"A STUDY OF ASSOCIATION OF METABOLIC SYNDROME WITH THE OCCURRENCE OF GALLSTONE DISEASE –A ONE YEAR CROSS-SECTIONAL STUDY AT TERTIARY CARE HOSPITAL, BELAGAVI."

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Sub: Institutional Ethical Clearance for the study.

With reference to the above, we wish to inform you that your proposed research project titled **"A STUDY OF ASSOCIATION OF METABOLIC SYNDROME WITH THE OCCURRENCE OF GALLSTONE DISEASE- A ONE YEAR CROSS-SECTIONAL STUDY AT TERTIARY CARE HOSPITAL BELAGAVI",** is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee.

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LIST OF ABBREVIATIONS:

MetS- Metabolic syndrome

NAFLD - Non-alcoholic Fatty Liver Disease

LDL – Low-Density Lipoprotein

HDL - High-Density Lipoprotein

TG - Triglyceride

LC - Laparoscopic Cholecystectomy

AC - Acute cholecystitis

NCEP ATP III - National Cholesterol Education Program's Adult Treatment Panel III

IR – Insulin Resistance

ASCVD - Atherosclerotic Cardiovascular Disease

AHA - American Heart Association

NHLBI - National Heart, Lung, and Blood Institute

ADA - American Diabetes Association

BMI – Body Mass Index

WC – Waist Circumference

TPN - Total Parental Nutrition

GSD – Gallstone disease

Abstract

Background: Gallstone disease is an important health concern that is becoming more common as a result of dietary, lifestyle, and metabolic risk factor. Gallstone development has been associated with the Metabolic Syndrome (MetS), a group of diseases that includes obesity, diabetes, hypertension, and dyslipidemia. The purpose of this study is to investigate the relationship between gallstone disease and MetS.

Methods: 120 individuals with gallstone disease at a tertiary care hospital participated in a cross-sectional study. Waist circumference, fasting blood sugar, lipid profile, and blood pressure were among the metabolic abnormalities evaluated in the patients.Statistical analyses were performed to determine associations between MetS components and gallstone disease.

Results: There was a significant association found between gallstone disease and MetS. Those between the ages of 51 and 60 had the highest prevalence of MetS. Compared to men, women were more commonly affected. Obesity, hyperglycemia, hypertension, and dyslipidemia were significantly related with gallstone disease.

Conclusion: The study emphasizes the need of early detection and management of metabolic risk factors by highlighting a significant relationship between MetS and gallstone disease. The burden of gallstone disease may be reduced by preventive measures like lifestyle changes and focused medical treatments.

Further longitudinal studies are recommended to establish causality and refine preventive measures.

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INTRODUCTION

Gallstones are common in the western world, but their incidence has increased recently in India. This is partly due to the extensive use of ultrasonography over the past 20 years, and it is also partially caused by changes in socioeconomic structure and other epidemiological factors, such as diet. Gallstone disease can have life-threatening complications and is a major contributor to health care expenses. Early detection and efficient management can prevent numerous serious and fatal complications.(1)

Gallstones are present in 6.12% of adult population (with 9.6% women and 3.07% men). In both males and females, the occurrence of gallstones rises with age, peaking during the sixth decade. Age-adjusted parous women had a considerably greater prevalence of gallstones than nullipara women. (1)

Biliary colic and gallstone-related issues, including cholecystitis, acute pancreatitis, cholangitis and choledocholithiasis, impact approximately 20% of individuals with gallstones.

Recent studies conducted globally have examined the co-relation between gallstones and metabolic disorders. Several studies have examined individual risk factors related with gallstones and metabolic syndrome, revealing significant commonalities such as obesity, gender, age and issues related with fat and carbohydrate metabolism. (2)

Metabolic Syndrome (MetS):

In 2001, "National Cholesterol Education Programme (NCEP) Adult Treatment Plan (ATP III)" clinically defined Metabolic Syndrome as having 3 of the below 5 components:

a. Obesity (measured as waist circumference)

b. Diabetes mellitus

c. Hypertension

d. Serum Hypertriglyceridemia

e. Decreased Serum High Density Lipoprotein (HDL) Levels

Non-alcoholic Fatty Liver Disease is associated with MetS, which in turn has been linked to gallstones in patients; these conditions typically exhibit traits such as obesity, high triglyceride levels, and diabetes. Several factors, including body mass index, sex, high lipid levels, alcohol consumption, contraceptive use, diabetes, lack of physical activity, multiparity in women, drinking water with elevated iron levels are also implicated.(3) The western nations have reported similar results.

