“ONE YEAR STUDY OF PREVALENCE OF HYPOTHYROIDISM IN PATIENTS WITH GALL BLADDER STONES AT KLE’S DR PRABHAKAR KORE HOSPITAL AND MRC, BELAGAVI -590010”

By

REG NO. BH0118003

Dissertation

Submitted to the

KLE University, Belagavi, Karnataka

In Partial Fulfillment

of the requirements for the degree of

MASTER OF SURGERY (M.S.)

in

GENERAL SURGERY

DEPARTMENT OF SURGERY,

JAWAHARLAL NEHRU MEDICAL COLLEGE,

BELAGAVI, KARNATAKA

APRIL - 2021

KLE ACADEMY OF HIGHER EDUCATION AND RESEARCH,

BELAGAVI, KARNATAKA

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Ref No: MDC/PG/ Date: 02-09-2020

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LIST OF ABBREVIATIONS USED

GB- Gall bladder

CBD- Common Bile Duct

CHD- Common hepatic duct

CD- Cystic duct

SO- Sphincter of Oddi

RBC- Red blood cells

WBC- white blood cells

HDL- High density lipids

TSH- Thyroid stimulating hormone

TPO- Thyroid peroxidase

OCP- oral contraceptive pills

ECG- Electrocardiogram

USG- Ultrasonography

MRCP-Magnetic resonance cholangiopancreatography

ERCP- endoscopic retrograde cholangiopancreatography

HIDA- hepatobiliary iminodiacetic acid

ABSTRACT

Background and objectives

Cholelithiasis is common biliary pathology and is multifactorial in cause. Contribution of hypothyroidism to gallstone formation is debated over years. With this background, the study intended to analyze the prevalence of undiagnosed hypothyroidism in patients with cholelithiasis and in different age groups and gender of the study population.

Methodology

This prospective, hospital based cross-sectional study was done on 100 patients admitted for gall stone disease after meeting the selection criteria in the Department of General Surgery in KLE's Dr Prabhakar Kore Hospital, Belgaum during January 2019 – December 2019. After testing their thyroid profiles and interpreting the lab values, they were grouped into euthyroid, subclinical hypothyroid and hypothyroid groups. Percentage of gall stones in different age groups, gender and types of occupation of the study population was calculated followed by prevalence of hypothyroidism and subclinical hypothyroidism in all the patients included in the study.

Results

Among the study population, 40 % were male and 60 % were female. 23 of them were identified to have subclinical hypothyroidism and 6 of were diagnosed with hypothyroidism. Majority of subclinical hypothyroid patients (39.13 %) were aged 41-60 years. Hypothyroid symptoms were shown by the study population with unknown thyroid status.

Conclusion and interpretation

The prevalence of hypothyroidism in cholelithiasis is 29% in the study and is significant. 23% were diagnosed with subclinical and 6% with clinical hypothyroidism. This study also shows higher prevalence among females aged more than 40 years of age. The study demands further studies to consider hypothyroidism as a cause /risk factor for biliary calculi.

Keywords

Hypothyroidism, gallbladder stones, prevalence, biliary tree

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CHAPTER 1

INTRODUCTION

The gall bladder stones are the most common pathology in biliary tree. Its prevalence in India has been rising due to change in food habits, advanced investigations and increasing affordability. Gall stones are of three types – cholesterol, pigment and mixed. 80% of them are pigment stones (black or brown) in Asian countries whereas in European countries cholesterol stones are more common.

Stone formation depends on cholesterol concentration, supersaturation, nucleation and abnormal gall bladder motility leading to biliary stasis. Various risk factors that leads to gall stone formation includes fertile females, obesity, sudden weight loss, gastric surgery, hemolytic disorders etc. Discussions done globally for decades on whether thyroid disorders can cause cholelithiasis explained various possibilities in thyroid failure which include 1) Altered liver cholesterol metabolism causing bile supersaturation 2) Altered pro-relaxing effect of thyroxine on sphincter of Oddi causing dysfunctional sphincter 3) Altered bile flow.

More than 10 million hypothyroid patients are found in India, more prevalent among elderly females. Many studies conducted in North India showed high prevalence of hypothyroidism in cholelithiasis. If situation is the same in South India, then it may have an important role in diagnostic and therapeutic work up of patients with gall stones.

In Belagavi, a larger number is affected with cholelithiasis and the prevalence of undiagnosed hypothyroidism in cholelithiasis has never been studied. With this background, the study intends to analyze the prevalence of undiagnosed hypothyroidism in patients with cholelithiasis and tries to establish hypothyroidism as a likely cause for biliary stones in KLE's Dr. Prabhakar Kore Hospital and MRC, Belagavi.

CHAPTER II

AIM AND OBJECTIVE

Aim

To understand the prevalence of hypothyroidism in patients with gallstones.

Primary objective

To calculate the prevalence of hypothyroidism in patients with gallbladder stones after grouping the study population into euthyroid, subclinical and clinical hypothyroidism.

Secondary objective

To calculate the prevalence of hypothyroidism in different age groups and gender of the study population.

CHAPTER III

LITERATURE REVIEW

The lithogenicity of gall bladder dates to the period of Egyptian era and cannot be overlooked just as a modern disease. From the embalmed mummies analyzed from the early Egyptian dynastic period, historians have brought out the evidence of gall bladder stones[1]. Double gall bladder, which is a rare anomaly was first reported by Pliny in a sacrificial victim even at the time of Roman Empires[2]. Altender Tralliamus, who was an acclaimed Greek physician had described choledocholithiasis in the 5th century. Jean Louis Petit, in 1740, identified an adherent gall bladder to abdominal wall and pointed out the possibility of removing calculi from gall bladder by puncturing it through abdominal wall[1]. In 1793, Hoffmann reported the possibility of asymptomatic gall stones. The term bile acid was first coined in 1838 by Demarcay and clarified the acidic fraction of bile identified earlier in 1807[3]. Presence of bile acids in human circulation was proposed by Hoppe-Seyler.

The evidence of gall bladder stones was radiologically described only in 1898 by Buxom and later in 1924, the advanced oral cholecystography was developed by Graham and Cole for detecting radio transparent calculi[1]. The Endoscopic retrograde methods and percutaneous transhepatic cholangiography were utilized in the 1970s[1.] Ultrasonography was used as a screening modality later. With the advent of magnetic resonance imaging, MRCP was developed.

With advancements in the field of surgery, first cholecystolithotomy was performed by an Indiana surgeon John Bobbs in 1867 on a lady whom he believed to have an ovarian mass. The first elective cholecystostomy was done by Sims in 1878 for obstructive jaundice and he extracted 60 calculi from the gall bladder. First cholecystectomy was successfully

performed in 1882 by Karl Langenbuch[1]. Calot's triangle by Calot in 1891 was described for safe dissection during cholecystectomy. By 1897, the number of cholecystectomies had increased to nearly 100 with a mortality rate less than 20%. In 1898, the first removal of calculi from the biliary tract was done by Thornton. In 1912, Kehr developed drainage procedure of biliary tract stones in the form of biliary intubation with the help of rubber T tubes[1].

Maki in 1966 alerted the association between bacterial infections and pigmented gallbladder stones[4]. Disappearance of radiolucent gallbladder stones after thyroxin administration was reported by Vassilakis et. al in 1981[5]. The use of Methyl Tertiary Butyl Ether (MTBE) for gallstone dissolution was successfully described by Allen et.al in 1985[6].

With the advent of minimally invasive approaches, laparoscopic cholecystectomy was first done by Muhe in 1985 and first video laparoscopic cholecystectomy was done by Mouret in France[1]. Ajay et.al in 1992 suggested laparoscopic cholecystectomy for symptomatic gallstone disease due to low morbidity and mortality[7]. Adreini et.al in 1994 noted markedly increased biliary secretion of cholesterol in hypothyroid rats after thyroxine administration and supported the hypothesis of involvement of microtubule or vesicle pathway in the secretion of important phospholipid and cholesterol component into the bile[8]. Study by Shyamal Kumar Gosh et al in 1995 highlighted that females have high risk for cholelithiasis and was supported two years later by Angelico et al from Italy[9]. J.R. Barton et al in 1996 proposed that endoscopic routes can be used to manage post-operative complications like bile leak[10]. Mini-laparotomy cholecystectomy was performed by Majeed and Assalia in 1996[11]. GPH, CVN Cheruvu et al in 1998 concluded that cholecystectomy is the gold standard treatment for cholelithiasis[12] and in the same year Hellstern et.al conducted a European survey and concluded that contact litholysis with MTBE gallbladder stones can

be resorted to patients who are not fit for surgery[13].VL Wills et al suggested laparoscopic management of minor post-operative bile leak in 2000[14]. Inkinen J et.al in 2000 found a significant association between CBD calculi and diagnosed hypothyroidism compared to gallbladder calculi, suggesting cholesterol metabolism as a likely mechanism[15]. The study by Canaris et.al in 2000 noticed that mild increase in S.TSH altered the lipid levels affecting the cardiovascular system[16]. Study by Schiffman et al noticed reduced lithogenecity in obese patients on diet focused on low calories as part of their lifestyle and increased incidence after gastric bypass surgeries. The pro-relaxing effect of thyroxine on the Sphincter of Oddi of pigs and the lack of thyroxine causing an increased SO tension was well explained in 2001 by Inkinen J et.al[17] and one year later Laukkarinen J et.al explained the mechanism of thyroxine's pro-relaxing effect on human SO[18]. Nakeeb et al in 2002 proved that 30% of gall stones are triggered by genetic factors[19]. Duntas et.al in the same year associated subclinical hypothyroidism with lipid disorders[20]. In 2003, Laukkarinen et.al concluded that delayed biliary emptying may occur in hypothyroidism which leads to CBD calculi formation[21]. Völzke et.al in 2005 found strong association between hypothyroidism and cholelithiasis in China[22]. Brenta G et.al in 2007 hypothesized that subclinical hypothyroidism is a pro-atheromatic state as they noted qualitative lipoprotein changes and insulin resistance[23]. Laukkarinen J et.al noted that subclinical hypothyroidism is common among choledocholithiasis hypothesizing its key role in calculi formation[24]. Study on hypophysectomized rats by Gaman et.al in 2008 noted that only thyroid hormone could normalize the hyper absorption of cholesterol on cholesterol challenge[26]. On the other side, Hassan et.al in 2009, did a cross sectional study and found no relation between hypothyroidism and gall stones in Iraq and recommended further studies with larger sample size[25]. Laukkarinen et.al in 2010 hypothesized that CBD calculi develops during untreated

phase of hypothyroidism and matures once the treatment starts questioning the efficiency of the treatment[27]. In 2011, Sigal et.al stated that subclinical hypothyroidism alters HDL metabolism that can be reversed to achieve euthyroid state with levothyroxine therapy[28]. In 2013, Ajdarkosh H et.al recommended thyroid profile in all patients with gall stones or CBD stones as there is strong association between them and thought hypothyroidism as a predisposing factor for the passage of gall stones to CBD[29]. In 2016, studies by N. P. Maru et.al in China[30] and Rana Ranjit Singh et.al in India[31] warranted further research in large scale to find the role of thyroid hormone in forming biliary tree calculi in humans. Studies done in North India in 2017 strongly found relationship between subclinical hypothyroidism and cholelithiasis[32,33]. Singh BR et al concluded that the burden of cholelithiasis can be prevented by treating hypothyroidism at early stages and with serial monitoring of S.TSH in 2018[34].

Chapter IV

Anatomy

GALLBLADDER AND BILE DUCTS

EMBRYOLOGY

During the third week of gestation, an outgrowth from the ventral foregut endoderm at the caudal end forms the liver primordium. This grows into the ventral mesogastrium. Traversing septum transversum, it divides into smaller pars cystica caudally and larger pars hepatica cranially. Former develops into gall bladder & cystic duct[38,39].

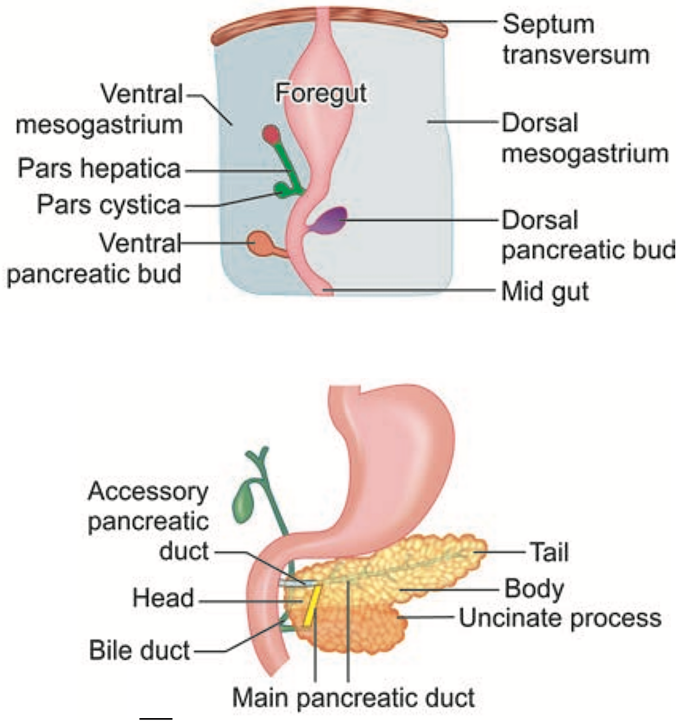

Fig. 1 Development of biliary tree and pancreas

Common hepatic duct is formed from part of pars hepatica distal to the origin of pars cystica. Common bile duct is formed from part between pars cystica and duodenal part of

foregut. CBD opens on the dorsomedial side of duodenum in company with ventral pancreatic bud after differential growth and rotation of duodenal loop.

ANATOMY OF GALLBLADDER

Only 50% of the population have normal biliary anatomy[40]. The gallbladder is a 7–10 cm long pear-shaped sac, with average capacity of 30- 50 ml. It can distend strikingly up to 10 times (approximately 300ml) in obstruction. It is situated in a fossa on the inferior surface of liver and divides into 4 anatomic areas: fundus, corpus/ body, infundibulum and neck[39].

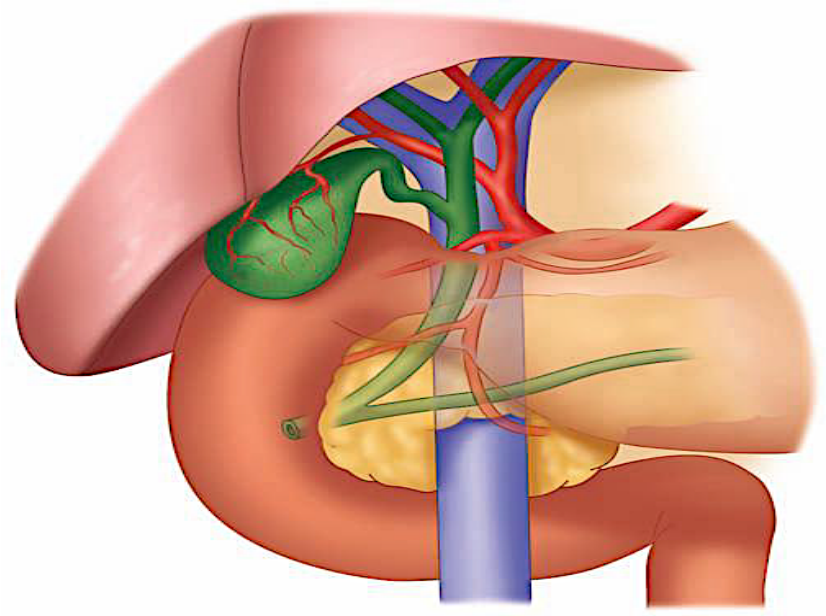

Fig. 2 Anatomy of biliary tree with boundaries

Fundus, a round blind end is extending ~2 cm beyond liver margin. Extending from fundus, is body which is the main storage area. Neck is a funnel-shaped area lying in the deepest part of the gallbladder fossa connecting the cystic duct. It enlarges to shape Hartmann's pouch/ infundibulum. Muscle fibers in neck is well developed and arranged in crisscross fashion. Its mucous membrane contains indentations into muscle coat which forms crypts of Luschka. Peritoneum covering the liver also covers inferior surface and fundus of gall bladder.

BILE DUCTS

Hepatic ducts

They are formed from left and right branches of pars hepatica. The left being longer than right duct has greater tendency for dilatation in case of obstruction distally. They both join to form common hepatic duct.

Common hepatic duct

It lies anterior to portal vein & to right of hepatic artery. It is 1-4 cm long & about 4mm in diameter. It joins cystic duct at an acute angle forming common bile duct. This point of union is variable and is surgically important.

Cystic duct

It starts from gall bladder and its length is variable. Its mucosa is spirally arranged into folds forming the valves of Heister, making its cannulation difficult and the wall is surrounded by the sphincter of Lütkens.

Common bile duct

It starts from junction of common hepatic duct & cystic duct. It is measuring about 7-10 cm long & lumen is ~ 5-10 mm. It has four segments:

1. Supraduodenal segment runs along the free edge of lesser omentum with length of about 2.5cm, lying anterior to portal vein & to right of hepatic artery.
2. Retroduodenal segment lies behind to Ist part of duodenum diverting away from portal vein and hepatic artery.
3. Infraduodenal (intrapancreatic) segment is on posterior surface of pancreatic head & traverses through it.

4. Intraduodenal segment joins with pancreatic duct and ends by opening to ampulla of Vater in 2nd part of duodenum. In 10% cases these two ducts open separately. This segment including distal part of common bile duct, terminal part of pancreatic duct, ampulla of Vater, major duodenal papilla is surrounded by sphincter of Oddi[41].

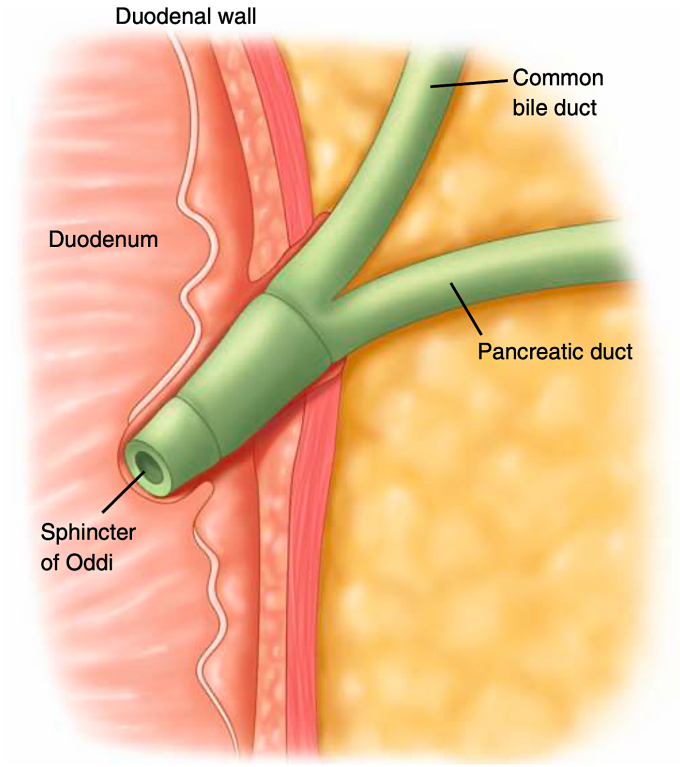

Fig. 3 Sphincter of Oddi

Sphincter of Oddi: a thick circular smooth muscle coat, 4-6 mm in length, around common bile duct at ampulla of Vater that manages flow of pancreatic juice & bile to duodenum. It also protects biliary tree from regurgitation of duodenal contents. It functions independently from duodenal musculature and its motility is controlled by interstitial cells of Cajal[39].

