) |
| Constipation                      | 6(12%)  | 44(88%) |
| Hoarseness                        | 1(2%)   | 49(98%) |
| Menstrual disturbance             | 3(6%)   | 47(94%) |
| Obesity                           | 5(10%)  | 45(90%) |
| Dry skin texture                  | 1(2%)   | 49(98%) |
| Hair loss                         | 3(6%)   | 47(94%) |
| Right hypochondrial tenderness    | 5(10%)  | 45(90%) |
Abdominal pain was the most common symptom, presenting in 34% i.e., 17 patients. Among the specific symptoms of hypothyroidism, easy fatiguability was the most common symptom presenting in 16% i.e., 8 patients.
Table 11: symptoms and signs based on thyroid status of the patients

| Clinical findings         | Euthyroid | Hypothyroid |
|---------------------------|-----------|-------------|
| Fatigue                   | Yes       | 0(0)        | 8(42%)      |
|                           | No        | 31(100%)    | 11(57.9%)   |
| Weight gain               | Yes       | 0(0)        | 7(36.8%)    |
|                           | No        | 31(100%)    | 12(63.2%)   |
| Constipation              | Yes       | 0(0)        | 6(31.6%)    |
|                           | No        | 31(100%)    | 13(68.4%)   |
| Menstrual disturbance     | Yes       | 0(0)        | 3(6.0%)     |
|                           | No        | 31(100%)    | 16(84.2%)   |
| Anaemia                   | Yes       | 3(9.7%)     | 2(10.5%)    |
|                           | No        | 28(90.3%)   | 17(89.5%)   |
| Obesity                   | Yes       | 0(0)        | 5(26.3%)    |
|                           | No        | 31(100%)    | 14(73.7%)   |
| Skin texture              | Normal    | 31(100%)    | 18(94.7%)   |
|                           | Dry       | 0(0)        | 1(5.3%)     |
| Hair pattern              | Normal    | 31(100%)    | 16(84.2%)   |
|                           | Hair loss | 0(0)        | 3(15.8%)    |

Among 8 patients of clinical hypothyroidism, 7 patients presented with symptoms of weight gain.
Table 12: USG findings among the study group

| USG findings      | No of patients | Percentage |
|-------------------|----------------|------------|
| MC                | 29             | 58.0       |
| SC                | 17             | 34.0       |
| MC+DGB            | 3              | 6.0        |
| SC+GB POLYP       | 1              | 2.0        |
| Total             | 50             | 100.0      |

Among the study group, 58.0% i.e., 29 patients had multiple calculi alone and 34.0% i.e., 17 patients had single calculi. Patients with multiple calculi were more common.
Table 13: Association of USG findings with thyroid status

| Age        | MC     | SC    | MC+ DGB | SC+GB POLYP |
|------------|--------|-------|---------|-------------|
| **Euthyroid** | 18(58.1%) | 10(32.3%) | 2(6.5%) | 1(3.2%)     |
| **Hypothyroid** | 11(57.9%) | 7(36.8%) | 1(5.3%) | 0(0)        |
| **TOTAL**   | 29(58%)  | 17(34.0%) | 3(6.0%) | 1(2.0%)     |

Among 19 patients of hypothyroidism, 11 patients had multiple calculi alone and 1 patient had multiple calculi with distended gall bladder.
DISCUSSION

Gall stone formation is a complex process involving various mechanisms affecting the flow of bile and bile content. Many factors like decrease in liver cholesterol metabolism, reduced hepatic bile secretion, reduced flow of bile into duodenum and impaired sphincter of oddi relaxation contribute to formation of gall stones in hypothyroidism. Hypothyroid patients are found to have biliary stasis because of slowed emptying of bile from the biliary tract into the duodenum. This is attributed to the decreased prorelaxing action of thyroxine on sphincter of oddi in hypothyroid individuals.

The hallmark laboratory investigation to detect hypothyroidism and also a sensitive indicator for diagnosing early thyroid dysfunction is serum TSH level. Serum TSH level is the most accurate indicator of thyroid function.