Approximately 30% of adults in India are affected by MetS. The prevalence has progressively risen across all age brackets, increasing from 13% among those aged 18–29 years to 50% among individuals aged 50–59 years. Furthermore, our findings indicated that urban residents were more frequently affected than their tribal or rural counterparts. Regarding gender differences in MetS, women exhibited a higher likelihood of being diagnosed with the condition compared to men (26%).(4)

Research has shown a substantial correlation between gallstone disease and the following factors: alcohol use, liver cirrhosis, diabetes mellitus, obesity, hyperlipidemia, advanced age, race, female gender, and MetS. Specifically, well-known cardiometabolic risk factors encompass MetS, diabetes, obesity, and high lipid

levels. NAFLD is often regarded as the hepatic related complication of MetS since metabolic disorders are predisposing variables.

Since diabetes mellitus and cholelithiasis are thought to be closely related conditions, some people may be more susceptible to cholelithiasis if they have impaired glucose metabolism. Determining the pathophysiological foundation of gallstone formation has been a major focus in recent years. Serum lipids have a significant role in the pathophysiology of cholelithiasis, which may indicate MetS. According to research, MetS may escalate the occurrence of gallstones.

The gallstone disease is 12.1% prevalent (13.1% males and 10.2% females). In men with greater metabolic problems, gallstone disease was more common; this trend was statistically significant. Gallstone disease risk was 3.4 times higher when all five MetS components were present.(5) In today's society, gallbladder stone disease is common reason for hospitalization due to gastrointestinal problems. A global health crisis is slowly emerging due to the rise of MetS. The link between cholelithiasis and MetS in South Asian nations is still not well comprehended. The research aims to prove the relationship between gallstones disease and Metabolic disease.

AIMS AND OBJECTIVES

AIMS:

- To study the correlation between MetS and gall stone disease

OBJECTIVES:

- To identify and classify the cases of metabolic disorder and gall stone disease.
- To study correlation between individual features of metabolic syndome with Gallstone disease.

REVIEW OF LITERATURE

Gallstone Disease

Historical Background

The history of cholelithiasis traces back to 2000 BC, when the Babylonians first recorded details about the bile duct system. Evidence of gallstones was also discovered in a mummy from the 21st Dynasty. Later, in the early 14th century, the Italian physician became the first to identify gallstones in humans. In 1661, Thomas Bartholinus identified biliary colic and linked the pain to the movement of stones through the Common Bile Duct. For the Swiss physician Paracelsus, gallstones resulted from "tartaric sickness." (6) Fourcroy performed the first chemical analysis of the composition of gallstones in 1789 . To evaluate the clinical outcome of a group of people with gallstones, a prospective follow-up had to be started. (7)

Prior to the first cholecystectomy, the only ways to treat gallstone and gallbaldder illness were to remove the stone, drain the abscess, or create a cholecystic fistula. A cholecystocutaneous fistula or cholecystoenterostomy emerged as a consequence of gallstone and gallbladder wall removal, where the wall was "attached" to either the skin or colon, as indicated by earlier articles.(7) To celebrate the achievement, the Berliner Klinische Wochenschrift published an essay titled "Fifty Anniversary" of cholecystectomy in the surgical archives. Master surgeon Carl Langenbuch operated on the biliary system.(8,9). In April 1883, it was stated that “The gallbladder should be removed not because it contains gallstones but because it develops them”. Additionally, he offered a historical overview of the progression of surgical procedures related to the biliary system, Langenbuch had performed 24 cholecystectomies by the end of 1896. He died of peritonitis in 1901 after suffering from appendicitis. In 1890, Courvoisier performed the first surgical removal of a

gallstone from the common bile duct through a direct incision. On March 25, 1902, A.W. Mayo Robson presented an article to the Royal Medical and Surgical Society that included that first discussed of gallstones (10). It was the most effective treatment for cholelithiasis for almost a century. Over the last decade, this method has evolved with the advent of laparoscopic techniques for performing cholecystectomy.