ANOMALIES

Gall bladder

Shape:

- Phrygian cap (A): Fundus double on itself forming a cap.
- Hartmann's pouch (B): The infundibulum projects downward to form a pouch.

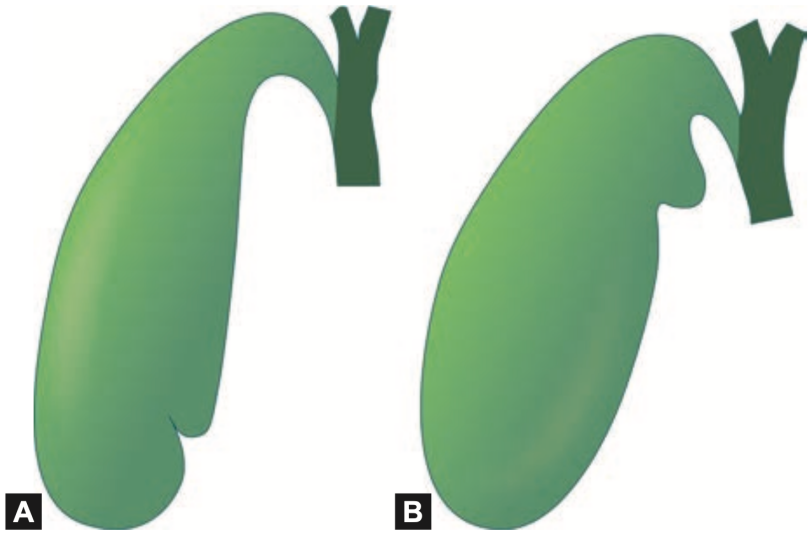

Fig. 4 (A) Phrygian cap (B) Hartmann's pouch

Position:

- Transverse position on inferior surface of either right / left lobe of liver.

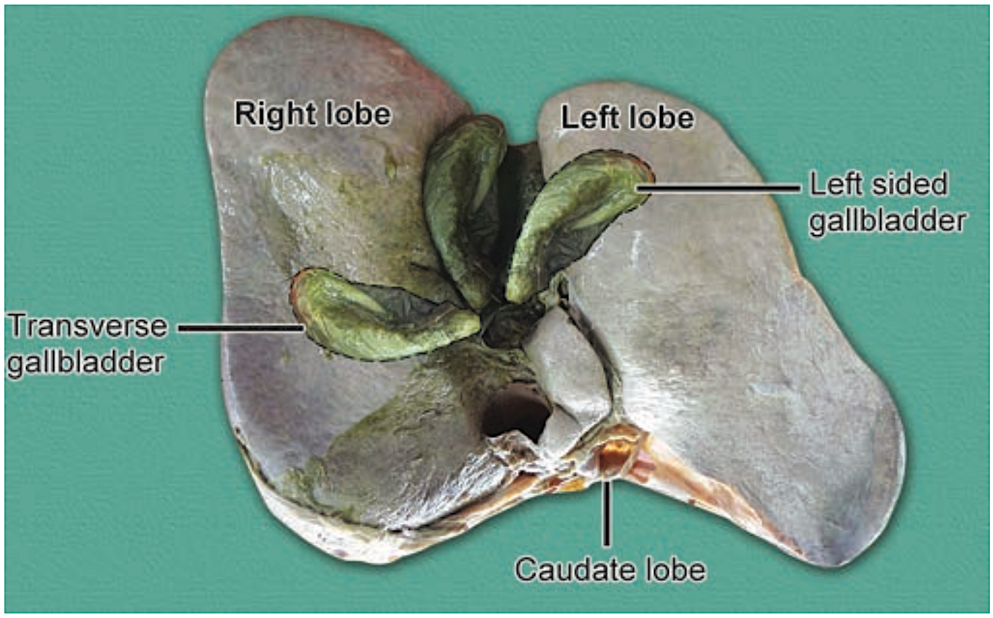

Fig. 5 Anomalies of position of gallbladder

- Floating gallbladder: A fold of peritoneum attaches gall bladder to the liver or may be completely free.
- Intrahepatic gallbladder: Present in the substance of liver

Duplication

- The lumen is divided by a septum partially or completely.
- The gallbladder may be completely or partially duplicated.

Other anomalies:

- Sessile gallbladder: The gallbladder may directly open into the bile duct instead of the cystic duct
- Agenesis/ Absent gallbladder

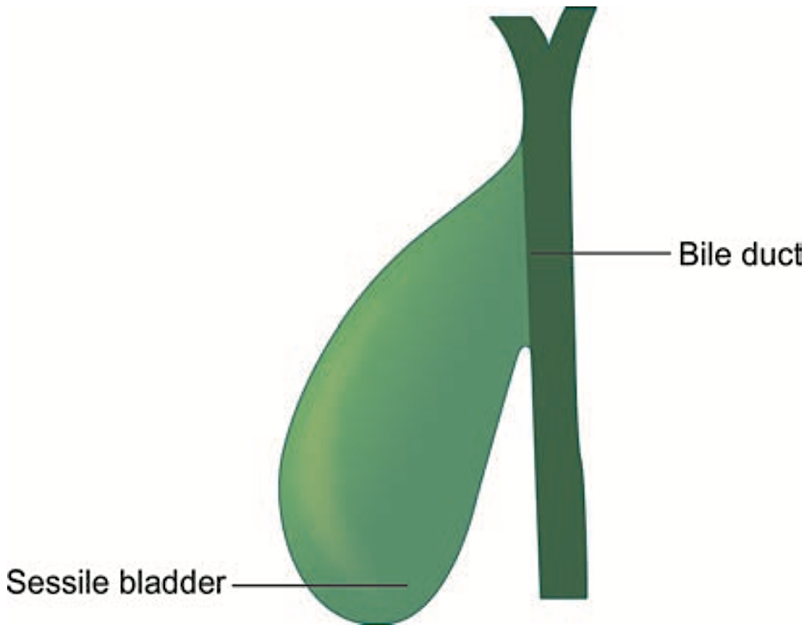

Fig. 6. Sessile gallbladder in which the gallbladder may open directly into the bile duct

Extrahepatic duct system

Abnormal length: long or short.

Abnormal termination

- Cystic duct passes either in front or behind common hepatic duct to reach its left side before joining it.
- Cystic duct opens into right hepatic duct.
- Cystic duct joins common hepatic duct by passing down and anterior to the duodenum.
- Bile duct opens directly into the stomach (pylorus/ cardiac end).
- Atresia: Parts/ whole of the duct system is not present.

Duplication:

- Part/ whole duct system is doubled.

- Accessory ducts arising from the right lobe may join directly the gallbladder, cystic duct, right hepatic duct or bile duct[38].

HISTOLOGY

Gall bladder has three layers- Serous, fibromuscular & mucous layer.

The yellowish-brown mucous membrane is lined by a single layer of columnar cells which is drawn into minute rugae, like stomach. Microvilli on the apical surface makes the bile concentrated by absorbing water and solutes from it. The mucus is secreted into the lumen by mucus granules present on the apical surface of some cells.

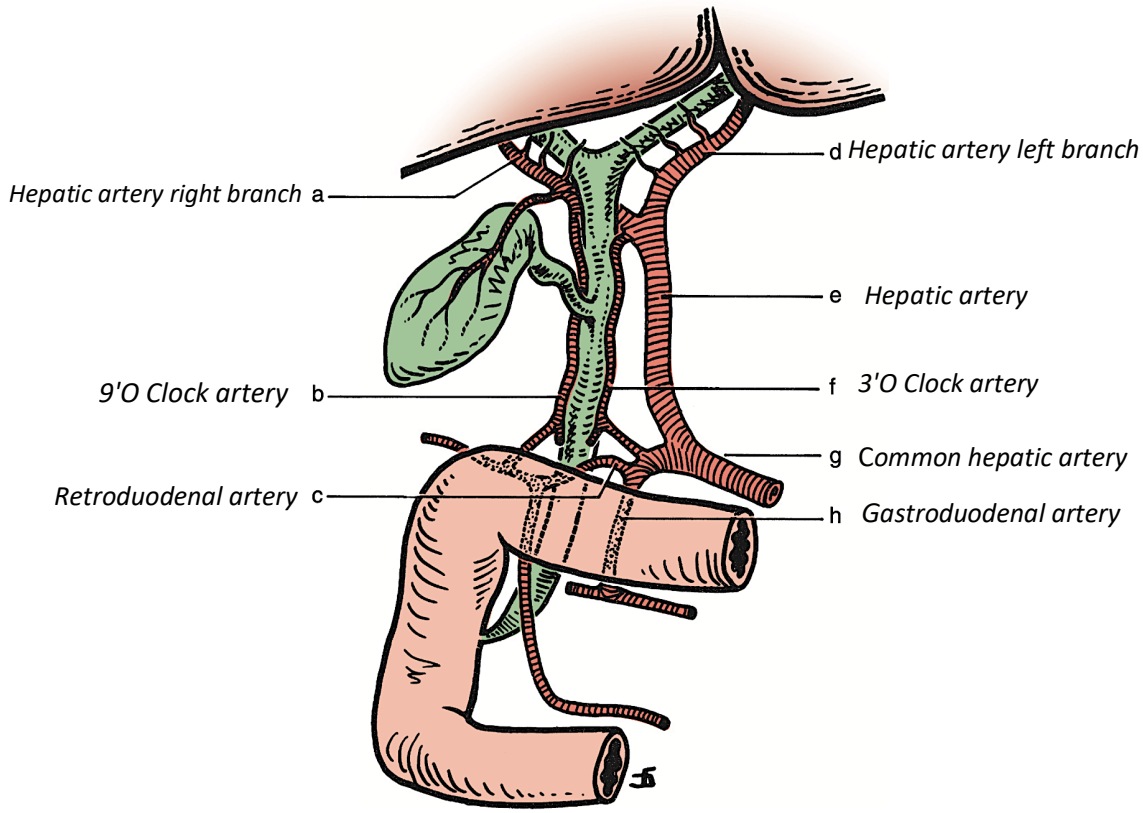

Fig. 7. Arterial supply of biliary tree.

BLOOD SUPPLY

Arterial supply

Cystic artery, branch of right hepatic artery gives major blood supply to gall bladder. It lies close to cystic duct in Calot's triangle. Rarely accessory cystic artery arises from hepatic artery proper / gastroduodenal artery. In 15% population, cystic / right hepatic artery crosses CHD or CD in front[1].

Caterpillar turn / Moynihan's hump: dangerous anomaly where cystic artery is short and right hepatic artery is tortuous.

Supraduodenal duct gets supply from superior pancreaticoduodenal artery, right branch of hepatic artery, cystic artery, gastroduodenal artery & retroduodenal artery, running along the lateral border of the duct as 9 o'clock & 3 o'clock arteries[41].

Venous drainage

Veins draining the bile ducts drain into 9 o'clock & 3 o'clock veins along common biliary channel. Veins draining the gallbladder empty directly to liver. Biliary tree has its own portal venous pathway to the liver[41].

LYMPHATIC DRAINAGE

Two pathways of lymphatic drainage. Superior pathway includes nodes along cystic duct, hepatic artery & celiac plexus. Nodes around cystic duct, lateral aspect of portal vein, posterior pancreas & aortocaval region includes the inferior pathway[40]. The subserosal gall bladder lymphatic channels communicate with subcapsular lymphatic channels of liver[1]

NERVE SUPPLY

Contraction of gallbladder & relaxation ampullary sphincter is stimulated through parasympathetic nerve supply by anterior vagal trunk (hepatic branch). Inhibition of

gallbladder contraction is through sympathetic supply from T7-9 cell bodies of celiac ganglion.

The right sympathetic fibers, which is the main afferent pain fiber pass over the T7-9 spinal segments, causing right infrascapular referred pain. Some afferent fibers from the right phrenic nerve go across the phrenic, celiac & hepatic plexuses to reach gallbladder causing right hypochondrial referred pain, radiating to back between the shoulder blades in gallstones.

SURGICAL IMPORTANCE OF GALLBLADDER

Calot's triangle: a triangular area surrounded by inferior surface of liver superiorly, laterally by cystic duct and medial border of gall bladder, medially by common hepatic duct. Cystic artery is found within this boundary[1].

Perforation is common in the fundus of the gallbladder; it is least vascular.

White bile occurs when the cystic duct is impacted with gallstones obstructing the flow of bile.

Impaction of gallstones commonly occurs in Hartman’s pouch.

PHYSIOLOGY OF GALLBLADDER

Liver secrets bile continuously in response to neurogenic, humoral and chemical stimuli. 500- 1000 mL of bile per day is produced within liver in a normal adult. It is stored in gall bladder and released into duodenum intermittently. The sphincter of Oddi controls the flow of bile.

During fasting, there is contraction of sphincter of Oddi creating a pressure gradient between gall bladder and bile duct causing filling of gall bladder.

After a meal, by coordinated gallbladder contraction & sphincter of Oddi relaxation, gall bladder empties bile into duodenum. This process is stimulated mainly by the hormone which duodenal mucosa secretes, in response to food & low pH, cholecystokinin (CCK). It directly acts on the smooth muscle receptors of gallbladder. CCK stimulation is mediated by cholinergic vagal neurons[39]. 95% of bile through enterohepatic circulation is absorbed in the terminal ileum[1].

Functions of gallbladder:

1. It is the reservoir of bile- GB stores 80% bile produced by liver, during fasting.
2. It concentrates the hepatic bile 5-10 times by absorbing water, sodium chloride and bicarbonate.
3. Secretes mucus to protect the mucosa from lytic action of bile.
4. Maintains the pressure within the biliary tree.

BILE COMPOSITION

Characteristics*	Hepatic Bile	Gallbladder Bile
Sodium	160	270
Potassium	5	10
Chloride	90	15
Bicarbonate	45	10
Calcium	4	25
Magnesium	2	4
Bilirubin	1.5	15
Proteins	150	200
Bile acids	50	150
Phospholipids	8	40
Cholesterol	4	18
Total solids	—	125
pH	7.8	7.2

Fig 8: Composition of hepatic and gallbladder bile

The gallbladder absorbs water both actively and passively hence concentrations of hepatic and gall bladder bile vary. Calcium and magnesium are readily absorbed by mucosa of gall

bladder. Absorption of bicarbonate and chloride along with secretion of hydrogen ions makes gallbladder bile acidic compared to basic hepatic bile[41].

BILE ACIDS AND SALTS

Primary - cholate / chenodeoxycholate

They are formed from cholesterol in liver. They conjugate with taurine & glycine to act as anions within bile and are balanced by sodium before excretion, thereby helping in the digestion and absorption of fat from intestine. 80% conjugated bile acids are absorbed from terminal ileum. Gut bacteria deconjugates rest and forms secondary bile acids which are absorbed in the colon. 95% bile acids enter enterohepatic circulation[39].

Secondary - deoxycholate / lithocholate

Tertiary -ursodeoxycholate

BILE PIGMENTS

Senescent RBCs breakdown in reticuloendothelial system forming the chief bile pigment-bilirubin. The presence of the pigment bilirubin diglucuronide gives color to the bile. Biliverdin is produced from bilirubin.

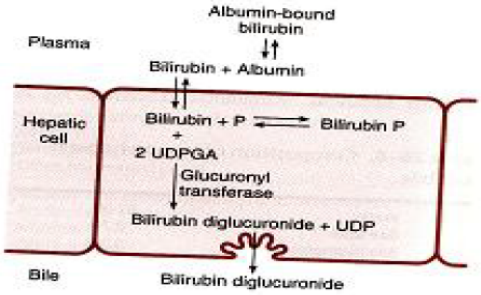

Fig. 9 Bilirubin metabolism in liver

GALLSTONES

Stones in the biliary tree is one of the most common pathology.

EPIDEMIOLOGY

Prevalence: Among adults in India, prevalence is found to be 6-20%[42]. More common in women than in men.

Risk: Multifactorial.

1. Age: Lithogenicity of bile increases with age.
2. Female and pregnancy: Threefold increased risk in females due to increased levels of estrogen which increases cholesterol secretion and progestin delays GB emptying. 30% increased risk in pregnancy.
3. Obesity: Bile is supersaturated with cholesterol and contractility of GB is decreased leading to stasis and stone formation.
4. Rapid weight loss: Caloric restriction along with increased mucin secretion leads to hepatic cholesterol production causing sludge formation. Use of ursodeoxycholic acids in patients on low caloric diet have shown to reduce the risk.
5. Drugs: Low dose estrogens, OCPs, third generation cephalosporin increases the risk. Around 40% unmetabolized form of ceftriaxone is secreted into the bile and binds with calcium to form insoluble salts forming sludge. Thiazides increases biliary cholesterol synthesis. Octreotide causes cholesterol supersaturation.
6. Systemic illness: Diabetes mellites increases the risk as insulin resistance is associated with hypercholesterolemia. Cirrhosis of liver causes decreased bile salt secretion and chronic hemolysis forming pigmented stones. Children with cystic fibrosis have shown increased prevalence.

7. GI conditions: Crohn's disease / terminal ileal resection causes malabsorption of bile salts leading to supersaturated bile. Gastric bypass surgery / truncal vagotomy interferes with gallbladder emptying causing stasis.
8. Hematological conditions: hemolytic anemia, hereditary spherocytosis, sickle cell disease and thalassemia have increased prevalence of pigmented gallstones in GB.

TYPES OF GALL STONES

1. **Cholesterol stones**

Pure stones that form only from cholesterol are rare. Accounts for <10% & are usually smooth surfaced single large stones with pale-yellow in color. Rest are in mixed form with most of them containing >70% cholesterol, bile pigments and calcium. Supersaturation of bile with cholesterol / low bile acid concentration forms unstable unilamellar phospholipid vesicle from which cholesterol crystals nucleates & forms calculi. Majority is radiolucent[39,41].

2. **Pigment stones: Black and Brown**

Calcium bilirubinate makes them dark in color and contain <20% cholesterol.

Black stones: Accounts for 20- 30%. Black, tiny, occasionally spiculated and brittle in nature. Supersaturation of insoluble calcium bilirubinate with calcium phosphate and calcium bicarbonate forms black stones in the gall bladder. Commonly seen in hemolysis, hereditary spherocytosis, sickle cell disease or cirrhosis of liver.

Brown stones: Brownish yellow, semi-solid, tiny in nature. They can be found in CBD or rarely in gall bladder, formed secondary to infected bile. They consist of calcium bilirubinate, calcium palmitate, calcium stearate and cholesterol. Also associated with

foreign bodies like as endoprosthesis in the bile ducts or parasites Clonorchis sinensis and Ascaris lumbricoides[39,41].

3. **Mixed stones**

These stones have pure central core and mixture of constituents on outer layers. They are multiple with faceted surface and color depends on constituents of stones. Epithelial debris and bacteria may be present if laminated central nucleus is sectioned suggesting inflammatory origin of stones.