This study done in Government Royapettah Hospital included 50 patients of cholelithiasis diagnosed in the Dept. of General Surgery. Out of 50 patients, 29 (52%) were females and 21(48%) were males. Among the study group, 60% i.e., 30 patients were in the age group of > 41yrs, 18% i.e., 9 patients each in age groups 21-30 yrs and 31-40 yrs and 4% below 20 yrs. Out of 50 patients, 19 (38%) patients were found to be hypothyroid. In that 11(22%) patients had subclinical hypothyroidism and 8 (16%) patients with clinical hypothyroidism.
In a study done by Hassan H.Zaini and Kussay M. Zwain, the results were as follows. Prevalence of hypothyroidism in Hassan study was 10.6% and peak age group between 51-60 years. In my study, prevalence of hypothyroidism is 38% and peak age group more than 40 years.

Among the symptoms of hypothyroidism, easy fatiguability was present in 16% i.e., 8 patients. In ultrasound findings of cholelithiasis, 58% i.e., 29 patients had multiple calculi alone.

This increase in prevalence could have effect on the diagnostic and therapeutic work up of cholelithiasis patients. So we should be aware of thyroid status in patients of cholelithiasis and should be screened for thyroid function. TSH should be measured as most are subclinically hypothyroid with special consideration to patients of more than 40 yrs of age. Hence hypothyroidism should also be considered as a separate risk factor in cholelithiasis patients.
SUMMARY

In the present study conducted in Government Royapettah Hospital, 50 patients with cholelithiasis were studied. Among the 50 patients under study, 21(42%) patients were males and 29(58%) patients were females.

Majority of patients i.e., 30(60%) patients were in the age group >40 yrs.

In this study, abdominal pain was the most common symptom. Among the specific symptoms of hypothyroidism, easy fatiguability was the most common.

Among the study group, majority of the patients i.e., 29(58%) had multiple calculi alone.

In the study group, 19(38%) patients had hypothyroidism and 31(62%) patients were in euthyroid state. Among the 19 patients, 5 patients are males and 14 patients are females.

Majority of patients had subclinical hypothyroidism when compared to clinical hypothyroidism. Among the 19 hypothyroid patients, 11 patients had subclinical hypothyroidism and 8 patients had clinical hypothyroidism.

Among the 21 male patients studied, 5 patients i.e., 23.8% had hypothyroidism. In that, 3 patients had sub clinical hypothyroidism and 2 patients had clinical hypothyroidism.
Among the 29 female patients studied, 14 patients i.e., 48.3% had hypothyroidism. In that, 8 patients had subclinical hypothyroidism and 2 patients had clinical hypothyroidism.

Among the 30 patients more than 40 yrs of age, 14 patients i.e., 46.7% had hypothyroidism. In that, 9 patients are subclinically hypothyroid and 4 patients are clinically hypothyroid.

So all patients diagnosed to have cholelithiasis should be evaluated for hypothyroidism.
CONCLUSION

There is an increase in prevalence of hypothyroidism in cholelithiasis in this study.

Subclinical hypothyroidism is more common than clinical hypothyroidism.

Hypothyroidism has a higher prevalence in females than males.

Patients more than 40 yrs of age with cholelithiasis are more likely to have hypothyroidism.

TSH should be measured as most are subclinically hypothyroid with special consideration to patients of more than 40 yrs of age.

This increase in prevalence could have effect on the diagnostic and therapeutic work up of cholelithiasis patients.

Hypothyroidism should be considered as a separate risk factor like age, sex, obesity in cholelithiasis patients. So we should be aware of thyroid status in patients of cholelithiasis and should be screened for thyroid function.
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**PROFORMA**

Name: 
Address: 

Age /sex: 
IP/OP No: 

Date of admission: 
contact No: 

Date of discharge: 

Chief complaints: 

H/O Abdominal pain 

H/O vomiting 

H/O weight gain 

H/O constipation 

H/O cold intolerance 

H/O hoarse voice 

H/O Memory disturbance 

H/O Menstrual disturbances 

Past history: 

General examination: 

Mentation 

Anaemia
Obesity

skin texture

Hair pattern

BP- PR-

Cardiovascular system

Respiratory system

Examination of Abdomen:

Investigations:

1. USG Abdomen

2. Thyroid function test – T3

   T4

   TSH

3. Routine blood investigations
KEY TO MASTER CHART

SC- single calculus

MC – multiple calculi

DGB- distended gall bladder

GB POLYP- gall bladder polyp

USG- Ultra Sonogram

ET- Euthyroid

SH- Subclinical hypothyroid

CH- Clinical hypothyroid
| S.No | Name | Age | Sex | IP/HOP NO | Abdominal Pain | Nourishing | Fatigue | Gain | Constipation | Cold Intolerance | Memory Disturbances | Menstrual Disturbances | Past H/O | Medication | Obesity | Skin Texture | Hair Pattern | BP | Pulse Rate | OES | NS | Abdomen | USG Abdomen | RTE T1 | RTE T2 | Test | thyroid Status |
|------|------|-----|-----|---------|---------------|------------|--------|-----|-------------|-----------------|-------------------|---------------------|----------|------------|--------|-------------|--------|-----|-----------|-----|-----|---------|-----------|-------|-------|------|---------------|
| 1    | Angel | 24  | F   | 277     | N             | N           | N      | N    | N           | N               | N                 | N                   | Normal   | Normal     | Normal | Normal      | Normal | 110/70 | 82       | Normal | Normal | SC       | 3.31  | 1.06 | 2.05 | Normal | ET |
| 2    | Kamaranishtha | 48  | F   | 290     | Y             | Y            | Y      | N    | N           | N               | Y                 | N                   | Normal   | Normal     | Normal | Normal      | Normal | 130/80 | 88       | Normal | Normal | MC      | 1.1    | 0.5  | 10.2 | Normal | CH |
| 3    | Moorthi | 37  | M   | 1129    | Y             | N            | N      | N    | N           | N               | N                 | N                   | Normal   | Normal     | Normal | Normal      | Normal | 130/70 | 90       | Normal | Normal | MC      | 4      | 1.5  | 3.9  | Normal | ET |
| 4    | Sasikala | 30  | F   | 1398    | Y             | N            | N      | N    | N           | N               | N                 | N                   | Normal   | Normal     | Normal | Normal      | Normal | 120/70 | 80       | Normal | Normal | MC      | 2.5    | 1.37 | 19   | Normal | ET |
| 5    | Manoranjitham | 58  | F   | 1426    | N             | N            | N      | N    | N           | N               | N                 | N                   | Normal   | Normal     | Normal | Normal      | Normal | 140/90 | 88       | Normal | Normal | SC      | 7      | 1.08 | 7     | Normal | ET |
| 6    | Balasaraswathy | 53  | F   | 1709    | N             | N            | N      | N    | N           | N               | N                 | N                   | Normal   | Normal     | Normal | Normal      | Normal | 130/90 | 84       | Normal | Normal | SC      | 2.71   | 1.47 | 3.77 | Normal | ET |
| 7    | Sundararajan | 68  | M   | 1918    | Y             | N            | N      | N    | N           | N               | N                 | N                   | Normal   | Normal     | Normal | Normal      | Normal | 140/80 | 88       | Normal | Normal | MC      | 2.5    | 1.6  | 3.4  | Normal | ET |
| 8    | Krishnan | 48  | M   | 2031    | N             | N            | N      | N    | N           | N               | N                 | N                   | Normal   | Normal     | Normal | Normal      | Normal | 130/80 | 82       | Normal | Normal | MC      | 2.01   | 1.07 | 6.4   | Normal | SH |
| 9    | Girja    | 21  | F   | 2259    | Y             | N            | N      | N    | N           | N               | N                 | N                   | Normal   | Normal     | Normal | Normal      | Normal | 110/80 | 80       | Normal | Normal | SC      | 2.6    | 1.4  | 3.6  | Normal | ET |