The first Laparoscopic Cholecystectomy (LC) on humans was performed by France's Mouret. On a particular day in March 1987, he performed gynecologic laparoscopy on a patient who also had gallstones that were causing symptoms, moving his laparoscope to the subhepatic region he found that gallbladder was quite loose and flexible. So, he opted to remove it using a laparoscopic method rather than performing an open surgery. Successful treatment was provided, and the patient recovered completely and without any problems.

Although the advantages of LC were initially viewed with considerable skepticism (11,12), Cohen MM et al. demonstrated that the patient demanded LC, along with the perception that the procedure involved lower risks, quicker recovery, and reduced postoperative discomfort . The number of cholecystectomies increased by 25–30% in 1995, a decade following the introduction of LC (13,14), with over 80% of these procedures being carried out laparoscopically.

National Institute of Health Consensus Statement supported LC (15), which recognized the use of LC as an effective method in a surgeon's arsenal for addressing symptomatic cholelithiasis. The prevalence of acute cholecystitis (AC) has increased as laparoscopy has become the main approach for treating symptomatic cholelithiasis, it has largely supplanted open surgery. (16).

Compared to an open cholecystectomy, this surgery had fewer postoperative discomforts, better cosmetic outcomes, shorter hospital stays, and less work

impairment (17,18). However, the overall risk of significant complications from LC remains higher than that of open cholecystectomy (17,18).

Anatomy : Gallbladder and Biliary System:

The gallbladder is a muscular organ shaped like a pear, located beneath the liver in the abdomen (upper right quadrant) (19). Its length is approximately 7–10 cm, while its width ranges from 3–4 cm, and it has a capacity of around 30–50 mL. It is connected to the liver through connective tissue and the peritoneum (20). The gallbladder consists of the neck, body, and fundus. The fundus is the widest section, narrows into the neck, which is linked to the cystic duct. (21).