PATHOGENESIS OF CHOLELITHIASIS

The causative factors are multifactorial. The imbalance between concentrations of cholesterol and bile acids in bile lead to stone formation.

- Supersaturated bile: Cholesterol is not soluble in water. Bile acids have a polar hydrophilic end and other nonpolar hydrophobic end. Micelles are formed in dilute solutions with nonpolar end inwards & polar end outwards. In a thermodynamically stable micelle, phospholipids hold cholesterol. About 30% cholesterol is transported in micelles. Reduced secretion of bile acids/ lecithin or hepatic bile with increased cholesterol cause supersaturation of bile forming cholesterol stones[1].
- Cholesterol nucleation: In cholesterol supersaturated bile or low bile acid concentrations, phospholipid unilamellar unstable vesicles are formed from which cholesterol crystals nucleates and form stones. Mucin and glycoprotein aid nucleation process. Bacterial infection like E. coli have beta glucuronidase which lyse bilirubin glucuronide and forms deconjugated insoluble bilirubin which binds with calcium and form stones in biliary tree[39].

- Impaired gallbladder functions: Gallbladder emptying is delayed in presence of stones causing stasis. Mucosa secretes mucin and glycoproteins and absorbs calcium which interferes with gallbladder contractility and emptying. Calcium and cholesterol have crystalline structure which give framework for stone formation.
- Enterohepatic circulation of bile acids: Ileal resection, deoxycholate, use of cholestyramine and fecal colonic flora affects the absorption of bile acids[41].

CLINICAL FEATURES

Silent gallstones (75-90%):

Most gallstones do not produce any symptoms throughout life and are incidentally found during imaging studies. 3% becomes symptomatic every year[39].

Symptomatic gall stones may present with:

1.Right upper quadrant pain/ epigastric pain:

It is usually continuous, colicky dull aching pain due to inflamed parietal peritoneum and often radiating to back[41]. Diffuse epigastric pain occurs with distension of gallbladder.

2. Flatulent dyspepsia: Occurs after a fatty meal.

3. Food intolerance to fatty foods.

4. Biliary colic (10-25%):

It is termed inapplicably and occurs in two-third of patients due to obstruction of cystic duct by stone causing tension in gallbladder wall. It is described as recurrent severe

right hypochondrial pain which peaks and goes with associated nausea & vomiting. It is often radiating to back/ chest. It lasts for 1-2 hours usually after a fatty meal.

5. Jaundice occurs if there is biliary obstruction.

6. Fever occurs if progressed to complications like acute cholangitis/ cholecystitis.

7. Rarely intestinal obstruction can occur which is termed as gallstone ileus.

Differential diagnosis can be acute appendicitis, perforated peptic ulcer disease or acute pancreatitis and rarely it can be acute pyelonephritis, myocardial infarction or right lower lobe pneumonia.

PHYSICAL SIGNS

1. Tenderness / rigidity in right hypochondrium due to inflamed parietal peritoneum.
2. Murphy's sign: exacerbated tenderness on deep inspiration and palpating hand exerting pressure on the right hypochondrium suggesting acute inflammation.
3. Palpable mass/ gallbladder due to mucocele, emphysema, omentum covering the inflamed gallbladder or double impaction of stones on in cystic duct and other in CBD.

COMPLICATIONS OF GALLSTONES

Symptomatic gallstones may progress to complications and sometimes present as presenting picture.

- Acute cholecystitis

90-95% of the cases are due to gallstones. The gallstone obstructs the cystic duct causing distension of gallbladder, inflammation and edema of the gallbladder wall.

Lysolecithin, bile salts and platelet activating factors aids this inflammatory process and not by bacterial origin. Pericholecystic collection is usually present. Inflammation resolves as the gallstone dislodges due to gallbladder tension in 80%. Clinical diagnosis can be made if positive murphy's sign along with fever and tachycardia are present. Ultrasonography is the investigation of choice and HIDA helps in atypical case. Definitive treatment is cholecystectomy. Percutaneous cholecystostomy can be opted for unfit patients.

- Mucocele

If the inflammation resolves without relieving the obstruction, gallbladder mucosa absorbs bile pigments and bile salts and mucin secretion continue forming mucocele (hydrops). Palpable nontender gallbladder is a striking feature. cholecystectomy is the definitive treatment.

- Empyema of gallbladder

Stone impaction causing prolonged obstruction of gallbladder is followed by secondary bacterial infection forming empyema or pus within the gallbladder.

- Perforation

Secondary bacterial infection develops acute gangrenous cholecystitis which are prone for perforation. It often causes localized subhepatic abscess or frank bile peritonitis. Patient will be toxic, and an emergency surgery will be required. Chronic perforation into duodenum or colon forms cholecystoeneteric fistula. They often present with diarrhea and barium studies shows reflux of contrast into gallbladder.

- Emphysematous gallbladder

Gas within the gallbladder lumen can be seen on imaging studies if the gas forming organisms like clostridium causes infection.

- Biliary obstruction- obstructive jaundice

Mirrizzi's syndrome, severe jaundice occurs as a result of bile duct mechanical obstruction due to severe pericholecystic collection secondary to the impacted stone in the infundibulum.

- Acute cholangitis

Gallstones commonly cause obstruction in cholangitis. It is a fatal condition where there is partial/ complete biliary obstruction in association with ascending bacterial infection and presents with intermittent fever, jaundice and upper right quadrant pain (charcot's triad). The condition may worsen rapidly causing septicemia and altered mental status (Reynold's pentad). E. coli, Klebsiella pneumoniae, S. faecalis, Enterobacter and Bacteroides fragilis are the common organisms grown in bile in case of cholangitis. There will be leukocytosis with deranged liver function test. Definitive test is endoscopic retrograde cholangiopancreatography. Initial treatment includes IV antibiotics, hydration and emergency biliary decompression and once cholangitis is settled definitive surgery is planned.

- Acute biliary pancreatitis

Pancreatitis occurs in patients with gallstones either by impaction or passage of stones through ampulla of Vater and obstructing pancreatic duct. It can be diagnosed with

raised serum amylase with gallstones on USG. ERCP with sphincterotomy and extraction of stones can be opted to reduce pancreatitis episodes.

- Gallstone ileus - intestinal obstruction
- Chronic cholecystitis

Recurrent episodes of biliary colic causes varying inflammatory changes ranging from mild mucosal to gross transmural fibrosis which forms a contracted fibrosed gallbladder enclosing the calculi.

- Gallbladder carcinoma

This rare aggressive tumor is strongly associated with gallstones probably due to the chronic inflammation. Around 1% of patients who underwent cholecystectomy for gallstones were incidentally found to have gallbladder carcinoma.

INVESTIGATIONS

Blood tests

- Complete blood picture: elevated WBC counts suggests cholecystitis / cholangitis.
- Liver function test: Bilirubin is raised in case of biliary obstruction. Liver enzymes are deranged usually.
- Serum amylase and lipase: elevated in biliary pancreatitis.

Oral or intravenous cholecystography

This was the diagnostic imaging of choice in the past and is replaced largely by better accurate imaging modalities.

Plain Xray abdomen

10% radiopaque gallstones can be detected[41]. Mercedes Benz / seagull sign is tri or biradiate appearances if radiolucent gas is present at the center of stone.

Ultrasonography abdomen

The initial imaging of choice. It is cheap and quick. The specificity and sensitivity of detecting calculi is >90%[39]. Size of gall bladder & wall thickness, polyps, number of calculi, pericholecystic collection, size of CBD, intrahepatic biliary radical dilatations and sometimes calculi in CBD can be demonstrated. The sound waves are reflected by the calculi even 1mm sized to the transducer of the ultrasound thereby detecting its acoustic shadow. Calculi keep changing its position and are distinguished from polyps which do not change position. Thickened gallbladder walls with poor halo suggests chronic cholecystitis. Overdistended gallbladder with thin walls can be mucocele. It is difficult to perform in obese or patients with distended bowels hence overnight fasting is ideal and higher frequency transducers are used for obese patients. Advantages of ultrasound are low cost, no radiation exposure and better anatomy of biliary system. Newer technology is endoscopic ultrasonography where an ultrasonic transducer is attached to the tip of endoscope enabling to visualize the biliary tree from within stomach or duodenum. It is more precise and detects smaller calculi.

Cholescintigraphy

It gives 95% accurate functional and anatomical information of liver, bile ducts, gallbladder & duodenum.

99mTechnetium-labeled derivatives of dimethyl iminodiacetic acid (HIDA, IODIDA) is given through veins. It is taken up by Kupffer cells of liver & excreted to bile. Uptake by

hepatocytes is visualized usually within 10 minutes of injection. In 90% of cases biliary tree and gall bladder can be seen within 30 minutes and bowel within an hour. Non visualization of gallbladder suggests acute cholecystitis. It also detects bill leaks or iatrogenic biliary obstruction.

Computed tomography

Inferior to ultrasonography in detecting in gallstones and are used as a screening study only in complicated gallstones to visualize extrahepatic biliary tree.

Magnetic resonance cholangiopancreatography (MRCP)

Noninvasive and provide accurate high definition images demonstrating biliary pathologies like stricture, intraductal pathologies & obstruction and pancreatic diseases.

Endoscopic Retrograde Cholangiopancreatography (ERCP)

It is of both diagnostic and therapeutic importance. Through ampulla of Vater, common bile duct is cannulated with a side viewing endoscope. Accurate bile duct images are obtained after injecting a water-soluble contrast into it and identifies the cause and level of obstruction in obstructive jaundice. During the same sitting, therapeutic techniques can be given like sphincterotomy, stenting or stones can be extracted to relive the obstruction. Bile aspirates or endoluminal brushings can be sent for cytological studies. Hence done in patients with complicated gallstones – jaundice, cholangitis or biliary pancreatitis. Complications like pancreatitis and cholangitis can occur in 5% of patients after diagnostic ERCP and bile duct injury/ rupture and minimal bleeding can occur after sphincterotomy / lithotripsy[39].

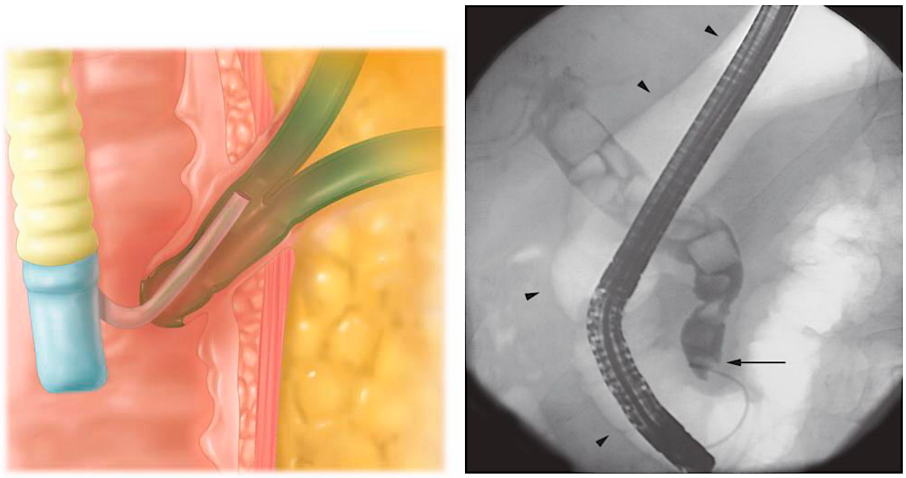

Fig. 10. Technique of ERCP and image showing stones in CBD and catheter in the ampulla of Vater.

Percutaneous Transhepatic Cholangiography (PTC)

Invasive procedure where percutaneous needle cannulation of hepatic bile duct is done under fluoroscopic/ radiological guidance through liver substance. Entry is confirmed after successful bile aspiration and water-soluble contrast is injected. Various images are taken to visualize the anatomy and pathology of biliary tree. This also helps in external biliary drainage and placing an indwelling catheter. Usually performed in complicated gallstones and complications include bleeding, bile leaks, catheter problems or cholangitis.

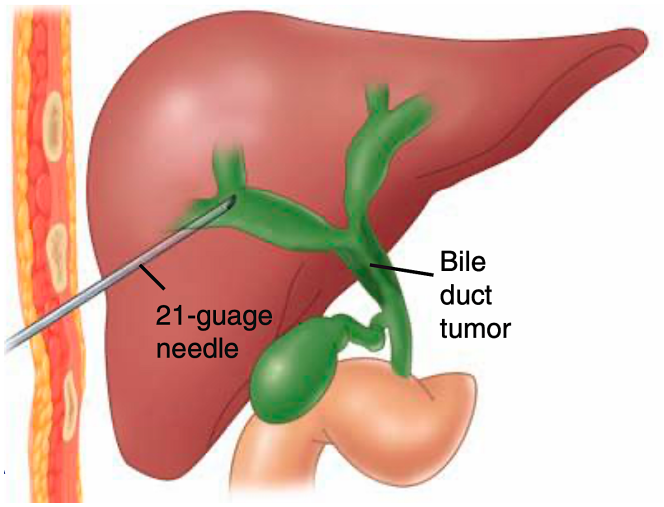

Fig. 11. Dilated intrahepatic bile duct is entered percutaneously with a fine needle.

Invasive operative imaging

Intraoperative cholangiography

During open or laparoscopic cholecystectomy or CBD exploration, catheter is passed through bile duct and contrast is passed to understand the biliary pathology. Intraoperatively images are reviewed after tilting down the operating table 20 degree at head end such that intrahepatic ducts can be viewed. Accidental air bubble injection could be mistaken for stones and should be avoided.

Choledochoscopy

Through choledochotomy, a fibreoptic flexible endoscope can be inserted into CBD to identify and remove calculi or place a T tube for drainage in doubt of residual stones.

TREATMENT

Asymptomatic cholelithiasis patients can be observed.

Definitive treatment is laparoscopic cholecystectomy.

Cholecystectomy

Laparoscopic cholecystectomy is the treatment of choice. 5% chance of conversion to open procedure can occur in elective cases[41].

Indications: cholelithiasis, mucocele, polyps in gall bladder, cholecystitis.

Contraindication: Absolute - uncontrolled coagulopathy, end-stage liver disease, peritonitis.

Difficult laparoscopic cholecystectomy should be predicted in case of acute cholecystitis, previous upper abdominal procedures, empyema/ gangrenous gallbladder, bilioenteric fistula, obesity, pregnancy, VP shunt and cirrhosis.

Preoperative requirements: complete blood count, liver function test, mini renal profile, coagulation profile, chest Xray, ECG, DVT prophylaxis, antibiotic coverage and an informed consent for the procedure.

Complications: mortality rate is 0.1%, injury to bile ducts in 0.5%, bile leaks, cholangitis. Late complication - post cholecystectomy syndrome, post cholecystectomy choledocholithiasis due to biliary tree infestation with Ascaris lumbricoids / Clinorchis sinensis.

Other alternatives

Dissolution therapy

Oral bile acids can dissolve cholesterol stones. Chenodeoxycholate and ursodeoxycholate decreases cholesterol supersaturation of bile.

Extracorporeal shock wave lithotripsy (ESWL)

Fragmentation of calculi is attempted with shock wave lithotripsy and remaining fragments are treated with dissolution therapy. Should be done on patients with patent cystic duct. Complications include pancreatitis and biliary colic.

THYROID GLAND

Thyroid is shield shaped gland located near thyroid cartilage posterior to strap muscles in the neck. It is covered by a loose connective fascia from deep cervical fascia. Lobule is the functional unit which contains 25-50 follicles, where thyroglobulin is stored. Arterial supply is from superior & inferior thyroid arteries and superior & middle thyroid veins drains into internal jugular vein at level of carotid bifurcation. Inferior thyroid vein drains directly into brachiocephalic vein. Cervical sympathetic ganglia give sympathetic innervation and parasympathetic innervation is through Vagus nerve.

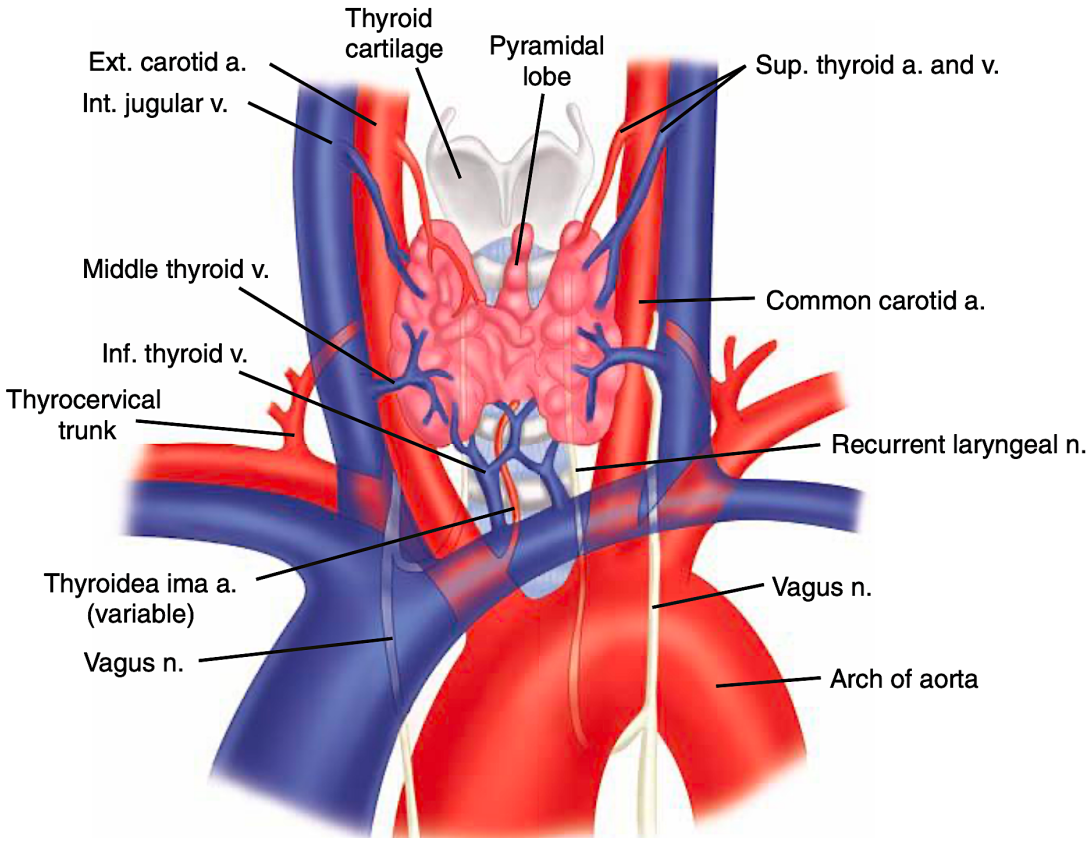

Fig. 12. Anatomy of the thyroid gland and surrounding structures

PHYSIOLOGY OF THE THYROID GLAND

Thyroid gland produces L- thyroxine (T4), triiodothyroxine (T3) and calcitonin. Iodine is essential for thyroid hormone synthesis. Daily iodine requirement is 0.1mg and is rich in milk, egg and milk. From stomach and jejunum, iodine is absorbed, and iodide is formed which rapidly goes to the bloodstream. >90% of body's iodide is in thyroid gland.