| 10   | Jayaraman | 63  | M   | 2661    | Y             | Y            | N      | N    | N           | N               | N                 | N                   | Normal   | Normal     | Normal | Normal      | Normal | 130/90 | 86       | Normal | Normal | SC      | 2.9    | 1.57 | 3.9  | Normal | ET |
| 11   | Kothandum | 46  | M   | 3377    | N             | N            | Y      | Y    | N           | N               | N                 | N                   | Normal   | Normal     | Normal | Normal      | Normal | 140/90 | 86       | Normal | Normal | MC      | 1.3    | 0.6  | 11.4 | Normal | CH |
| 12   | Velu     | 26  | M   | 3590    | Y             | N            | N      | N    | N           | N               | N                 | N                   | Normal   | Normal     | Normal | Normal      | Normal | 120/70 | 88       | Normal | Normal | MC      | 2.9    | 1.39 | 3.06 | Normal | ET |
| 13   | Udaya    | 28  | F   | 3643    | N             | N            | N      | N    | N           | N               | N                 | N                   | Normal   | Normal     | Normal | Normal      | Normal | 110/80 | 78       | Normal | Normal | SC      | 3.2    | 1.1  | 2.9  | Normal | ET |
| 14   | Rani     | 50  | F   | 4770    | Y             | Y            | Y      | Y    | Y           | N               | N                 | N                   | Normal   | Normal     | Normal | Normal      | Normal | 130/80 | 84       | Normal | Normal | MC      | 1.5    | 0.6  | 10.6 | Normal | CH |
| 15   | Kalayarasi | 38  | F   | 6119    | Y             | Y            | Y      | N    | N           | N               | N                 | N                   | Normal   | Normal     | Normal | Normal      | Normal | 130/80 | 82       | Normal | Normal | MC      | 1.3    | 0.5  | 11    | Normal | CH |
| 16   | Dhanapal | 62  | M   | 6335    | N             | N            | N      | N    | N           | N               | N                 | N                   | Normal   | Normal     | Normal | Normal      | Normal | 140/80 | 82       | Normal | Normal | SC+G+POLY | 3.8    | 1.4  | 4.1  | Normal | ET |
| 17   | Vijayalakshmi | 57  | F   | 6407    | N             | N            | N      | N    | N           | N               | N                 | N                   | Normal   | Normal     | Normal | Normal      | Normal | 120/90 | 76       | Normal | Normal | MC      | 2.2    | 0.9  | 8    | Normal | CH |
| 18   | Thirupal | 58  | M   | 6769    | Y             | Y            | N      | N    | N           | N               | N                 | N                   | Normal   | Normal     | Normal | Normal      | Normal | 140/90 | 86       | Normal | Normal | MC      | 3.5    | 1.2  | 4.5  | Normal | ET |
| 19   | Ravi     | 58  | M   | 7016    | Y             | N            | N      | N    | N           | N               | N                 | N                   | Normal   | Normal     | Normal | Normal      | Normal | 130/90 | 84       | Normal | Normal | SC      | 2.96   | 1.7  | 4.9  | Normal | ET |
| 20   | Susana    | 41  | F   | 7499    | Y             | N            | N      | N    | N           | N               | N                 | N                   | Normal   | Normal     | Normal | Normal      | Normal | 130/80 | 84       | Normal | Normal | SC      | 3      | 1    | 7.8  | Normal | SH |
| 21   | Mubarak    | 52  | M   | 8066    | N             | N            | N      | N    | N           | N               | N                 | N                   | Normal   | Normal     | Normal | Normal      | Normal | 140/80 | 88       | Normal | Normal | MC      | 3.1    | 1.2  | 4.4  | Normal | ET |