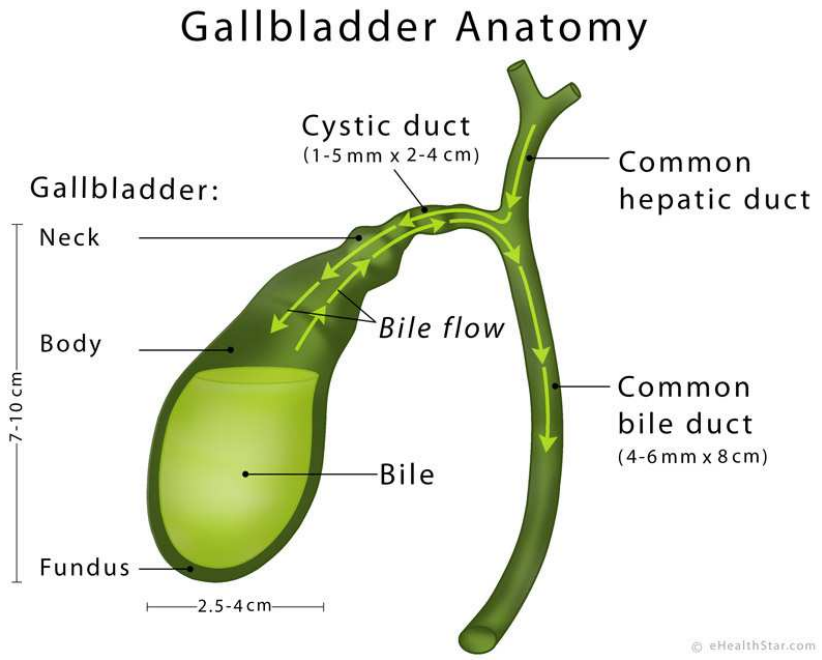


Figure 1. – Anatomy of Gallbladder

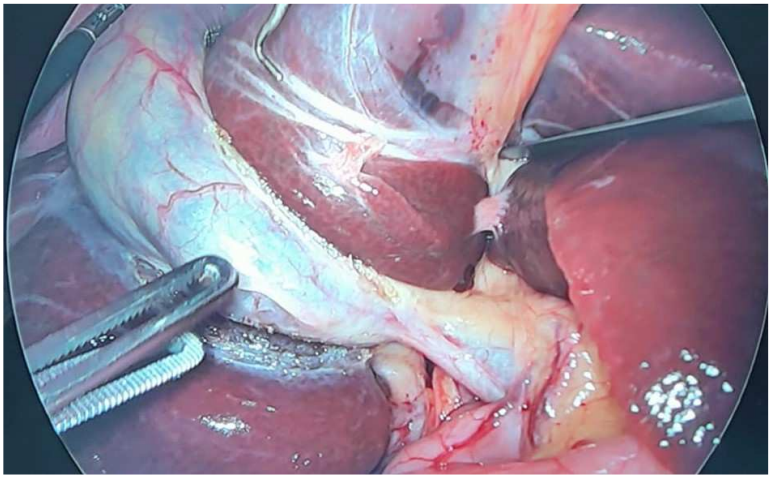


Figure 2. – Intra-operative picture of Gallbladder with Gallstones

The gallbladder plays an essential role in concentrating and storing bile ; it flows through the hepatic ducts into the gallbladder, where it becomes concentrated by the absorption of water and electrolytes. (19). The duodenum releases the hormone cholecystokinin (CCK) during digestion, especially after fatty meals; this triggers the contraction of the gallbladder, leading to bile being discharged into the duodenum. (20).

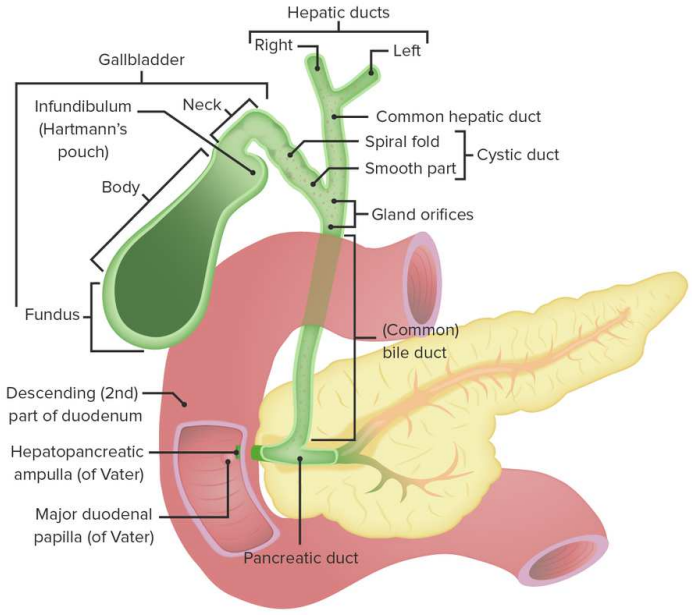


Figure 3. – Anatomy of Biliary system

Biliary Metabolism:

The process of bile metabolism includes the creation of bile acids and the release and reuse, which are needed for fat metabolism. The liver generates two main bile acids from cholesterol: chloric acid and chenodeoxycholic acid. Before being secreted into bile, these primary bile acids are combined with taurine or glycine. Within the colon, they are transformed by bacterial enzymes into lithocholic acid, deoxycholic acid, and secondary bile acids. These bile acids are then reabsorbed through the enterohepatic circulation and brought back to the liver. This recycling mechanism helps to conserve bile acids and maintain cholesterol balance. Impaired biliary metabolism, such as inadequate bile acid output or altered bile composition, can lead to bile stasis and gallstone development.(22,23)