THYROID HORMONE SYNTHESIS

L- thyroxine (T4) & triiodothyroxine (T3)

1. Inorganic iodide trapping
2. Iodide to iodine oxidation
3. Tyrosine binding with iodine to form iodotyrosine
4. Monoiodotyrosine and triiodotyrosine coupling to form T3 and T4.

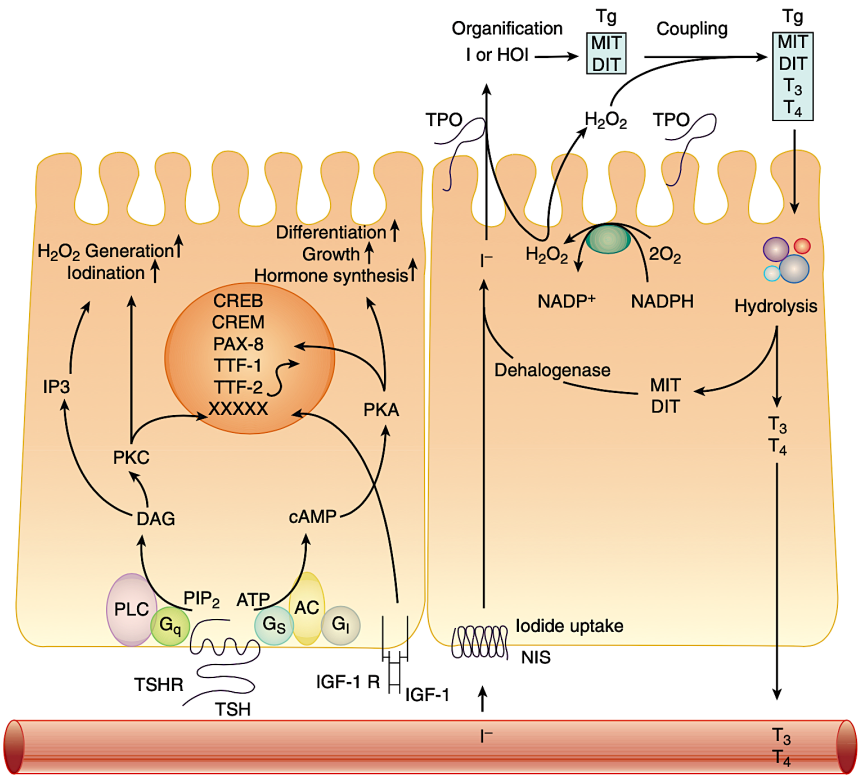

Fig. 13. Key steps in thyroid hormone synthesis

Apical surface of basal thyroid follicle membrane is in contact with circulation. TSH binds to TSH receptor, a G protein coupled transmembrane receptor which initiate hormone synthesis process by rise in cyclic adenosine monophosphate and phosphorylation of protein kinase A. Higher TSH doses activates protein kinase C (PKC) pathway and target cytosolic and nuclear proteins. Via Na/I symporter (NIS), iodide is actively taken up and transported across electric gradient to apical membrane. Oxidation of iodide & tyrosyl iodinated residues on thyroglobulin (Tg) with thyroid peroxidase (TPO) occurs. Coupling of mono & diiodotyrosyl (MIT, DIT) residues occurs forming T3 & T4. Pinocytosed thyroglobulin with T4 and T3 undergoes hydrolysis thereby releasing thyroid hormones to the circulation and MIT & DIT are recycled after deiodination.

Calcitonin is secreted by parafollicular C cells which reduces absorption of calcium and serum calcium in peripheral circulation.

Regulation of Thyroid Hormone Secretion

TSH stimulates thyroid cell differentiation and its growth, hence is a major growth factor for the thyroid. Anterior pituitary gland secretes TSH in a pulsatile manner and has two subunits, α and β. Increased peripheral levels of s.T3 and s.T4 cause a negative feedback to affect TSH secretion. In the pituitary gland, T4 gets converted to T3 affecting the synthesis and release of TSH. Wolff-Chaikoff effect, if there is excess iodine then there is an initial increased organification followed by suppression.

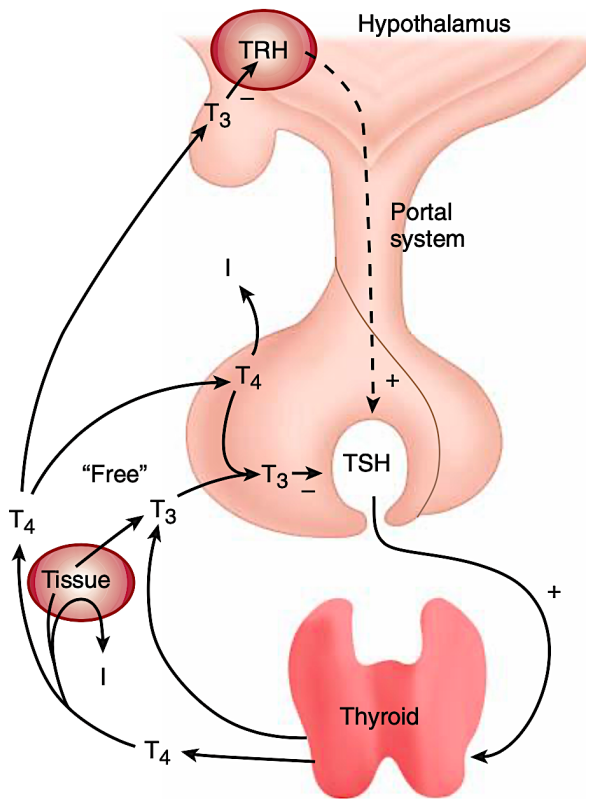

Fig. 14. Hypothalamic-pituitary-thyroid hormone axis.

HYPOTHYROIDISM

Condition where circulating thyroid hormones levels are reduced.

Primary hypothyroidism

Condition with raised TSH levels.

Causes: Hashimoto's thyroiditis, excess iodine intake, post RAI therapy, antithyroid drugs, post thyroidectomy or rarely dyshormogenesis.

Secondary hypothyroidism

Condition with low TSH levels.

Causes: pituitary tumors, pituitary resection or ablation.

Tertiary hypothyroidism: occurs in case of thyroid hormone resistance or hypothalamic insufficiency.

CLINICAL FEATURES

In children, characteristic facies like Down's syndrome and neuro-intellectual defects is usually present- Cretinism. Irreversible damage occurs if not diagnosed or treated early. Umbilical hernia and rectal prolapse are also common in them.

In adults, common features include weight gain, tiredness, cold intolerance, hair loss, constipation and menorrhagia in women.

Myxedema due to glycosaminoglycan deposition in subcutaneous tissues causing facial and orbital puffiness. Reduced conversion of carotene to vitamin A causes yellowish hued skin. Secretions from sebaceous and sweat glands are reduced causing dry and rough skin and hair. Madarosis- loss of outer two third of the eyebrows. Carpal tunnel syndrome occurs due to compression of median nerve.

Fatigue can be explained due to the reduced uptake of glucose by tissues.

Cardiovascular features: bradycardia, reduced cardiac output, cardiomegaly and pericardial effusion can occur. ECG shows prolonged PR interval, ST changes, low amplitude QRS & P wave and T wave inversion.

Respiratory features: pleural effusion

GI complaints: reduced appetite, weight gain, peristalsis is reduced causing constipation, myxedema Ileus- colicky pain abdomen and vomiting due to gaseous distension.

Impaired slow speech due to swollen tongue.

Infertility and loss of libido in both sexes. Decreased secretion of luteinizing hormone causes abnormal endometrial proliferation causing breakthrough bleeding.

Pernicious / macrocytic anemia can occur in hypothyroidism. Bleeding tendency is more due to reduced factor VIII and IX.

THYROIDITIS

Acute thyroiditis

Occurs secondary to infection, 70% due to Streptococci or anaerobes. Common among children. Infectious agents enter either through hematologic/ lymphatic route, penetrating injury, direct spread from adjacent infections or in immunosuppressed state. IV antibiotics and drainage can improve the condition.

Subacute/ painful thyroiditis

Occurs post viral infection where follicular cells are damaged by cytotoxic T lymphocytes, stimulated by the macrophages. Patients complaint of radiating neck pain to ear/ mandible. 20-30% have a hypothyroid phase. It is often self-limiting, and thyroidectomy is advised if not resolved.

Painless thyroiditis

It is often autoimmune, common among women 6 weeks postpartum with raised TPO antibodies. It can be treated with thyroid hormones and beta blockers.

Hashimoto's/ lymphocytic thyroiditis

It is a chronic autoimmune process. Thyroid antigen specific CD4 T lymphocytes are formed which round up cytotoxic CD8 T cells to thyroid and destructs thyrocytes.

Apoptosis is again aided by autoantibodies against TPO, Thyroglobulin or TSH-R. It is common in mid aged women.

Reidel's Thyroiditis

It is a rare condition where fibrous tissue replaces part or whole of thyroid parenchyma and invades nearby tissues. Definitive treatment is thyroidectomy. Hormone replacement therapy and steroids are also given.

Iodine deficiency (Endemic Goiter)

More than 10% of the population is affected. Prevalence is high in hilly areas and has been reduced greatly with the introduction of iodized salt in the diet.

Iodide excess

Intake of large amount of inorganic/ organic iodine can cause goiter in patients with history of autoimmune disease, radio iodine ablation therapy or hemithyroidectomy. Organic binding inhibition and failure of escape occurs leading to increased iodide transport. Increased TSH levels secondary to reduced hormone synthesis tries to increase organic binding further creating a vicious cycle.

Drugs Blocking Thyroid Hormone synthesis & release

Lithium: thyroid hormone release is inhibited.

Salicylic acid, ethionamide blocks organic binding of iodine.

Interfere With Binding to TBG

Salicylates
Carbamazepine
Diazepam
Furosemide
Sulfonylureas
NSAIDs
Heparin (intravenous)
Enoxaparin

Increased TBG Concentrations

Estrogen
Heroin, methadone
Clofibrate
5-Fluorouracil
Tamoxifen

Decreased TBG Concentrations

Androgens and anabolic steroids
Glucocorticoids
Nicotinic acid

Goitrogens in food

Cabbages, turnips etc contain thiocyanate

Genetic conditions

Autosomal recessive condition. Thyroid agenesis, aplasia or dysplasia.

Pendreds Syndrome: hypothyroidism with deafness.

Post –ablative hypothyroidism

Hypothyroidism occurring secondary to destruction of remnant thyroid tissue by radioiodine ablation therapy. Incidence depends on the amount of remnant thyroid tissue and frequency of ablation given.

Central hypothyroidism

Hypothyroidism secondary to congenital or acquired hypothalamic or pituitary disorders. It is less severe than other types of hypothyroidism.

Resistance to Thyroid hormones

Mutations in one allele of TR-22 beta (TR-β) gene is responsible for resistance by affecting the binding capacity of TSH- R. They usually show both hypo and hyperthyroid symptoms.

SUB CLINICAL HYPOTHYROIDISM

Condition where the patient is asymptomatic with elevated S.TSH and normal circulating thyroid hormone levels.

THYROID PROFILE

1. Thyroid stimulating hormone
2. Free T3
3. Free T4

TSH is an indicator for thyroid functional reserve. In primary hypothyroidism, TSH levels are markedly increased with low hormone levels. In all types of hypothyroidism, hormone levels are reduced except in case of hypothyroidism due to resistance. In case of normal TSH levels with low thyroid hormone levels, the possibility of other endocrine disease should be ruled out. Post-hyperthyroid hypothyroidism is a condition where there is continued TSH suppression even though hypothyroidism is induced by thyroidectomy or ablation therapy.

GALLSTONES AND HYPOTHYROIDISM

There are many factors contributed by hypothyroidism which can lead to formation of gallstones in the literature.

Hepatic cholesterol metabolism and bile secretion

Hypothyroidism causes reduced metabolism of cholesterol in the liver thereby increasing serum cholesterol levels. Hepatic bile acid secretion is reduced. This leads to derangement in cholesterol- bile acid ratio causing supersaturation of bile forming cholesterol stones.

Bile flow into duodenum

Delayed bile flow and biliary contents into duodenum in hypothyroidism causes bile stasis.

Sphincter of Oddi (SO) dysfunction

Thyroxine is said to have a prorelaxing effect on SO that express Thyroid Receptor, TR beta 1 and TR beta 2. Low thyroxine levels thus keep SO contracted leading to biliary stasis. This gives time for cholesterol crystals to nucleate and form calculi.

Binding of thyroxine to nuclear proteins inside the nucleus (thyroid receptors) initiates the regulation of TH responsive genes that encodes TR b1 and TRb2. They are demonstrated to be expressed in the SO in the literature. The opening of cell membrane K+ channels which is regulated by protein translated by mRNA and simultaneous closure of Ca2+ channels occurs in the cell membrane reducing the influx of Ca2+. This results in reduced contraction of SO. This theory explains the SO dysfunction in hypothyroidism[18].

CHAPTER V

MATERIALS AND METHODOLOGY

A prospective, hospital based cross-sectional study was done on patients admitted for the management of gall stone disease in the Department of General Surgery in KLE's Dr Prabhakar Kore Hospital, Belgaum during January 2019 – December 2019.

INCLUSION CRITERIA- Patients with cholelithiasis.

EXCLUSION CRITERIA- Patients with

1.History of hypothyroidism/ thyroidectomy.

2.History of hemolytic diseases.

3.Patients with concomitant co-morbidities especially diabetes mellitus type II, renal stones, stones in pancreatic duct.

4.Women taking oral contraceptive pills.

5.Pregnancy.

6.Sepsis or cholangitis.

7. Drugs such as phenytoin, carbamazepine, metoclopramide, amiodarone, and lithium.

SAMPLING TECHNIQUE: Universal sampling.

SAMPLE SIZE AND CALCULATION:

The sample size calculation was calculated based on the following formula.

$$n = \frac{Z^2 \times p \times q}{d^2}$$

Where,

n = Sample size

Z = 1.96 approximated to 2 (considering confidence as 95%)

p = prevalence

q = 100- p

d = Absolute precision

One-year cross sectional study by Maharajan et.al[43] in Tamil Nadu showed a prevalence of 38% hypothyroidism among patients with gallbladder stones.

In this current study, expecting similar results with 95% confidence levels and 10% absolute precision in the result, the study requires a minimum of 94 subjects. So, p = 38, q = 62 and d = 10.

n = (4 x 38 x 62) / 100

= 94.24

METHODOLOGY:

The patients were screened firstly as per the proforma. To all selected patients meeting the inclusion criteria, an informed written consent to participate in the study were given and were explained about the study and its implications. Detailed history was obtained with special reference to symptomatology and the risk factors as per proforma. Clinical examination was performed, and findings were recorded as per proforma. Thyroid function test was done on all eligible patients with GB stone.

S.TSH level is usually the initial laboratory test for screening of dysfunction of thyroid if absence of hypothalamic / pituitary pathology is confirmed. Thyroid dysfunction is confirmed in presence of raised or reduced S.TSH levels but can't diagnose the cause. Hyperthyroidism is diagnosed with reduced TSH & high serum levels of free T4 and/or free T3.

Patients were divided according to history, clinical examination and laboratory test (FT3, FT4, and TSH) into three groups according to hospital values,

S.TSH – 0.27-4.2microIU/ml

F.T4- 0.93-1.7mg/dl

F.T3- 2-4.4 mg/dl

Group 1: **Euthyroid group** - clinical and laboratory tests were normal.

Group 2: **Subclinical hypothyroidism** - asymptomatic and with TSH concentration above the upper limit of normal range and FT4 and / or FT3 within normal limits. (According to our laboratory readings)

Group 3: **Clinical hypothyroidism** - symptomatic and with TSH level above the upper limit and FT4 and/ or FT3 decrease below the normal limit.

STATISTICAL ANALYSIS

Data collected was entered in MS Excel spread sheet, analyzed & expressed as percentage.

Percentage of gall stones in different age groups, gender and types of occupation of the study population was calculated followed by prevalence of hypothyroidism and subclinical hypothyroidism in all the patients included in the study.

CHAPTER VI

CLINICAL OBSERVATIONS

This section deals with the discussion of various data and clinical history of patients for investigating the prevalence of hypothyroidism in gall bladder stones. A total of 100 random patients meeting the inclusion criteria were selected and their data was collected.

Gender Ratio of Patients

In this study, out of the 100 patients, 40 % were male and 60 % were female.

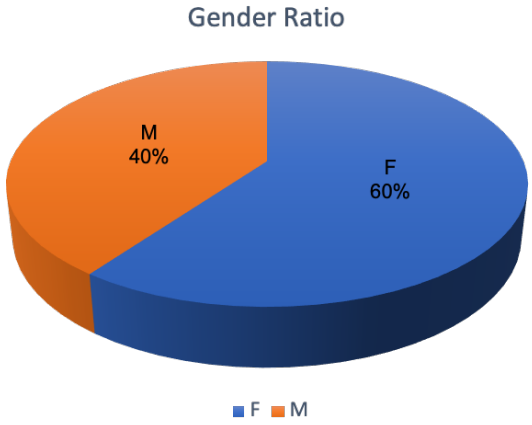

Fig. 15 Gender Ratio

Age Distribution of Patients

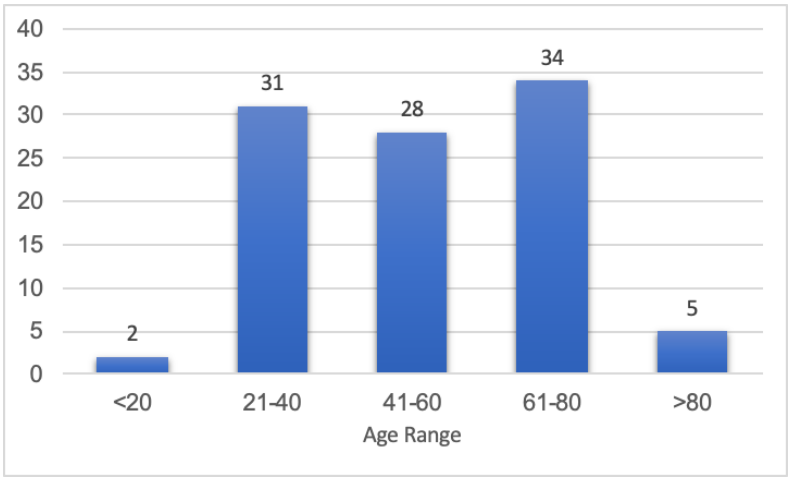

Fig. 16. Age Distribution of Patients

Among the 100 patients, 2 patients were below 20 years, 31 patients were in the range of 21 – 40, 28 were between 41 to 60, 34 patients fall between 61 to 80 years of age. There were 5 patients who are above 80 years.

Occupation Distribution of Patients

In the current study, the majority of the patients i.e., 46 % were semi-skilled. 26% belonged to un-skilled category. 14% were found to be skilled labors and only 2 % were professionally employed. 12% patients were unemployed.