| 22   | Arul mariathan | 62  | M   | 8069    | Y             | N            | N      | N    | N           | N               | N                 | N                   | Normal   | Normal     | Normal | Normal      | Normal | 130/70 | 86       | Normal | Normal | MC      | 2.9    | 1.06 | 3.5  | Normal | ET |
| 23   | Sumathi | 29  | F   | 8435    | Y             | N            | N      | N    | N           | N               | N                 | N                   | Normal   | Normal     | Normal | Normal      | Normal | 120/70 | 78       | Normal | Normal | SC      | 3      | 1.12 | 4     | Normal | ET |
| 24   | Mahalakshmi | 42  | F   | 8572    | N             | N            | N      | N    | N           | N               | N                 | N                   | Normal   | Normal     | Normal | Normal      | Normal | 130/90 | 86       | Normal | Normal | MC      | 2.7    | 1.3  | 2.8  | Normal | ET |
| 25   | Meena     | 47  | F   | 9418    | Y             | Y            | Y      | Y    | Y           | Y               | Y                 | Y                   | Normal   | Normal     | Normal | Normal      | Normal | 140/80 | 84       | Normal | Normal | MC      | 1.6    | 0.58 | 10.4 | Normal | CH |
| S.L No | Name         | Age | Sex | IP/OP/AD | Abdominal Pain | Vomiting | Fatigueness | Weight Gain | Constipation | Hoarse Voice | Memory Disturbances | Menstrual Disturbances | Past H/O | Migraine | Anaemia | Obesities | Skin Texture | Hair Pattern | BP | Pulse Rate | CVS | RS | Abdomen | USG Abdomen | Free T3 | Free T4 | TSH | Thyroid Status | Blood-Inn |
|-------|--------------|-----|-----|----------|----------------|----------|-------------|-------------|--------------|-------------|---------------------|------------------------|-----------|----------|---------|-----------|--------------|--------------|----|-----------|-----|-----|---------|-------------|--------|--------|-----|-------------|----------|
| 26    | Patchaiyamal| 32  | F   | Y N N N N N N N N N | N N N N N N | Normal | N N N N N N | Normal | Normal | Normal | 130/70 | 78 | Normal | Normal | Normal | MC | 4 | 1.5 | 4.1 | Normal | ET |
| 27    | Geetha       | 40  | F   | 10171 Y N N N N N N N N N | N N N N N N | Normal | N N N N N N | Normal | Normal | Normal | 140/80 | 84 | Normal | Normal | Normal | SC | 2.1 | 1.1 | 8.2 | Normal | SH |
| 28    | Malar        | 28  | F   | 10281 N N N N N N N N N N | N N N N N N | Normal | N N N N N N | Normal | Normal | Normal | 120/70 | 86 | Normal | Normal | Normal | MC | 3.6 | 1.3 | 2.1 | Normal | ET |
| 29    | Devaprassath | 51  | M   | 10553 Y N N N N N N N N N | N N N N N N | Normal | N N N N N N | Normal | Normal | Normal | 140/90 | 82 | Normal | Normal | Normal | MC | 2.9 | 1.0 | 1.4 | Normal | ET |
| 30    | Thajunisha begum | 25  | F   | 11008 Y N N N N N N N N N | N N N N N N | Normal | N N N N N N | Normal | Normal | Normal | 130/70 | 84 | Normal | Normal | Normal | SC | 1.9 | 0.9 | 7.1 | Normal | SH |
| 31    | Subramani     | 39  | M   | 11090 Y Y N N N N N N N N | N N N N N N | Normal | N N N N N N | Normal | Normal | Normal | 130/80 | 88 | Normal | Normal | Normal | SC | 2.1 | 1.1 | 8.2 | Normal | SH |
| 32    | Gambeeram    | 60  | M   | 12461 Y N N N N N N N N N | N N N N N N | Normal | Y N N N N N N | Normal | Normal | Normal | 140/90 | 86 | Normal | Normal | Normal | SC | 2.1 | 1.1 | 8.2 | Normal | SH |
| 33    | Nallathambe   | 45  | M   | 13811 Y Y Y Y Y Y N N N N | N N N N N N | Normal | N Y N N N N | Normal | Normal | Normal | 130/70 | 80 | Normal | Normal | Normal | MC | 3.1 | 1.2 | 4.5 | Normal | ET |