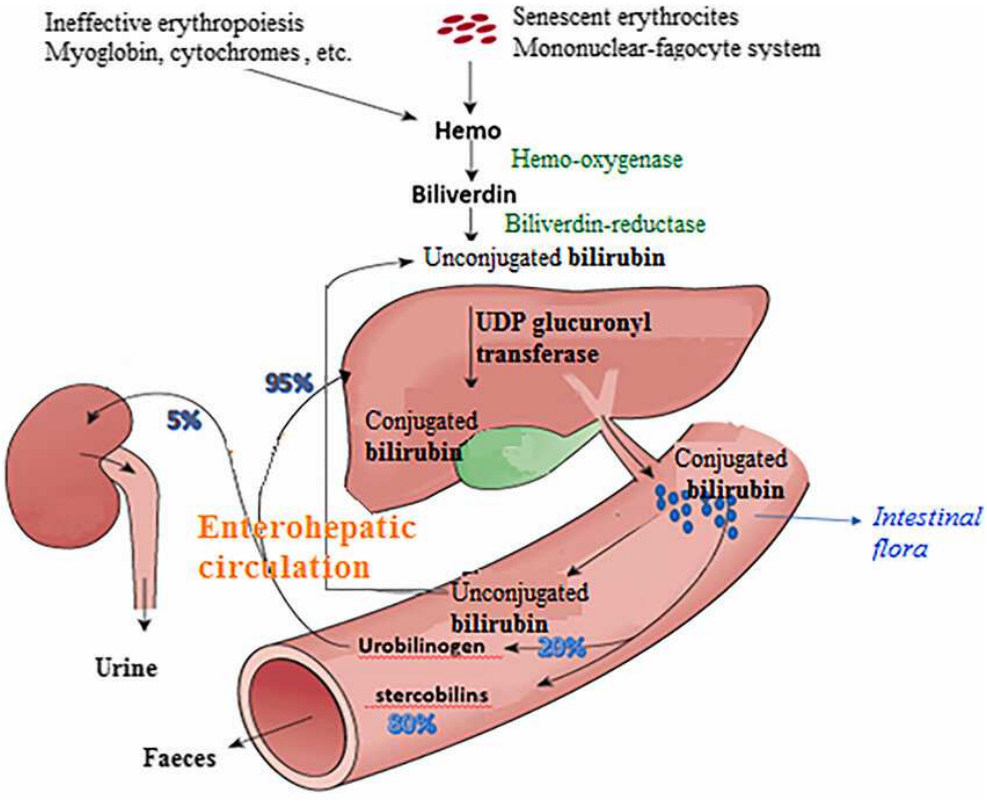


Figure 4. – Mechanism of Biliary Metabolism

Gallstone Formation:

Gallstones develop in the gallbladder as a result of an imbalance in the bile's composition. In the formation of gallstones, elevated bilirubin levels, bile stasis, and excessive cholesterol saturation are the primary factors. The stones develop as the concentration of cholesterol in bile exceeds the capacity of phospholipids and bile salts to maintain its solubility. [24]. Bile stasis can be caused by reduced gallbladder motility, which is frequently linked to MetS, obesity, and extended fasting. This can further encourage the production of gallstones [25]. Furthermore, pigment stone development can result from excessive bilirubin secretion, which is observed in disorders of the liver and hemolytic anemia [26]. High-fat diets, fast weight reduction, feminine gender, and genetic predisposition are additional risk factors [27]. It is essential to comprehend the pathophysiology of gallstone formation in order to create effective treatment plans and preventative measures.