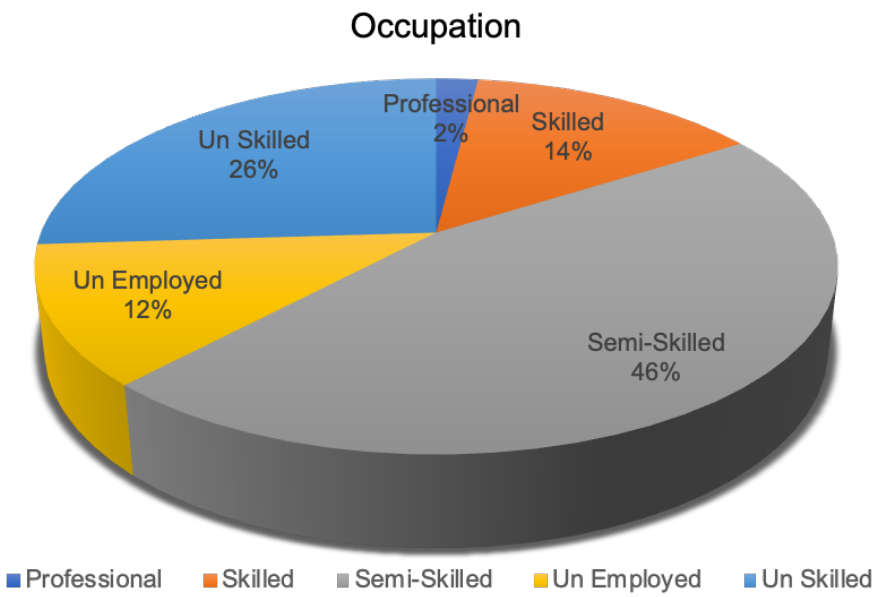

Fig. 17 Occupation of patients

Educational Qualification of Patients

Out of 100 patients, 35 had primary education and 28 of them had appeared till high school. 18 % of the patients completed degree and 18% of them completed intermediate. Only 1% patents were illiterate.

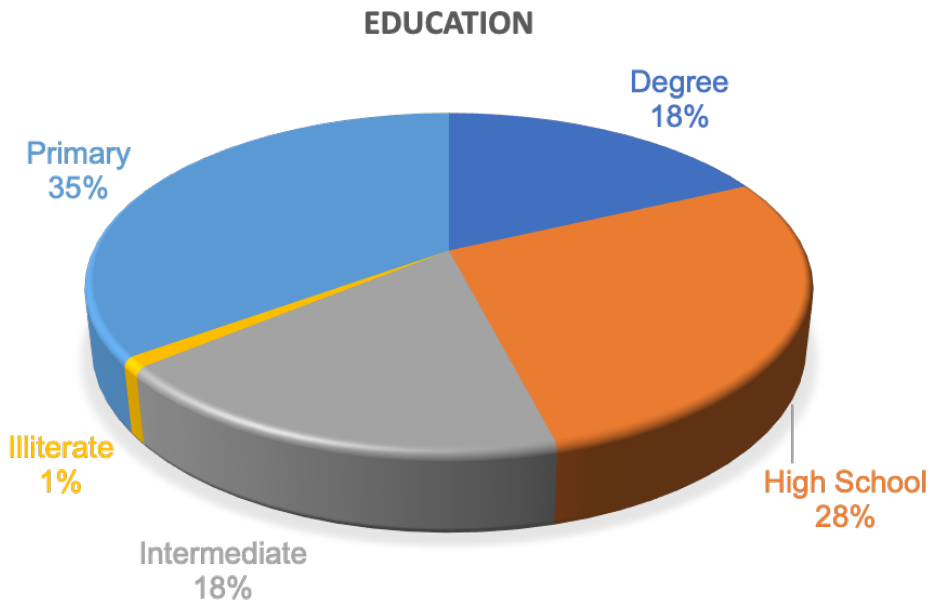

Fig. 18 Education of patients

Thyroid Status of Patients

Among 100 patients, 71 of them were euthyroid and 23 of them were identified to have subclinical hypothyroidism and 6 of were diagnosed with hypothyroidism.

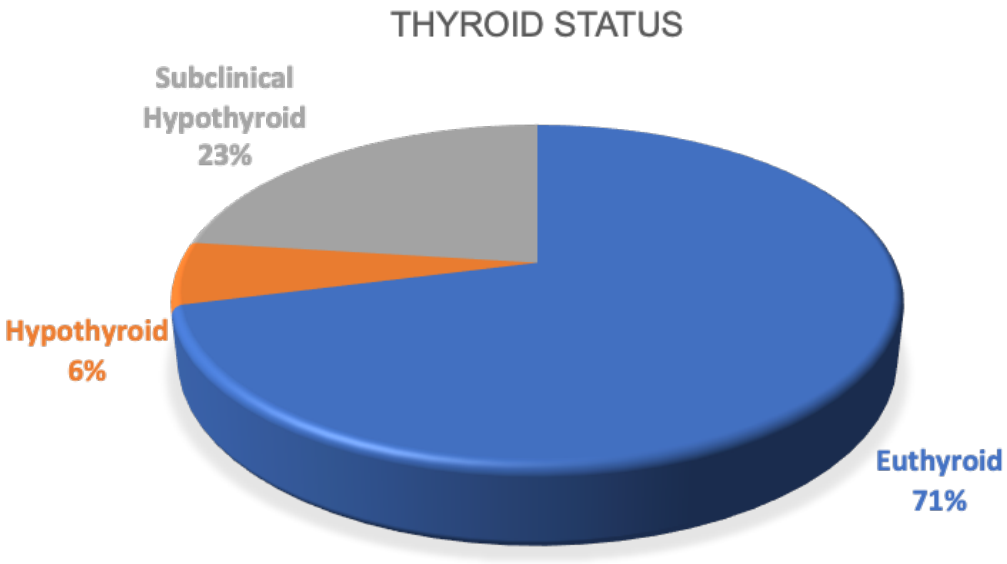

Fig. 19 Thyroid status of patients

Gender Distribution of Hypothyroid Patients

Of 71 euthyroid patients, 38 were female and 33 were male. In the case of subclinical hypothyroidism, there were 17 females and 6 males. Out of 6 % diagnosed with clinical hypothyroidism, there were 5 females and only 1 male. 75.8% females and 24.1% males were diagnosed as hypothyroid in the study.

Table 1: Gender Distribution of Thyroid Status

SEX	Euthyroid	Hypothyroid	Subclinical Hypothyroid
Female	38	5	17
Male	33	1	6

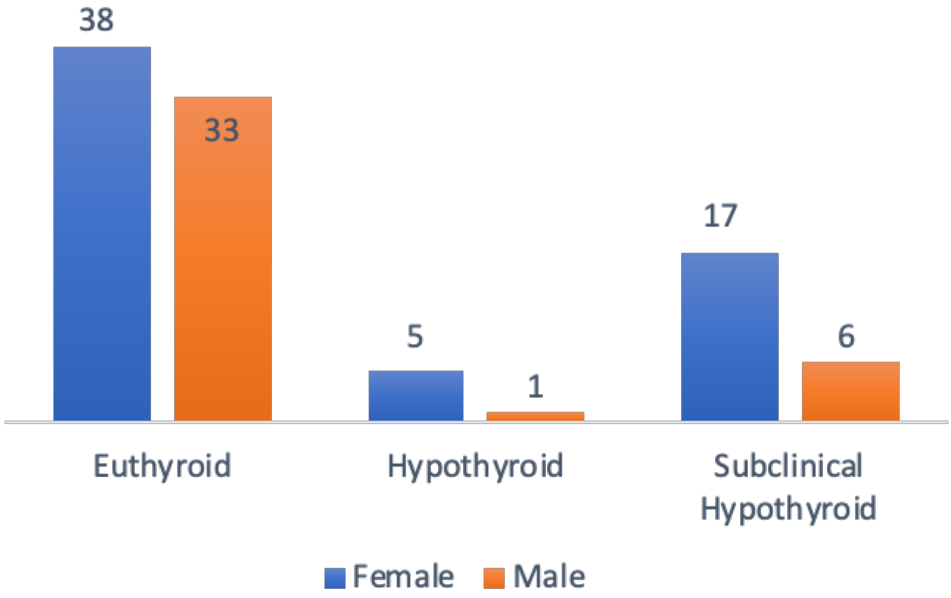

Fig. 20 Gender Distribution of Thyroid Status

Age Group Distribution of Thyroid Status - Euthyroid

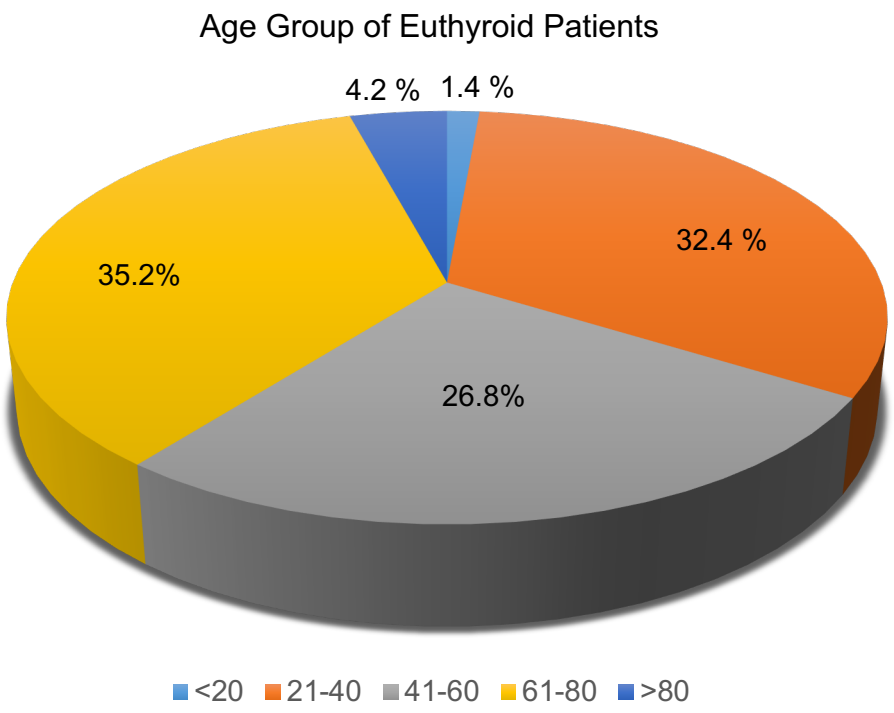

Fig. 21 Age Group Distribution of Thyroid Status – Euthyroid

Among the 71 euthyroid patients, 35.2 % were aged between 61-80 years. 32.4 % was in the range of 21-40 years. 26.6 % is found to be between 41-60 years. Patients aged <20 years and >80 years were found to be 4.2 % and 1.4 %.

Age Group Distribution of Thyroid Status – Subclinical Hypothyroid

In the subclinical hypothyroid group, majority (39.13 %) were aged 41-60 yrs. Age groups < 20 years and greater than 80 years were in equal distributions of 4.35 %. Age groups of 21-40 years and 61-80 years have a distribution of 30.43 % and 21.74 % respectively.

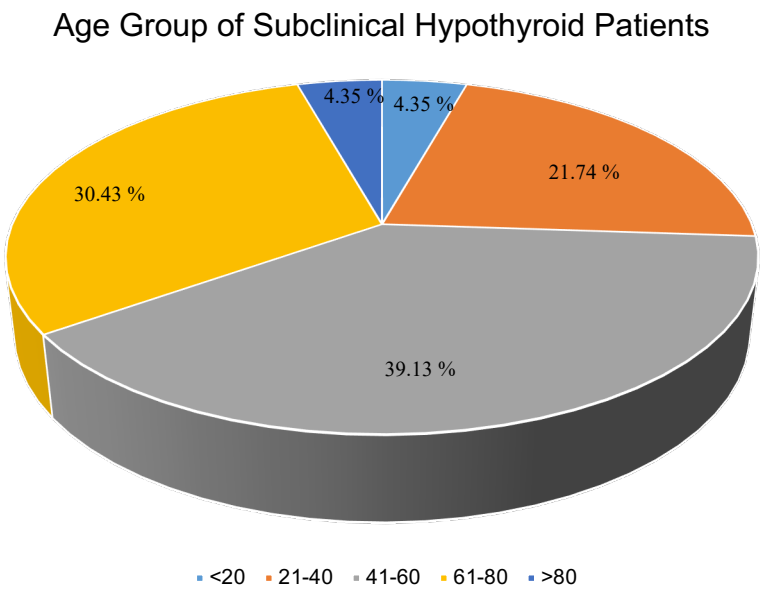

Fig. 22 Age Group Distribution of Thyroid Status – Subclinical Hypothyroid

Age Group Distribution of Thyroid Status – Hypothyroid

Among the hypothyroid group of 6 patients, most of them (50 %) were in the range of 21-40 years of age. There were no patients in the range of less than 20 years and in between 41 to 60 years. 17 % of the patients were above 80 years of old and 33 % were in between 61 years and 80 years.

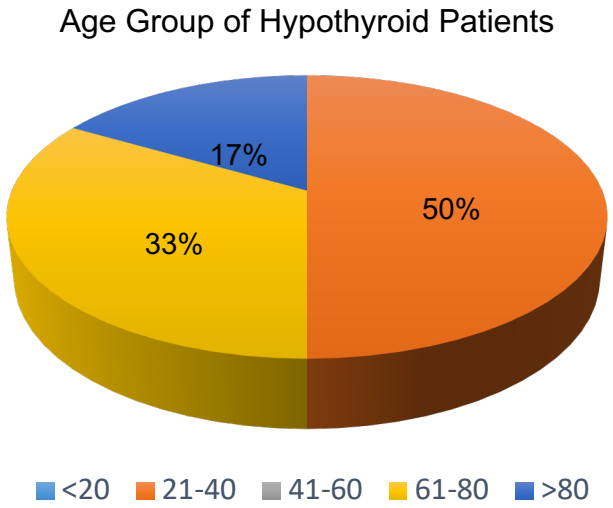

Fig. 23 Age Group Distribution of Thyroid Status –Hypothyroid

Table 2: Thyroid Status of Patients Against Age and Gender

Age range	Euthyroid		Subclinical Hypothyroid		Hypothyroid	
	Female	Male	Female	Male	Female	male
<20 years	1	0	1	0	0	0
21-40 years	19	4	5	0	3	0
41-60 years	9	10	7	2	0	0
61-80 years	7	18	4	3	1	1
>80 years	2	1	0	1	1	0

Among the 71 euthyroid patients, there were only 1 female patient in the age group of below 21 years. Between 21-40 years, 19 were female and 4 were male. However, in 41 - 60 years, female & male patients were 9 and 10 respectively. There were higher number of male patients (18 patients) in the age range of 61-80 years where female patients were only 4. There were 2 female and 1 male patients in the age group of above 80 years.

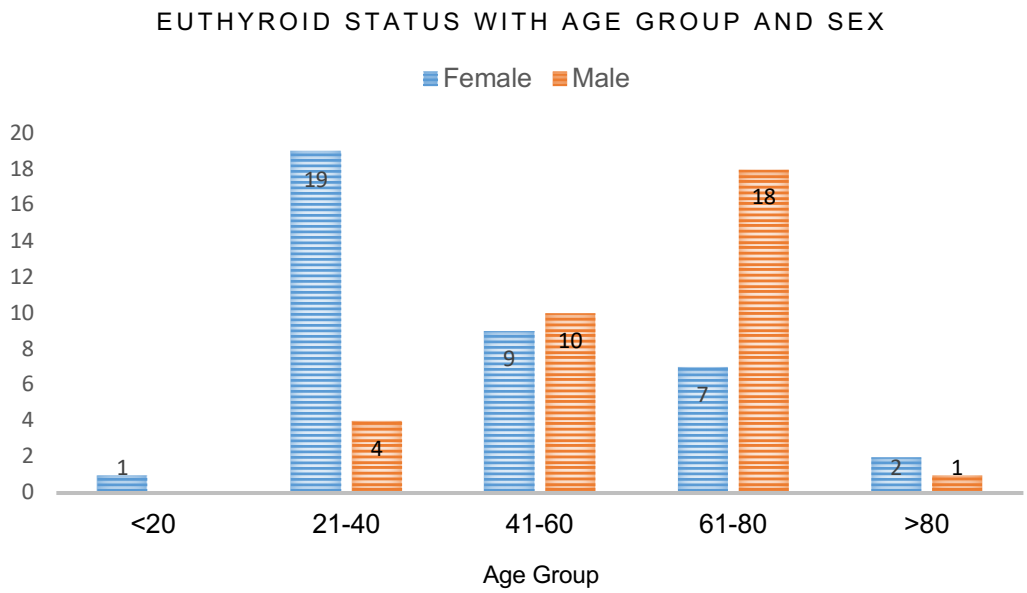

Fig. 24 Euthyroid status with age group and sex

Among the 23 subclinical hypothyroid patients, only 1 female patient was in the group range of below 20 years. Similarly, in 21 -40 years age group, there were 5 female patients, and no male was found. Of 9 patients in group of 41-60 years, 78 % were female & 22 % were male. Among the 7 between 61-80 years, 4 were female patients and 3 were male. Only 1 female patient was found in the age range of more than 80 years.

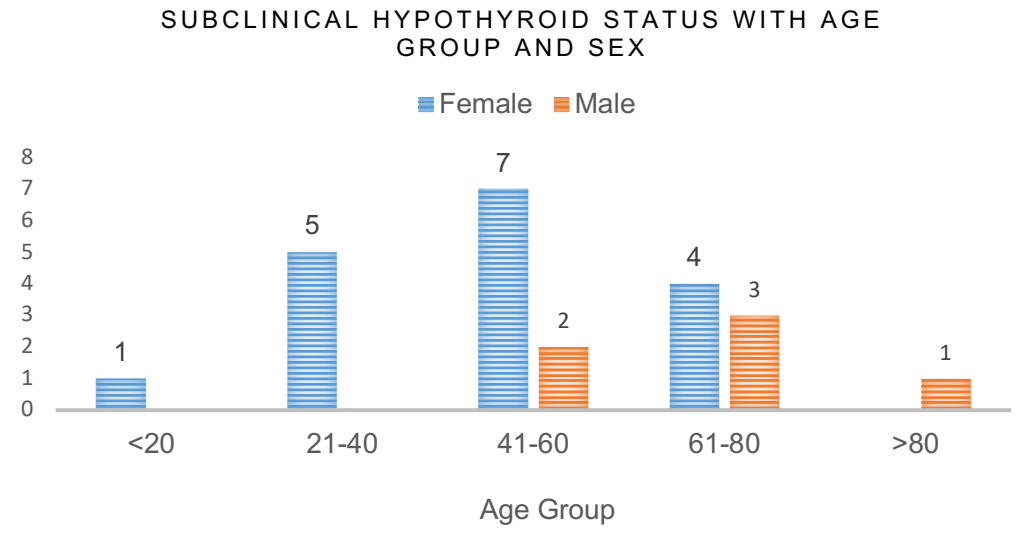

Fig. 25 Subclinical hypothyroid status with age group and sex

Out of the 6 cases of hypothyroids, 50 % were female, in group of 21-40 years. One female & male patients were in age group of 61-80 years. Above 80 years, only one female patient was found.