| 34    | Alima         | 30  | F   | 12520 N N N N N N N N N N | N N N N N N | Normal | N N N N N N | Normal | Normal | Normal | 120/80 | 78 | Normal | Normal | Normal | MC | 2.6 | 1.4 | 0.98 | Normal | ET |
| 35    | Dhatchhayini   | 49  | F   | 13039 N N N N N N N N N N | N N N N N N | Normal | N N N N N N | Normal | Normal | Normal | 130/90 | 86 | Normal | Normal | Normal | SC | 2.1 | 1.1 | 8.2 | Normal | SH |
| 36    | Perumal       | 39  | M   | 13041 Y N N N N N N N N N | N N N N N N | Normal | N N N N N N | Normal | Normal | Normal | 130/80 | 82 | Normal | Normal | Normal | SC | 2.6 | 1.4 | 0.98 | Normal | ET |
| 37    | Mahalingam    | 62  | M   | 13228 Y N N N N N N N N N | N N N N N N | Normal | Y N N N N N N | Normal | Normal | Normal | 140/80 | 86 | Normal | Normal | Normal | MC | 2.4 | 1.37 | 2 | hb-9gm | ET |
| 38    | Kala          | 42  | F   | 13345 Y N N N N N N N N N | N N N N N N | Normal | N N N N N N | Normal | Normal | Normal | 120/70 | 80 | Normal | Normal | Normal | MC | 2.9 | 7.4 | Normal | SH |
| 39    | Kesavan       | 52  | M   | 13609 N N N N N N N N N N | N N N N N N | Normal | N N N N N N | Normal | Normal | Normal | 130/90 | 84 | Normal | Normal | Normal | MC | 2.71 | 1.47 | 3.77 | Normal | ET |
| 40    | Zareena       | 19  | F   | 13769 Y N N N N N N N N N | N N N N N N | Normal | N N N N N N | Normal | Normal | Normal | 120/70 | 76 | Normal | Normal | Normal | MC | 3.16 | 2.79 | Normal | ET |
| 41    | Lavanya       | 17  | F   | 13851 N N N N N N N N N N | N N N N N N | Normal | N N N N N N | Normal | Normal | Normal | 110/80 | 82 | Normal | Normal | Normal | SC | 2.56 | 1.15 | 1.27 | Normal | ET |
| 42    | Kumudha       | 39  | F   | 13955 Y Y Y Y Y Y N N N N | N N N N N N | Normal | N N N N N N | Normal | Normal | Normal | 140/80 | 88 | Normal | Normal | Normal | SC | 1.51 | 0.55 | 10.4 | Normal | CH |
| 43    | Omprakash     | 32  | M   | 14799 N N N N N N N N N N | N N N N N N | Normal | N N N N N N | Normal | Normal | Normal | 130/70 | 80 | Normal | Normal | Normal | MC | 2.34 | 1.13 | 0.95 | Normal | ET |
| 44    | Minnala       | 60  | F   | 14806 Y Y N N N N N N N N | N N N N N N | Normal | N N N N N N | Normal | Normal | Normal | 130/90 | 84 | Normal | Normal | Normal | MC | 2.1 | 1.32 | 2.32 | Normal | ET |
| 45    | Srinivasan    | 68  | M   | 14920 Y N N N N N N N N N | N N N N N N | Normal | N N N N N N | Normal | Normal | Normal | 140/90 | 82 | Normal | Normal | Normal | SC | 3.2 | 1.39 | 2.23 | Normal | ET |
| 46    | Abdul kalam   | 52  | M   | 15079 Y Y Y Y Y Y N N N N | N N N N N N | Normal | N N N N N N | Normal | Normal | Normal | 130/90 | 88 | Normal | Normal | Normal | MC | 2.5 | 1.08 | 6.8 | Normal | SH |
| 47    | Murugeshwari  | 52  | F   | 16011 N N N N N N N N N N | N N N N N N | Normal | N N N N N N | Normal | Normal | Normal | 120/90 | 76 | Normal | Normal | Normal | MC | 3.01 | 0.94 | 2.03 | Normal | ET |
| 48    | Machagandha   | 38  | F   | 16037 N N Y Y Y Y N N N N N | N N N N N N | Normal | N N N N N N | Normal | Normal | Normal | 130/80 | 84 | Normal | Normal | Normal | MC | 1.6 | 0.57 | 9.7 | Normal | CH |
| 49    | Sulochana     | 50  | F   | 16606 Y N N N N N N N N N | N N N N N N | Normal | N N N N N N | Normal | Normal | Normal | 140/70 | 78 | Normal | Normal | Normal | MC | 1.94 | 0.88 | 7.1 | Normal | SH |
| 50    | Chandramathi  | 68  | F   | 16764 Y N N N N N N N N N | N N N N N N | Normal | Y N N N N N N | Normal | Normal | Normal | 130/90 | 86 | Normal | Normal | Normal | SC | 2.66 | 1.25 | 1.69 | hb-9gm | ET |