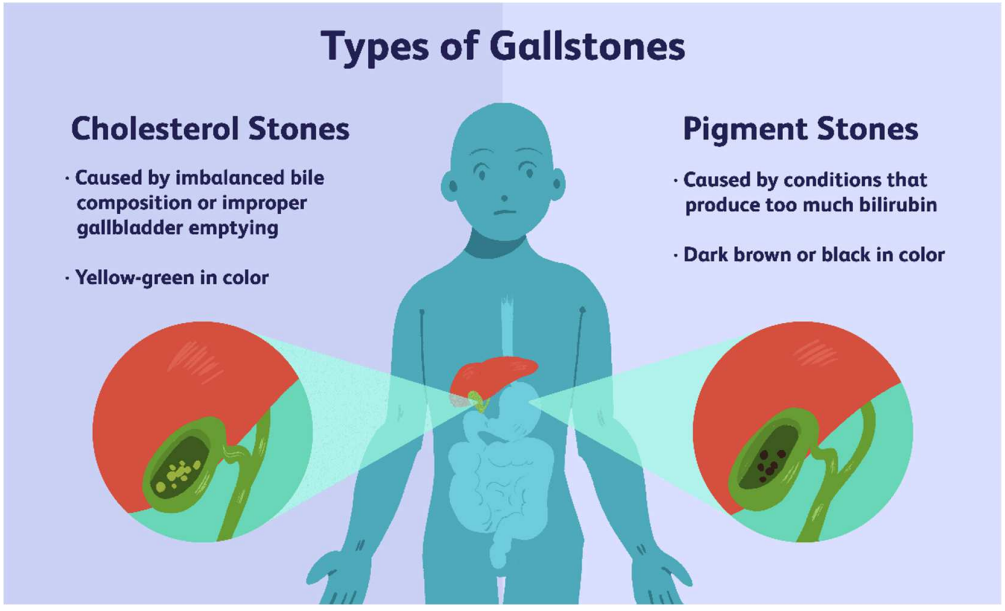


Figure 5. – Formation of Gallstones

Types of Gallstones:

1. Cholesterol Gallstones: Around 80% of all gallstones are cholesterol gall stones, making it the most prevalent. Gallstones occur when bile is excessively rich in cholesterol, resulting in crystallization and the development of stones. They are primarily made of cholesterol. Obesity, high-fat diets, fast weight loss, and metabolic problems are among the conditions that enhance the development of cholesterol gallstones.(28)

2. Pigment Gallstones: These are primarily made up of bilirubin and calcium salts and are more frequently found in people who experience chronic hemolysis (like sickle cell disease), liver cirrhosis, or infections of the biliary system. There are two types of gallstones based on colour, brown and black. Brown stones are linked to bacterial infections and found in the bile ducts. On the other hand, black stones are usually located in the gallbladder.(29)

3. Mixed Gallstones: They are frequently seen in individuals suffering from chronic cholecystitis. Cholesterol, bilirubin, and calcium salts form the major component of mixed stones. (30)

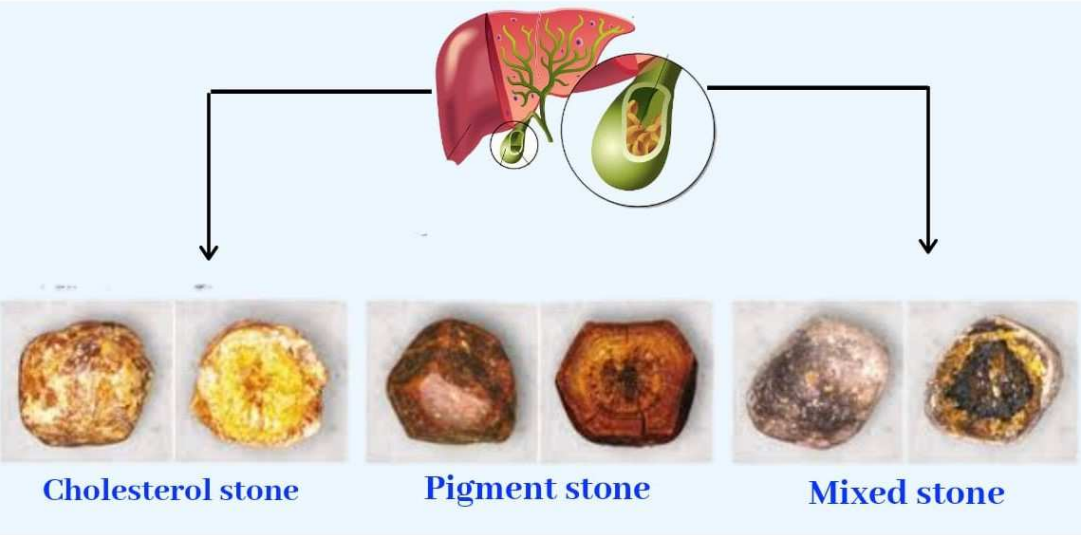


Figure 6. – Types Of Gallstones

Factors contributing to the formation of gallstones:

The formation of gallstones is a complicated process, as indicated by various case-control studies that analyze individuals with and without cholelithiasis. Some aspects cannot be changed, such as female gender, age, genetics, and race. On the other hand, factors such as food, exercise, fast weight reduction, and obesity, are thought to be variable.