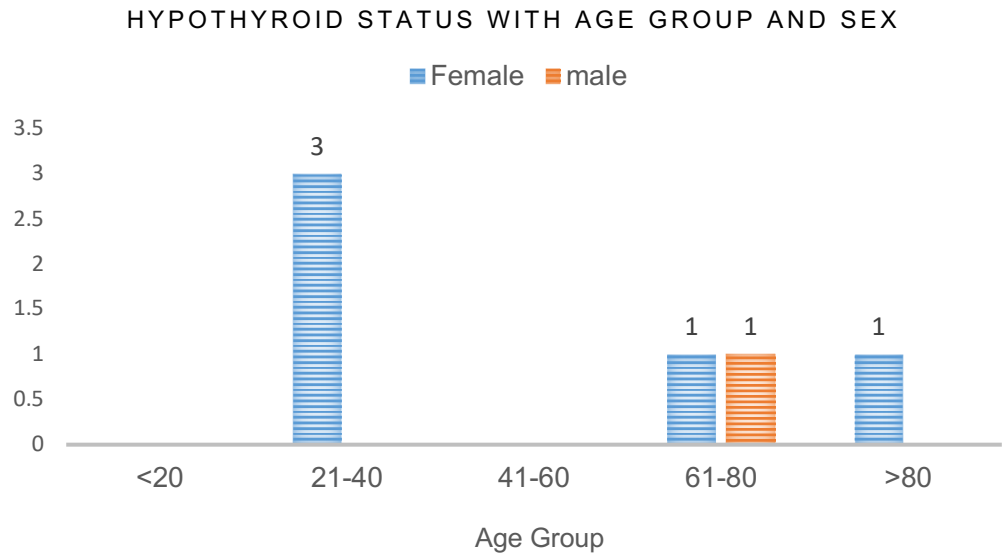

Fig. 26 Hypothyroid status with age group and sex

Symptoms and Thyroid Status of Patients – Abdominal Pain

Among the 71 patients under euthyroid category, 54 % of the patients (38 patients) was found to have abdominal pain for a period of less than a month and 46 % (33 patients) had abdominal pain for more than 1 month.

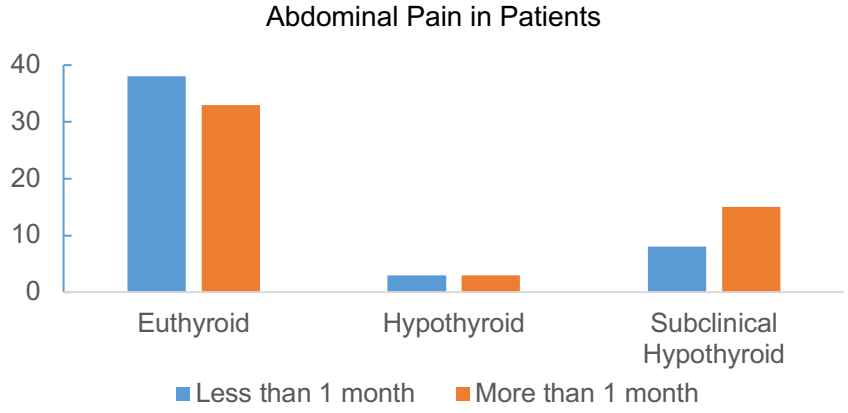

Fig. 27 Pain abdominal and thyroid status

Among the total 23 cases of subclinical hypothyroid group, 35 % of the patients (8 patients) had abdominal pain for a period of less than 1 month and 65% of them (15 patients) had abdominal pain for more than 1 month.

However, in the case of hypothyroid category, out of 6 patients, 50 % had less than one month of abdominal pain and other 50 % had it over a period of more than one month.

Symptoms and Thyroid Status of Patients – Cold Intolerance

None of the euthyroid patients had cold intolerance. Among subclinical hypothyroid group, 13% of them (3 patients) had shown cold intolerance.

In case of hypothyroid category, majority (66 %) had reported cold intolerance and 34% of the patients did not have cold intolerance.

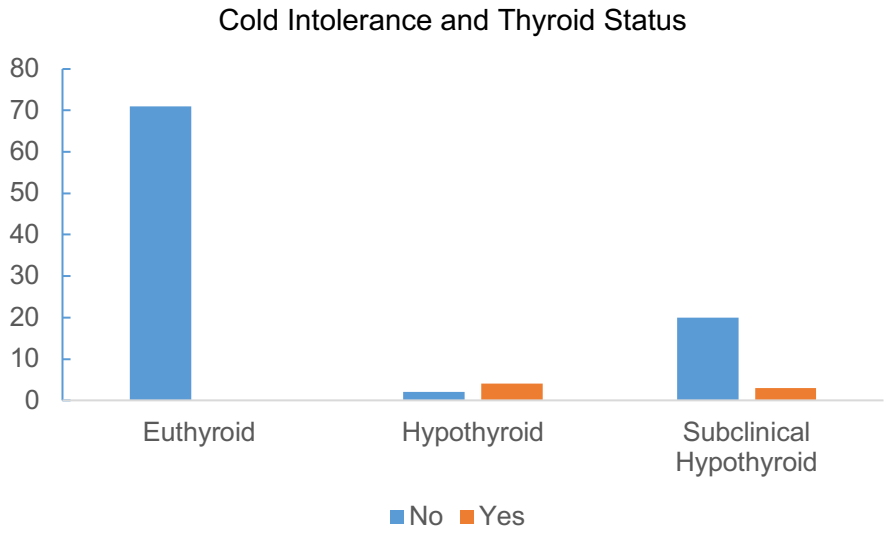

Fig. 28 Cold intolerance and thyroid status

Symptoms and Thyroid Status of Patients – Constipation

Under euthyroid category, only 3 % (2 patients) had constipation.

Among the 23 cases of subclinical hypothyroid group, 16 patients had complaints of constipation.

However, in the case of hypothyroid category, out of 6 patients, 66 % had history of constipation.

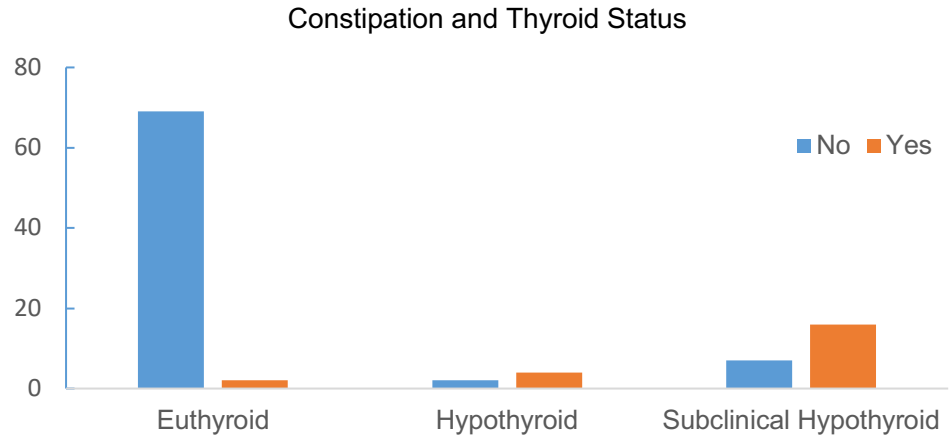

Fig. 29 Constipation and thyroid status

Symptoms and Thyroid Status of Patients – Loss of Appetite

Among the 71 patients under euthyroid category, a majority (66 patients) had no complaints of loss of appetite and rest 4 % (5 patients) had loss of appetite.

In subclinical hypothyroid group, 57 % (13 patients) had loss of appetite and 43% of them (10 patients) had no complaints of loss of appetite.

In hypothyroid group, out of 6 patients, most patients (83%) had issues with loss of appetite.

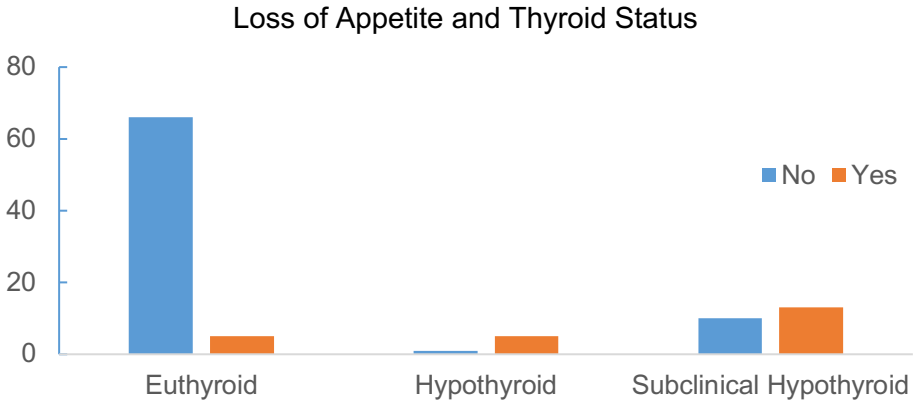

Fig. 30 Loss of appetite and thyroid status

Symptoms and Thyroid Status of Patients – Tiredness

Among euthyroid patients, majority (64) had no complaints of tiredness and rest 10% (7) reported tiredness.

In subclinical hypothyroid group, 43 % of the patients (10) had reported tiredness and 18% of them (13) had not reported tiredness.

In hypothyroid category, out of 6 patients, 50 % of the patients in hypothyroid category had reported tiredness.

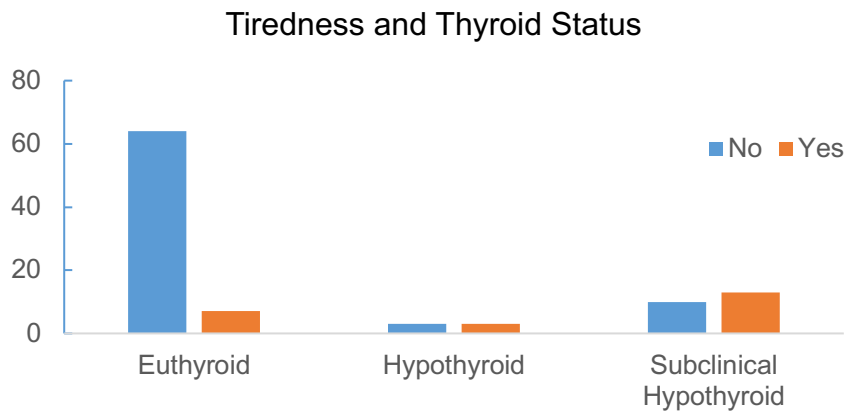

Fig. 31 Tiredness and thyroid status

Symptoms and Thyroid Status of Patients – Weight Gain

Under euthyroid category, majority with 94% patients (67 patients) had no weight gain and rest 6 % (4 patients) had weigh gain.

Among subclinical hypothyroid group, 48 % (11 patients) had not shown weight gain and 52% of them (12 patients) had reported weight gain.

In the case of hypothyroid category, out of 6 patients, 83 % had reported weight gain and 17% of the patients did not have.

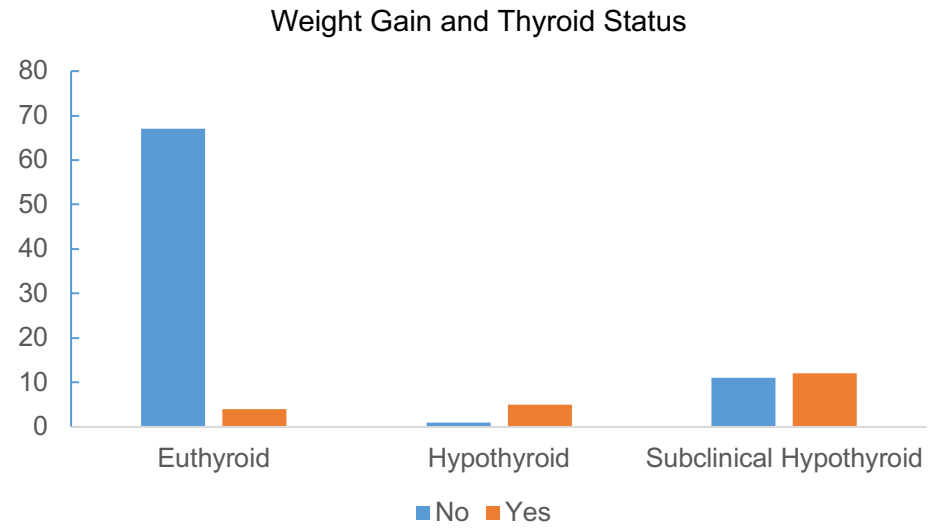

Fig. 32 Weight gain and thyroid status

Symptoms and Thyroid Status of Patients – Menstrual Irregularities

Among the 38 female euthyroid patients, most patients 95% (36 patients) had not reported any menstrual irregularity and rest of 5 % (2 patients) had reported menstrual irregularities.

Among 17 females of subclinical hypothyroid group, 53 % (9 patients) had no menstrual irregularity and 47 % (8 patients) had reported menstrual irregularities.

In hypothyroid category, out of 5 patients, 40 % had not reported any menstrual irregularity. However, 60 % of the female patients with hypothyroid case had irregular menstrual cycles.

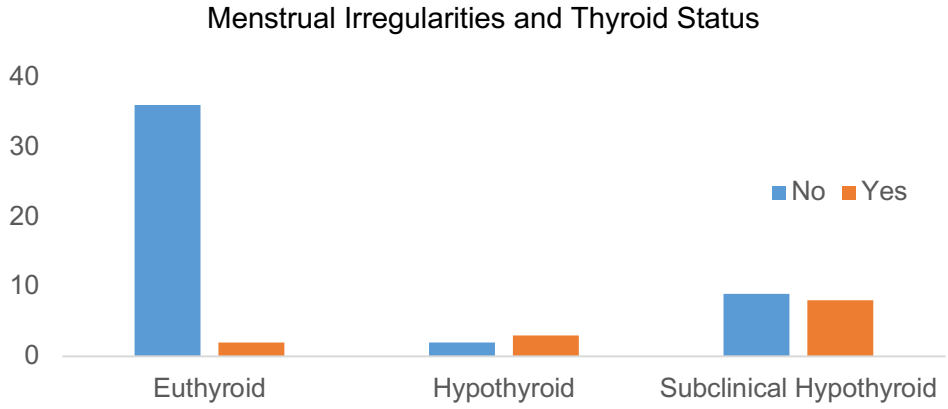

Fig. 33 Menstrual irregularities and thyroid status

Ultrasonography and Thyroid Status

Among the 71 patients under euthyroid category, 7 % (5 patients) were found to have single calculi and 93 % (66 patients) had multiple calculi on ultrasonography.

In subclinical hypothyroid group, 22 % of the patients (5 patients) were found to have single calculi and 78% of them (18 patients) had multiple calculi.

However, in the case of hypothyroid category, all the 6 patients were having multiple calculi.

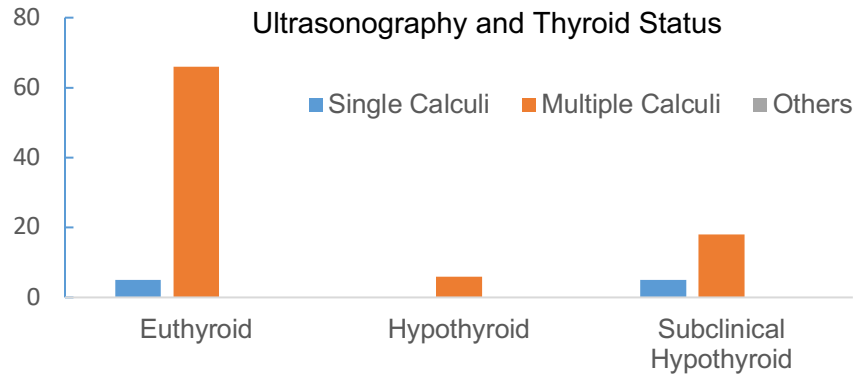

Fig. 34 Ultrasonography and thyroid status

Goitre and Thyroid Status

None of the euthyroid or subclinical hypothyroid patients had goiter. In hypothyroid category, out of 6 patients, only 20 % had reported Goiter.

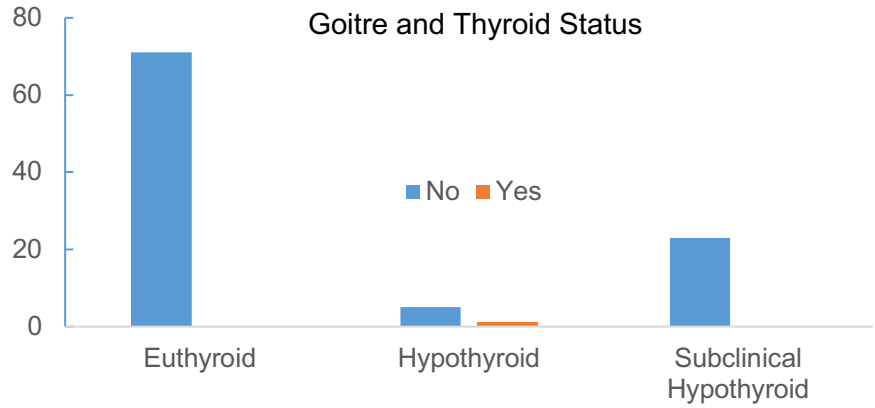

Fig. 35 Goitre and thyroid status

Chapter VII

DISCUSSION

Pathogenesis of gallstone is multifactorial & complex, which affects bile composition and its flow. This study focuses on the prevalence of hypothyroidism in gall stones since hypothyroidism is known to alter hepatic cholesterol metabolism and it reduces bile secretion in liver. Studies have identified presence of thyroid receptors in Sphincter of Oddi causing a pro-relaxing effect. This reflects the formation of gallstones in hypothyroidism.

In this study, 100 random patients meeting the selection criteria were included after taking an informed consent. This study was carried out in Department of General Surgery, KLE's Dr Prabhakar Kore Hospital & MRC, Belagavi during one year between January - December 2019. Out of 100 study population, 40 % were males and 60 % were females. After assessing symptoms and signs, thyroid profile was sent for all. Among 100 patients, 29% were found to have hypothyroidism of which 23 were identified to have subclinical hypothyroidism and 6 were diagnosed with hypothyroidism.

It was observed that, out of subclinical hypothyroid and clinical hypothyroid cases, majority were females accounting 73% and 83% respectively. This clearly highlighting higher prevalence in females for the current study. 35.2 % of euthyroids were aged between 61-80 years. Among hypothyroid group of 6 patients, 50 % were in the range of 21-40 years of age. In the subclinical hypothyroid group, 60.87 % were in the age group more than 40 years with females as majority. This observation suggests that prevalence is more in elderly females than young adults.

Comparing duration of pain abdomen among study population, it was noted that 65% of subclinical and 50% of clinical hypothyroid patients had symptoms for more than one month compared to euthyroid patients. This reflects that, prolonged untreated hypothyroid state buys time for gallstone formation and its growth.

None of the euthyroid patients had cold intolerance whereas 13% of subclinical hypothyroid group and 66% of hypothyroid category had reported cold intolerance. 66% of hypothyroid, 69% subclinical hypothyroid and only 3 % of euthyroid had constipation. Among the 71 patients under euthyroid category, a majority (66 patients) had no complaints of loss of appetite. In hypothyroid group,83% had loss of appetite and it was 57% in subclinical hypothyroid group. Among euthyroid patients, majority (64 patients) had no complaints of tiredness and rest 10% (7 patients) had tiredness. In subclinical hypothyroid group, 43 % and in hypothyroid category, 50 % of the patients in hypothyroid category had reported tiredness. 94% of euthyroid patients had no history of weight gain whereas in subclinical hypothyroid group, 52% and 83% in hypothyroid category reported weight gain. Among the 38 female euthyroid patients only 5 % reported menstrual irregularities but it was 60% and 47% respectively in case of hypothyroid and hypothyroid women. These data show that hypothyroid symptoms are present in patients with gallstones with unknown thyroid status, suggesting routine thyroid profile preoperatively.

Many challenging studies are done all over the world to know the association between thyroid status and biliary stones over years. In 2003, Laukkarinen et al. conducted a case control study in 2 stages by doing 99mTc cholescintigraphy on untreated hypothyroid patients, before and after levothyroxine supplementation & making them euthyroid in Finland[21]. Laukkarinen et al. concluded that delayed biliary emptying may occur in hypothyroidism which leads to CBD calculi formation[21].The current study did not include

but gives a scope for a future interventional study with thyroxin supplementation and study on effects of thyroxin on the size of gall bladder calculi.

In Pomerania, China, Völzke et al. conducted a case control study which included 3749 residents, one of the largest studies and found strong association between hypothyroidism and cholelithiasis in 2005[22] supporting the current study.

A case control study by Laukkarinen J et al., in 2007, included patients with CBD calculi as cases & healthy individuals as controls in Finland[24]. Laukkarinen J et al., noted that subclinical hypothyroidism was 3-4 times common among patients with choledocholithiasis hypothesizing its key role in calculi formation[24]. In 2010, by conducting another similar study, Laukkarinen J et al., hypothesized that CBD calculi develops during untreated phase of hypothyroidism & matures once the treatment starts questioning the efficiency of the treatment[27].

In 2009, Hassan H. Zaini et al. studied on 225 patients with gall bladder stones to know the prevalence of hypothyroidism over one year in Iraq[25]. Hassan H. Zaini et al. reported 10.9% hypothyroidism among study population with a higher prevalence of 9.7% in females over males. In the current study, higher prevalence of 29% hypothyroidism was recorded and was more prevalent among elderly females equivalent to this study. However, Hassan H. Zaini et al., could not find any significant relation between gall stones and hypothyroidism statistically.

Sigal et al. in 2011, did a case control study to understand the association between subclinical hypothyroidism & lipid metabolism in Brazil[28]. Sigal et al. stated that subclinical hypothyroidism alters HDL metabolism and can be reversed to achieve euthyroid state with levothyroxine therapy [28].

In Iran, Ajdarkosh et.al., did a case control study in 2013 to know the association between clinical & subclinical hypothyroidism and stones in biliary tract[29]. Among cases, they reported that 30% had subclinical hypothyroidism & 11% was diagnosed with clinical hypothyroidism and more prevalence were shown among females like in the current study. Ajdarkosh et.al study recommends thyroid profile test in all patients with gall stones or CBD stones as there is strong association between them and thought hypothyroidism as a predisposing factor for the passage of gall stones to CBD[29].

An observational study on 100 patients with biliary calculi was done by Rana Ranjit Singh et.al in Punjab during 2014-2016 to understand the prevalence of hypothyroidism in them. Their gender distribution was similar to the current study. Rana Ranjit Singh et.al. observed that of 41 males, 61% had cholelithiasis and 39% had choledocholithiasis & it was 70% and 30% respectively out of 59 females[31]. 24% males & 24.4% females with cholelithiasis and 18% males & 27.7% females with choledocholithiasis were diagnosed with hypothyroidism. Rana Ranjit Singh et.al also noted that 12% males & 1% females with cholelithiasis and 18.75% males & 1.1% females with choledocholithiasis respectively were found to have hyperthyroidism strikingly. Considering this observation, Rana Ranjit Singh et.al concluded that there is no significant relation between thyroid status and biliary calculi. In the current study, the prevalence of thyroid dysfunction among patients with only cholelithiasis were studied and noted that 36.6% females and 17.5% males were diagnosed with hypothyroidism. None of the patients in current study was diagnosed to have hyperthyroidism. The current study is contradicting with Rana Ranjit Singh et.al study[31] and showed a significant prevalence of 29% hypothyroidism in patients with gallstones.

Cross sectional study by Debabrata Singha et.al among 500 patients with cholelithiasis was done during 2014-2016 in North-East India[32]. They reported 13.8% hypothyroidism in their study, and all were females. Of which 13.6% were subclinical hypothyroid and 0.2% were diagnosed with clinical hypothyroidism. The prevalence rate was higher in the current study compared to Debabrata Singha et.al with sex distribution of 75.8% females and 24.1% males, highlighting the higher prevalence among females.

Yawar Zahoor Watali et.al studied the association of hypothyroidism in gallbladder stones in Delhi on 200 patients with upper abdominal pain for a duration of one year in 2017[33]. They grouped patients depending on presence of gallstones in USG and found no association between prevalence and gender. They noted that, in case control group of 100 patients each, 14 cases with gall stones and 9 controls without gall stones were diagnosed with hypothyroidism. Hence, Yawar Zahoor Watali et.al showed no association between hypothyroidism and gallstones. Incidence of hypothyroidism noted in Yawar Zahoor Watali et.al's study was high in patients aged above 50 years, which goes along with this current study.

Similar study done in Madhya Pradesh, India by Brijendra S R et.al, during 2015-2016 was done on 50 patients with gallstones[34]. Gender distribution was 84% females and 16% males which is higher compared to the current study distribution of 60% females and 40% males. Brijendra S R et.al reports 24% prevalence of hypothyroidism in the total study population with a majority of 91% among females. However, Brijendra S R et.al could not show any significant relation between gallstones specific to gender and hypothyroidism.

The study by Manjusha et.al done in South India during 2016- 2018 on 100 patients with cholelithiasis showed a prevalence of 14% hypothyroidism and majority of the patients were aged more than 40[36]. The current study showed a higher prevalence of 29%

hypothyroidism in gallstones. Gender distribution of Manjusha et.al was 42% males and 58% females like the present study which was 40% males and 60% females. Even though this current study excluded patients with known comorbidities causing gallstones, by Manjusha et.al found no significance between subclinical hypothyroidism and patient comorbidities like diabetes, hypertension, hypercholesterolemia, obesity, smoking or alcohol consumption. Manjusha et.al noticed that, patients diagnosed with hypothyroidism had larger gallstones compared to euthyroid patients. Moderate positive correlation was found between the two and suggested strong significance between hypothyroidism and size of gall stones. Only 75% hypothyroid patients had multiple calculi in Manjusha et.al study, whereas, present study observed that 100% patients with clinical hypothyroid and 78% with subclinical hypothyroidism was having multiple calculi in gall bladder. This reflects that hypothyroid state is having more risk of developing larger and multiple stones in gallbladder.

A study done in North East India for a duration of 6 months in 2018 by Mousumi Das et.al was a case control study to know the prevalence of hypothyroidism in gallstones[37]. They included 50 patients with gall stones as case group & 50 healthy individuals as control group and compared their thyroid profiles which showed a significant association between hypothyroidism and gallstones statistically.

One-year cross sectional study by Maharajan et.al in Tamil Nadu showed a prevalence of 38% among elderly females and have also noted 16% of the population with hypothyroid symptoms mainly easy fatigability[43]. His study also highlighted the presence of hypothyroid symptoms in patients with cholelithiasis with unknown thyroid status equivalent to this current study.

The current study shows a significant prevalence of 29% hypothyroidism in patients with gall bladder stones with higher prevalence among elderly females. The higher prevalence among females could not be proved statistically in most of the studies since prevalence of gall stones itself in female gender is high. The current study lacks information about relationship between S.TSH levels and size & number of the calculi to find if raised TSH level can increase calculi size and number. Further studies are needed to proove, if early detection and treatment of hypothyroidism will reduce the size of calculi.

Chapter VIII

SUMMARY

Cholelithiasis is common biliary pathology and is multifactorial in cause. Contribution of hypothyroidism to gallstone formation is debated over years. The present study conducted during January – December 2019 was to know the prevalence of hypothyroidism in patients with gallbladder stones in the Department of General Surgery, KLE's Dr Prabhakar Kore hospital and MRC, Belagavi.

The study was done on 100 random patients with gall stones after meeting inclusion and exclusion criteria. After informed consent and recording symptoms & clinical examination in proforma, thyroid profile was sent for all patients. They were grouped into euthyroid, subclinical and clinical hypothyroid groups after interpreting the laboratory values. Recorded data was entered in MS Excel spread sheet & expressed as percentage.

It showed a significant prevalence of 29% hypothyroidism in patients with gallstones. 23% were having subclinical hypothyroidism and 6% had hypothyroidism. Higher prevalence among elderly females was noted. It was exposed that patients with cholelithiasis with unknown thyroid status had symptoms related to hypothyroidism. 65% of subclinical and 50% hypothyroid patients had prolonged symptoms like pain abdomen compared to euthyroid patients agreeing with results of previous studies that untreated hypothyroid state augment formation and growth of gallstones.

The study concludes with significant prevalence of hypothyroidism in gallbladder stones and demands further studies to consider hypothyroidism as a cause /risk factor for biliary calculi.

Chapter IX

CONCLUSION

The prevalence of hypothyroidism in cholelithiasis is 29% in the study and is significant. 23% were diagnosed with subclinical and 6% with clinical hypothyroidism. This study also shows higher prevalence among females aged more than 40 years of age.

Hypothyroid symptoms were shown by the study population with unknown thyroid status which highly recommends thyroid profile testing preoperatively. This also helps in workup of patients with gallstones therapeutically.

Further studies on early diagnosis and treatment of hypothyroidism causing prevention or reduction in the size of biliary calculi should be done so that we can conclude with hypothyroidism as a specific risk factor for cholelithiasis and all patients with gall stones should be screened for thyroid dysfunction.

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K.L.E. ACADEMY OF HIGHER EDUCATION AND RESEARCH
(Deemed – to- be- University)
Accredited 'A' Grade by NAAC (2nd Cycle) Placed in Category 'A' by MHRD (GoI)
JAWAHARLAL NEHRU MEDICAL COLLEGE,
NEHRU NAGAR, BELAGAVI-590010 (KARNATAKA-INDIA)
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Fax No. +91 (0)831 – 2470759

Ref: MDC/DOME/03 **Date: 24/11/2018**

To,

Reg. No: BH0118003

PG student in Surgery,
J.N.Medical College,
BELAGAVI.

Sub: Institutional Ethical Clearance for the study.

With reference to the above, we wish to inform you that your proposed research project titled **"ONE YEAR STUDY OF PREVALENCE OF HYPOTHYROIDISM IN PATIENTS WITH GALL BLADDER STONES AT KLE'S DR PRABHAKAR KORE HOSPITAL AND MRC, BELAGAVI",** is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee on Human Subjects Research.

(Dr. Arathi Darshan)
Member Secretary
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

(Dr. Roopa M Bellad)
Chairman,
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

ANNEXURE I

CONSENT FOR PARTICIPATION IN RESEARCH STUDY

Mr. /Mrs. /Miss. _____ we are requesting you to enroll yourself in study titled "ONE YEAR STUDY OF PREVALENCE OF HYPOTHYROIDISM IN PATIENTS WITH GALL BLADDER STONES AT KLE'S DR PRABHAKAR KORE HOSPITAL & MRC, BELAGAVI -590010" conducted by Postgraduate student (Reg. No: BH0118003) in M.S. General Surgery, Jawaharlal Nehru Medical College, Belagavi under KLE University, Belagavi.

Respected Sir/Madam,

We request you to enroll yourself to participate in our study as you are eligible for the study.

Purpose of the study

Gall stones are the most common gallbladder pathology. There has been a discussion for decades, whether thyroid disorder could cause gall stone diseases. Since hypothyroidism and gall stone disease are affecting a larger population in developing countries especially in elder women, this study intends to analyse the prevalence of previously undiagnosed hypothyroidism in patients with gall stones and try to establish hypothyroidism as a likely cause for gallstones. The role of hypothyroidism with respect to gall stone formation in human beings is currently not well investigated and further research is needed. If an increased prevalence of thyroid disorder is found in patients associated with gall stones, it may influence diagnostic and therapeutic workup of the patients with gall stones.

Type of study: This is a cross-sectional study.

Participant selection

We are inviting all gallbladder stone patients who visit our hospital in General Surgery department for further management to participate in this study.

Voluntary participation

Your participation in research is voluntary. It is your choice whether to participate or not. Your decision whether to participate in the study or not will not change present or future health care services offered to you and will not affect your relationship with J.N. Medical College. If you choose not to participate in this study, you will still be offered the routine treatment given at our hospital. You will continue to receive the routine care at our hospital even if you decline to participate in this study. If you decide to participate you are free to withdraw at any time.

Procedure

Once you have signed the informed consent, necessary personal information, detailed medical history and clinical examination will be taken by the investigator. After this, you will be divided according to history, clinical examination and lab estimation. Sub-clinical hypothyroidism - symptom free patient with TSH concentration above upper limit of normal range and T3 /T4 or both decrease below normal limit. Clinical hypothyroidism - in which there are symptoms of hypothyroidism with TSH levels above the normal limit and T3/T4 or both decrease below normal limit. Euthyroid group: where clinical and lab tests within normal range.

Risks and Benefits

No possible risks are expected.

Benefit of the study: It may influence diagnostic and therapeutic workup of gall stones and helps to detect and treat undiagnosed hypothyroidism as well, thereby decreasing morbidity.

Alternatives

Your participation in this study is entirely voluntary. You are free to refuse to participate or withdraw from the study at any time. You will still receive standard medical care from the hospital. The investigator holds the right to terminate the study at any time. You will be informed about any new information that may affect your decision to participate in the study.

Privacy and Confidentiality

Any information collected during the study will remain confidential. The only people who will know that you are the research subject will be the members of the research team. No information about you or information provided by you during the research will be disclosed to others without your written permission except:

1. In emergency to protect your rights and welfare.
2. If required by law.

Financial Incentives for participation

No financial incentives are being offered to enrolled patients. It is purely being done with the idea of research and all the cost of the study will be borne by the investigator.

Authorization to Publish Results

The information about you will be analysed together with other study participants. Results of this study will be published and presented in scientific groups for scientific purposes, but no information will be displayed that would disclose your identity. Any information that is obtained in connection with this study and that can be identified with you will remain confidential.

Right to refuse or withdraw from study:

You do not have to participate in this research if you do not wish to. You can withdraw at any time from the study. There will be no penalty for withdrawal. Your treatment and care in this hospital will not change irrespective of whether you agree to participate or not. You can be removed from the study if necessary.

Institutional Policy

In the event of any injury related to the study, treatment will be made available through KLE's Hospital & MRC, Belgaum. There is no compensation or payment for such medical treatment by law. If you are injured you may contact Department of General Surgery, KLE's Hospital& MRC.

Contact details:

In case you have any questions related to the study, in future or in case of study related injury or illness, you can contact, Department of General Surgery, KLE University's JN Medical College, Belagavi. Your participation in this study is voluntary. In case you need any further information regarding your rights as study participants, you may contact Dr Roopa M Bellad, Professor of Pediatrics, as Chairman of JNMedical College Institutional

Ethics Committee on Human Subjects Research, Phone no: 0831 247 3777 ext-1527 at J.N. Medical College, Belagavi. You are free to stop participation in this at any time and for any reason.

CONSENT STATEMENT

Study title: "ONE YEAR STUDY OF PREVALENCE OF HYPOTHYROIDISM IN PATIENTS WITH GALL BLADDER STONES AT KLE'S DR PRABHAKAR KORE HOSPITAL & MRC, BELAGAVI -590010"

Initial Box

1) I confirm that I read the contents and understood the information sheet for the above study and have had the opportunity to ask questions.
2) I understood that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.
3) I understood that sponsor of the clinical trial; others working on the sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of current study and further research that may be conducted in relation to it, even if I withdraw from the trial.
4) I agree to this access. However, I understood that my identity will not be revealed in any information released to third parties or published.
5) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purposes.
6) I agree to take part in the above study.

Participant's name _____

Participant's signature/left thumb print

Date:

Experimenter’s name _____

Experimenter’s signature _____

Date:

Witness's name _____

Witness's signature _____

Date:

ANNEXURE II

SCREENING FORM AND PROFORMA

SCREENING FORM

SCREENING NUMBER:

DATE OF SCREENING (DD/MM/YY):

NAME :

AGE :

IP NUMBER :

ADDRESS : _____

_____

_____

PHONE NUMBER : 1. _____

2._____

EXCLUSION CRITERIAS 1. YES 2. NO

1)H/O GALL BLADDER STONES

IF YES, DURATION: ----------

TREATMENT TAKEN: ----------

2)PRIOR HISTORY OF CHOLECYSTECTOMY

IF YES, WHEN OPERATED: ----------

3)PRESENCE OF GALL STONES ON ULTRASOUND

4)HISTORY OF HYPOTHYROIDISM

IF YES, DURATION OF TREATMENT: _____

MEDICATION: _____

SYMPTOMS: _____

5) DIABETES MELLITUS TYPE II

IF YES, DURATION: _____

MEDICATION AND DURATION: _____

6) RENAL STONES,

IF YES, DURATION: _____

MEDICATION AND DURATION: _____

SURGICAL INTERVENTION: _____

7)STONES IN PANCREATIC DUCT

IF YES, DURATION: _____

MEDICATION AND DURATION: _____

SURGICAL INTERVENTION: _____

8)HEMOLYTIC DISEASES

DURATION: _____

MEDICATIONS: _____

BLOOD TRANSFUSIONS: _____

9)WOMEN TAKING ORAL CONTRACEPTIVE PILLS

IF YES, DURATION: _____

10)TAKING- PHENYTOIN, CARBAMAZEPIN, METOCLOPRAMIDIE, AMIODARONE & LITHIUM.

IF YES, DURATION: _____

11)PREGNANT: _____

FINAL RESULT

1.INELIGIBLE FOR STUDY

2.ELIGIBLE BUT REFUSED

3. ELIGIBLE AND PARTICIPATING IN THE STUDY

PROFORMA

ONE YEAR STUDY OF PREVALENCE OF HYPOTHYROIDISM IN PATIENTS WITH GALL BLADDER STONES AT KLE'S DR PRABHAKAR KORE HOSPITAL AND MRC, BELAGAVI- 590010.