The prevalent stone type and the frequency of gallstone disease are strongly influenced by geography, especially ethnicity. Brown stones are frequently found in Asian populations, while cholesterol gallstones are more common in affluent Western nations. The highest prevalence of cholelithiasis, which affects 64.1% of women and 29.5% of males, is reported by Native Americans in North America.(31) Similar to this, gallstone prevalence is remarkably high in South American indigenous groups, such as the Mapuche Indians in Chile, where 12.6% of men and 49.4% of women suffer from the condition. Gallstone disease is more prevalent among Mexican

Americans compared to White Americans. (32,33) The prevalence of gallstones is about 9% in White American men and 17% in women. Among Black Americans and Asians, rates are intermediate, affecting around 5% of men and 14% of women. In wealthier nations, cholesterol stones are most common (> 85%).(34,35)

In East Asia, infections caused by parasites are the primary reason for the high occurrence of brown pigment stones. Conversely, in developed countries, these stones typically result from infections and inflammation linked to biliary strictures and cancers. They are made from fatty acids, like calcium palmitate and calcium stearate, which provide them with oily consistency. They also contain components of mucinous glycoproteins and cholesterol, which are byproducts of bacterial biofilms. These stones may develop in the intrahepatic bile ducts or in the common bile duct, leading to hepatolithiasis and choledocholithiasis respectively. They are often associated with biliary parasites such as Clonorchis sinensis, species of Opisthorchis, and Fasciola hepatica, along with bacterial infections and partial blockages in the bile ducts.

Brown pigment stones can lead to conditions such as Oriental cholangiohepatitis, which is characterised by strictures, biliary tree dilatation, and recurrent cholangitis. Different East Asian countries have different incidence rates of hepatolithiasis; in China and Taiwan, rates might approach 20%, while in Japan, Singapore, and Hong Kong, rates fall sharply to two to three percent.(36)

Cholelithiasis is significantly influenced by genetic predisposition. Research shows a higher risk, with relatives of gallstone sufferers almost five times as likely to get gallstones themselves. In monozygotic twins, this risk increases to 12%, and in dizygotic twins, it rises to 6%.(37) It's noteworthy that partners of those affected do not show a heightened risk, suggesting that shared environmental influences, such as

family members' food and lifestyle choices, are not the main causes of this relation. Gallstone disease arises from genetic factors and environmental influences, particularly related to nutrition and genes. (38–41)

Research using genome-wide association studies has identified specific genetic polymorphisms, linked to gallstone susceptibility. These variants are associated with hepatic cholesterol production and contribute to approx. 10% of the overall risk of developing gallstones. (42). Therefore, rather than being caused by a single genetic component, cholelithiasis is probably a condition influenced by numerous genes.

Burden of the gallstone disease:

In developed countries, gallstone disease affects 10%-15% of the population, which translates to an approximate 10 to 25 million people (43-46). The economic burden associated with gallbladder disorders in the US is approximately $6.2 billion, representing a significant health issue that has increased by more than 20% over the previous three decades.(45–47) Furthermore, conditions associated with gallstones are the primary reason for gastrointestinal-related hospital admissions, comprising approximately 1.8 million outpatient visits annually (47). Despite a low fatality rate (0.6%), gallstone disease poses a significant burden in the U.S. Thankfully, the rates of case fatalities have been consistently decreasing, having declined by more than 50% between 1979 and 2004.

There are risks associated with gallstone disease itself. Based on population-based surveys, individuals from the United States and Pima Indians suffering from cholelithiasis exhibited increased overall mortality rates, which are mostly attributable to cardiovascular disease and cancer. (48,49) Additionally, there is a connection

between the increasing occurrence of gallstone disease and an elevated risk of complications, including pancreatitis secondary to gallstones.

Since 1950, the number of cholelithiasis surgeries performed in developed countries has significantly increased.(50) The rate of cholecystectomy saw a significant rise in 1989 due to the advent of LC. For instance, there was 28% growth in cholecystectomies from 1990 to 1993. (51) This was due to the advent of laparoscopic surgery, which provided a less intrusive, more aesthetically pleasing alternative with less surgical risks. It is likely that more procedures were conducted on patients who were once considered high-risk or had only minor symptoms due to this change (52).