I.D NO

NAME OF THE PATIENT: _____

AGE: _____

GENDER: 1. MALE 2. FEMALE

DOA:

IP NUMBER:

OCCUPATION: 1. UNEMPLOYED

2. UNSKILLED

3. SEMI-SKILLED

4. SKILLED

5. PROFESSIONAL

EDUCATION: 1. ILLITERATE

2. PRIMARY (1-7TH STD)

3. HIGH SCHOOL (8-10TH STD)

4.INTERMEDIATE

5. DEGREE AND ABOVE

SOCIO-ECONOMIC STATUS:

1. LOW 2. MIDDLE 3. HIGH

DATA COLLECTING INSTRUMENT

1. PRESENCE OF GALL STONES ON USG ABDOMEN 1.YES 2. NO

IF YES, USG Abdomen

Gall bladder: No of stones-_____

Wall thickening-_____

Contracted or Normal-_____

Any other abnormality-_____

Associated findings:

CBD -_____

Pancreas-_____

Liver-_____

Others-_____

2.DURATION OF GALL BLADDER STONES (PAIN ABDOMEN)-

1. LESS THAN 1 MONTH 2. MORE THAN 1 MONTH

3.DURATION OF HYPOTHYROID SYMPTOMS (IF ANY)-

1. LESS THAN 6 MONTHS 2. MORE THAN 6 MONTHS

1.LOSS OF APPETITE: _____

2.GAINING WEIGHT: _____

3.TIREDNESS: _____

4.CONSTIPATION: _____

5.COLD INTOLERANCE: _____

6.MENSTRUAL IRREGULARITIES: _____

7.PRESENCE OR ABSENCE OF GOITRE: _____

4.TSH LEVELS (0.24-4.2)

1. ELEVATED 2. NORMAL 3. LOW

5.FT4 LEVELS (0.93-1.7)

1. ELEVATED 2. NORMAL 3. LOW

6.FT3 LEVELS (2-4.4)

1. ELEVATED 2. NORMAL 3. LOW`

ANNEXURE III

KEY TO MASTER CHART

UE- Unemployed

US- Unskilled

SS- Semi-Skilled

S- Skilled

PR- Professional

IL- Illiterate

P- Primary (1-7TH STD)

HS- High school (8-10TH STD)

I- Intermediate

D- Degree and above

MC- Multiple calculi

SC- Single calculi

Y- Yes

N- No

NA- Not applicable

LOA- Loss of appetite

USG- Ultrasonography

ET- Euthyroid

SH- Subclinical hypothyroid

H- Hypothyroid

Master Chart

S.No	Name	Sex	Age	IP No	Occupation	education	Social status	Pain abdomen	USG Abdomen	LOA	Gaining wt	Tiredness	Constipation	Cold Intolerance	Menstrual Irregularities	Goitre	S. TSH	S. Free T4	S. Free T3	Thyroid Status	USG Neck
1	Anita cyril	F	57years	920738	S	D	HIGH	>1 Months	MC	N	Y	Y	Y	N	N	N	6.74	1.2	2.2	**SH**	Not done
2	Kempawwa	F	40Years	921517	UE	HS	MIDDLE	>1 Months	MC	N	N	N	N	N	N	N	2.1	1.1	2.4	ET	Not done
3	Shivaji	M	61Years	922640	SS	P	MIDDLE	<1 Months	MC	N	N	N	N	N	NA	N	3	1.5	3.1	ET	Not done
4	Renuka	F	40Years	922676	US	P	LOW	<1 Months	MC	N	N	N	N	N	N	N	3.1	1.2	2.4	ET	Not done
5	Masira	F	21Years	923696	SS	I	LOW	<1 Months	MC	N	N	N	N	N	N	N	3.4	0.98	2.3	ET	Not done
6	Almas	F	37Years	923205	US	HS	LOW	>1 Months	MC	N	N	N	N	N	N	N	4	1.6	3.4	ET	Not done
7	Kalavati	F	57years	922285	US	HS	MIDDLE	<1 Months	MC	N	N	N	N	N	N	N	3.2	1.1	2.2	ET	Not done
8	Laxmi	F	25Years	926255	US	P	LOW	<1 Months	SC	N	N	N	N	N	N	N	2.2	1.5	2	ET	Not done
9	Sonali	F	36Years	927889	S	I	MIDDLE	>1 Months	MC	N	Y	N	Y	N	N	N	34.31	0.5	1.7	**H**	Not done
10	Koustubh	M	24Years	926337	S	D	HIGH	>1 Months	MC	N	N	N	N	N	NA	N	3.8	1.6	3.7	ET	Not done
11	Tahera	F	59Years	911826	UE	HS	MIDDLE	>1 Months	MC	N	N	N	N	N	N	N	3.13	1.1	3.3	ET	Not done
12	Shabina	F	38Years	927503	UE	P	MIDDLE	>1 Months	MC	N	N	N	N	N	N	N	0.89	1	3	ET	Not done
13	Reminika	F	18Years	927358	PR	D	HIGH	<1 Months	MC	N	N	N	N	N	N	N	1	1.4	3.4	ET	Not done
14	Sangeetha	F	33Years	935694	SS	HS	MIDDLE	<1 Months	MC	N	N	N	N	N	N	N	0.67	0.9	3	ET	Not done
15	Mithali	F	25Years	940981	PR	D	HIGH	<1 Months	SC	N	N	N	N	N	N	N	1.6	0.98	3	ET	Not done
16	Jameela	F	67Years	929260	US	HS	MIDDLE	>1 Months	MC	Y	Y	Y	N	N	N	N	9.2	1.3	4	**SH**	Not done
17	Shamshad	M	52Years	930375	US	P	MIDDLE	>1 Months	MC	N	Y	Y	N	N	NA	N	11.6	1.5	2.2	**SH**	Not done
18	Putala	M	70Years	930806	UE	P	MIDDLE	>1 Months	MC	N	N	N	N	N	NA	N	4.1	0.99	2.1	ET	Not done
19	Tayavva	F	70Years	933252	UE	I	LOW	>1 Months	MC	N	N	N	N	N	N	N	4	1.3	3	ET	Not done
20	Kumar	M	53Years	934063	SS	HS	MIDDLE	>1 Months	MC	Y	N	Y	N	N	NA	N	0.2	1.5	4	ET	Not done
21	Ramanna	M	87Years	934364	SS	HS	HIGH	>1 Months	MC	N	N	Y	Y	N	NA	N	0.6	1	2.2	ET	Not done
22	Gundu	M	40Years	931470	SS	HS	LOW	<1 Months	MC	N	N	N	N	N	NA	N	1.1	1.4	3	ET	Not done
23	Surekha	F	30Years	929160	SS	HS	LOW	<1 Months	MC	N	N	N	N	N	N	N	1.3	1	2	ET	Not done
24	Sana	F	30Years	930866	S	I	MIDDLE	<1 Months	MC	N	N	N	N	N	N	N	0.6	1.3	3.2	ET	Not done
25	Vilas	M	58Years	934450	SS	I	MIDDLE	>1 Months	MC	N	N	N	N	N	NA	N	1.4	1.2	3	ET	Not done
26	Paramanand	M	46Years	937331	SS	I	MIDDLE	<1 Months	MC	N	N	N	N	N	NA	N	3.1	1.4	4.1	ET	Not done
27	Chandravva	F	74years	936898	US	P	LOW	<1 Months	MC	N	N	N	N	N	N	N	0.98	1	2.2	ET	Not done
28	Sanaa	F	23Years	938304	UE	P	LOW	>1 Months	MC	N	Y	Y	N	N	Y	N	17.83	0.83	1.46	**H**	Not done
29	Shwetha	F	19Years	939076	SS	I	MIDDLE	>1 Months	MC	N	N	Y	Y	N	Y	N	7.23	1	2.2	**SH**	Not done
30	Savita	F	35Years	940022	US	P	LOW	>1 Months	MC	N	N	N	N	N	Y	N	3.34	1.2	3.2	ET	Not done
31	Ismailsab	M	74years	941184	SS	I	MIDDLE	>1 Months	MC	Y	Y	N	N	N	NA	N	8.98	1.05	2.64	**SH**	Not done
32	Dyamappa	M	63Years	941448	US	P	LOW	>1 Months	MC	N	N	N	N	N	NA	N	0.79	1.12	2.5	ET	Not done
33	Pratibha	F	32Years	941782	US	P	LOW	>1 Months	MC	N	N	N	N	N	N	N	1.81	0.99	4	ET	Not done
34	Prema	F	48Years	942371	UE	P	LOW	>1 Months	MC	Y	N	Y	Y	N	Y	N	4.37	1	2.13	**SH**	Not done
35	Akbarsaheb	M	72Years	942337	SS	P	MIDDLE	<1 Months	SC	N	N	Y	N	N	NA	N	3.98	1.31	2.04	ET	Not done
36	Renuka	F	42Years	943912	UE	I	LOW	>1 Months	SC	N	Y	Y	Y	N	Y	N	7.9	1.56	4.32	**SH**	Not done

37	Saradar	M	56Years	942071	US	P	LOW	<1 Months	MC	N	N	N	N	N	NA	N	3.55	0.99	3.45	ET	Not done
38	Yallawwa	F	46Years	943966	SS	HS	MIDDLE	>1 Months	MC	Y	N	N	N	N	Y	N	1.05	1.6	2.1	ET	Not done
39	Shankar	M	56Years	945417	S	D	HIGH	>1 Months	MC	N	N	N	N	N	NA	N	2.9	1	2.3	ET	Not done
40	Khairunbi	F	70Years	945248	US	P	LOW	>1 Months	MC	N	N	N	N	N	N	N	1.4	1.24	3.56	ET	Not done
41	Dasharath	M	54years	945399	SS	I	MIDDLE	<1 Months	MC	N	N	N	N	N	NA	N	3.44	1.25	3.65	ET	Not done
42	Bheemappa	M	41Years	944431	S	D	MIDDLE	>1 Months	MC	N	N	N	N	N	NA	N	1.54	1.2	2.2	ET	Not done
43	Parvathi	F	50Years	944790	SS	HS	MIDDLE	>1 Months	MC	Y	N	Y	Y	N	N	N	4.86	1.6	2.3	**SH**	Not done
44	Asiya	F	30Years	944744	SS	HS	LOW	>1 Months	MC	N	N	N	N	N	Y	N	4.61	1.28	2.89	**SH**	Not done
45	Savakka	F	34years	941768	US	HS	LOW	>1 Months	SC	N	N	N	N	N	N	N	2.82	1.65	4.13	ET	Not done
46	Shilpa	F	34years	945485	SS	P	LOW	>1 Months	MC	N	N	N	N	N	N	N	2.41	0.99	3.46	ET	Not done
47	Linganna	M	65Years	946679	US	P	LOW	>1 Months	MC	N	N	N	N	N	NA	N	0.77	1.13	3.2	ET	Not done
48	Sadashiv	M	58Years	946364	SS	HS	LOW	< 1 Months	MC	N	N	N	N	N	NA	N	2.02	1.23	2.44	ET	Not done
49	Sunanda	F	63Years	945903	S	I	MIDDLE	>1 Months	MC	N	N	N	N	N	N	N	4.3	1.43	3.24	**SH**	Not done
50	Karishma	F	29years	951646	SS	HS	MIDDLE	<1 Months	MC	N	N	N	N	N	Y	N	5.01	1.1	2.2	**SH**	Not done
51	angadharayy	M	84Years	955004	US	P	MIDDLE	>1 Months	MC	Y	N	Y	Y	N	NA	N	34.8	1	2.6	**SH**	Not done
52	Anita	F	51Years	949467	SS	HS	MIDDLE	>1 Months	MC	N	N	N	N	N	N	N	1.43	0.95	2.98	ET	Not done
53	Tanuja	F	35Years	961193	US	P	LOW	>1 Months	SC	Y	N	N	Y	N	N	N	4.21	1.5	3.2	**SH**	Not done
54	Malati	F	54years	964659	US	P	LOW	<1 Months	MC	N	N	N	N	N	N	N	1.07	1.12	2.31	ET	Not done
55	Ayesha	F	70Years	962263	UE	IL	LOW	>1 Months	MC	Y	N	Y	Y	Y	N	N	10	0.8	1.14	**H**	Not done
56	Geetha	F	40Years	963794	SS	P	LOW	>1 Months	MC	N	N	N	N	N	N	N	3.24	1.39	4.24	ET	Not done
57	Mallappa	M	76Years	962576	US	P	LOW	>1 Months	MC	Y	N	Y	N	N	NA	N	3.35	1.5	2.3	ET	Not done
58	Sunita	F	43Years	965805	SS	HS	LOW	<1 Months	SC	Y	N	Y	N	N	Y	N	14.16	0.98	2	**SH**	Not done
59	Laxmi	F	40Years	966931	SS	P	LOW	<1 Months	SC	N	N	N	N	N	Y	N	5.41	1.2	2.3	**SH**	Not done
60	Paridabgum	F	59Years	967000	US	P	LOW	<1 Months	SC	Y	Y	Y	N	N	N	N	1.95	1.64	2.42	ET	Not done
61	Bebiayesha	F	59Years	967996	US	P	LOW	<1 Months	MC	Y	N	Y	Y	Y	N	N	5.2	1.2	2.3	**SH**	Not done
62	Shabana	F	34years	968305	US	HS	LOW	<1 Months	MC	N	N	N	N	N	Y	N	29.02	0.78	1.98	**H**	Not done
63	Veerabhadra	M	44years	969719	UE	P	LOW	> 1 Months	MC	N	N	N	N	N	NA	N	3.14	1.5	2.2	ET	Not done
64	Savitha	F	29years	972240	SS	HS	MIDDLE	< 1 Months	MC	N	N	N	N	N	N	N	2.04	1	3.1	ET	Not done
65	Manjula	F	31years	973378	SS	HS	MIDDLE	<1 Months	MC	Y	N	Y	N	N	Y	N	6.95	1.36	3.07	**SH**	Not done
66	Vijay	M	74years	976311	S	D	HIGH	<1 Months	MC	N	N	N	N	N	NA	N	0.33	1	2.5	ET	Not done
67	Girija	F	62years	976800	US	P	LOW	>1 Months	MC	N	N	N	N	N	N	N	3	1.2	4	ET	Not done
68	eerabhadrapp	M	68Years	977318	UE	P	LOW	>1 Months	MC	Y	N	Y	Y	N	NA	N	15.21	1.27	3.04	**SH**	Not done
69	Shabana	F	38Years	977748	SS	HS	HIGH	>1 Months	MC	N	N	N	N	N	N	N	3.2	1.1	2.4	ET	Not done
70	Gourappa	M	34years	977733	SS	I	MIDDLE	<1 Months	MC	N	N	N	N	N	NA	N	1.62	1.5	2.2	ET	Not done
71	Nirmal	M	53years	978253	S	D	HIGH	>1 Months	SC	Y	Y	N	N	N	NA	N	10.5	1.2	2.1	**SH**	Not done
72	Kasturi	F	60Years	976915	US	HS	MIDDLE	>1 Months	MC	N	N	N	N	N	N	N	2.76	1.5	3	ET	Not done
73	Shalabai	F	70Years	977412	SS	I	MIDDLE	>1 Months	MC	N	Y	Y	Y	Y	N	N	7.17	1.6	4	**SH**	Not done
74	Yashoda	F	86Years	978749	SS	D	HIGH	<1 Months	MC	N	N	N	N	N	N	N	0.53	1.2	3.4	ET	Not done
75	Ruthamma	F	99Years	979845	US	I	MIDDLE	<1 Months	MC	N	N	Y	Y	Y	N	Y	28.5	0.52	1	**H**	MNG

76	Madhukar	M	75Years	979899	S	I	HIGH	<1 Months	MC	Y	N	N	Y	N	NA	N	10	0.9	2	**H**	Not done
77	Mahaveer	M	78Years	980127	SS	HS	MIDDLE	<1 Months	MC	N	N	N	N	N	NA	N	1.71	1.4	2.5	ET	Not done
78	Deepak	M	26Years	974774	SS	D	HIGH	<1 Months	MC	N	N	N	N	N	NA	N	0.25	1.1	2	ET	Not done
79	Roopa	F	37Years	980593	SS	D	MIDDLE	>1 Months	MC	N	N	N	N	N	N	N	0.78	1.29	2.56	ET	Not done
80	Saraswati	F	62years	981390	S	I	MIDDLE	<1 Months	MC	Y	N	N	N	Y	N	N	4.89	1.3	2.58	**SH**	Not done
81	Amirabi	F	62years	978358	SS	D	MIDDLE	<1 Months	MC	N	Y	N	N	N	N	N	3.53	1.01	2	ET	Not done
82	Kasturi	F	70Years	980268	US	P	MIDDLE	<1 Months	MC	N	N	N	N	N	N	N	2.29	1.05	2.41	ET	Not done
83	Annaraya	M	68Years	978963	SS	HS	MIDDLE	<1 Months	MC	N	N	N	N	N	NA	N	4.73	1.14	3.21	**SH**	Not done
84	Vimala	F	82Years	982331	SS	D	MIDDLE	<1 Months	MC	N	N	N	N	N	N	N	1.04	1.05	2.37	ET	Not done
85	Ramachandra	M	67Years	982796	SS	HS	MIDDLE	<1 Months	MC	N	N	N	N	N	NA	N	1.1	1.98	2.47	ET	Not done
86	Yasin	M	70Years	983261	SS	D	HIGH	>1 Months	MC	N	N	N	N	N	NA	N	2.82	1.98	3.1	ET	Not done
87	Bharmappa	M	67Years	983724	S	HS	MIDDLE	<1 Months	MC	N	N	N	N	N	NA	N	1.87	2.1	3.67	ET	Not done
88	Mahadev	M	65Years	962981	SS	D	MIDDLE	<1 Months	MC	N	N	N	N	N	NA	N	1.72	1.98	3.4	ET	Not done
89	Sangappa	M	67Years	984012	SS	HS	MIDDLE	>1 Months	MC	N	N	N	N	N	NA	N	1.89	2.2	4.1	ET	Not done
90	Shivlila	F	69Years	983668	UE	P	MIDDLE	>1 Months	MC	N	Y	Y	Y	N	N	N	4.14	0.97	3.97	ET	Not done
91	Shantavva	F	50Years	985695	SS	P	MIDDLE	<1 Months	MC	N	N	N	N	N	N	N	4.98	1.33	3	**SH**	Not done
92	Kamala	F	34years	987300	SS	D	MIDDLE	>1 Months	MC	N	N	N	N	N	N	N	3.57	1.22	2.78	ET	Not done
93	Ramachandra	M	64years	987320	S	D	MIDDLE	<1 Months	MC	N	N	N	N	N	NA	N	2.2	1.32	2.43	ET	Not done
94	Vijayalakshm	F	51years	988764	SS	P	LOW	<1 Months	MC	N	N	N	N	N	N	N	1.6	0.99	3.43	ET	Not done
95	Pratap	M	68Years	988680	S	D	HIGH	<1 Months	MC	N	Y	N	N	N	NA	N	0.64	1.76	4	ET	Not done
96	Yallappa	M	48Years	989848	SS	I	MIDDLE	<1 Months	MC	N	N	N	N	N	NA	N	4.1	0.98	3.24	ET	Not done
97	Shrishail	M	64years	989104	SS	P	MIDDLE	<1 Months	MC	N	N	N	N	N	NA	N	4.13	1.37	3.42	ET	Not done
98	Gurappa Katt	M	65Years	989492	US	P	LOW	<1 Months	MC	Y	N	Y	N	N	NA	N	0.54	1.6	3.44	ET	Not done
99	Mugudsab	M	73Years	986670	SS	I	MIDDLE	<1 Months	MC	N	N	N	N	N	NA	N	3.01	1.34	3.46	ET	Not done
100	Sumitra	F	50Years	987149	SS	P	MIDDLE	>1 Months	MC	N	N	N	N	N	N	N	1.32	1.02	3	ET	Not done