With a relative risk of 4.9, a prior medical history of gallstones is linked to a greater likelihood of gallbladder cancer. Most people with gallbladder cancer (between 69% and 100%) have had cholelithiasis before. It's interesting to note that these two disorders frequently coexist in particular groups, suggesting that gallstones may exacerbate gallbladder cancer. Interestingly, Indigenous Americans face an increased likelihood of developing gallbladder cancer, alongside a prevalent occurrence of cholesterol gallstone disease.

In contrast, cholelithiasis is more common in contrasted circumstances but gallbladder cancer is less common A higher risk of cancer is linked to factors such as larger stone size (greater than 3 cm), along with an increased quantity, volume, and weight. The hypothesis that gallstones increase the likelihood of developing gallbladder carcinoma is backed by the finding that the rate of cancer increases as the frequency of cholecystectomy decreases. Despite the commonality of cholelithiasis and the infrequency of gallbladder cancer, there is currently no widespread agreement on performing prophylactic cholecystectomy in cases involving asymptomatic stones.

However, specific situations, such as the existence of large stones exceeding 3 cm, which carry a 4% risk over a span of 20 years, or among older American Indian women with gallstones, may warrant further examination. (53)

Clinical characteristics of gallstone disease :

1. **Asymptomatic:**

Approximately one in ten Americans will experience gallstones at some stage in their lives, making it a public health issue.(54) Around 80% of these, remain without symptoms, indicating that they may never develop concerns like biliary discomfort or related consequences such as acute cholecystitis, cholangitis, or pancreatitis.(55) Cholelithiasis frequently, unintentionally, found during abdominal ultrasonography performed for unrelated medical purposes.(56) Although a small percentage of people with asymptomatic cholelithiasis may later experience biliary pain that necessitates treatment, the risk ranges from 2% to 3%, and it has increased to 10% over a five-year period.(57,58) In addition, a tiny proportion—roughly 1% to 2% per year—face serious gallstone-related problems.(59)

Nonetheless, in certain circumstances, taking the initiative is advised:

1. Risk of Gallbladder Cancer

Individuals with significantly large gallstones (over 3 cm) or those whose gallbladder contains a large number of stones have a high risk of developing gallbladder cancer, which may require a preventative cholecystectomy.(60,61).

2. Sickle Cell Disease

Pigmented gallstones are common among patients with sickle cell disease and often require surgical removal. Early surgery is frequently recommended due to the difficulties in differentiating between symptoms of sickle cell crisis and gallstone-related problems. With a 1% death rate and postoperative complication (>30%), there is still a significant risk, even with prompt surgical intervention.(62,63)

3. Solid organ transplantation:

Solid organ transplantation, which includes organs including the kidney, pancreas, lung, and heart, poses special difficulties. Solid organ transplantation presents even more challenges than stem cell or bone marrow transplantation, which are complicated by cholelithiasis and the formation of biliary sludge. Gallstones that form during such transplant operations frequently cause symptoms and complications, most notably cholecystitis, particularly in the first two years. The gallbladder is usually removed during the hepatectomy procedure, which makes liver transplantation unique in this regard. The advantages of routine ultrasonography monitoring vs the possible advantages of preventive cholecystectomy before and after the transplantation operation are being debated in relation to patients with asymptomatic gallstone problems receiving solid organ transplants.(64)

4. Postoperative Considerations

In certain abdominal procedures, performing a cholecystectomy concurrently might be beneficial because of the heightened risk of developing gallstones. People should therefore think about the possible advantages of preventative cholecystectomy,

particularly those who are severely obese and undergoing weight-loss procedures.(65).

2. Symptomatic gallstones:

Given that most gallstones don't cause any symptoms, it's critical to distinguish between symptoms that are actually caused by gallstones and those that aren't, such as true biliary pain or related problems and common abdominal complaints like dyspepsia.(66) Biliary pain has distinct characteristics such as intense, episodic upper abdominal pain that lasts longer than 30 minutes, along with some accompanying symptoms like radiating pain, nausea, vomiting, and nighttime onset. The primary objective of determining actual biliary discomfort is to accurately predict the potential improvement after cholecystectomy. Currently, despite known gallstones, Cholecystectomy fails to alleviate biliary pain in a specific subgroup of individuals (10–33%).(67,68) The signs of gallstones need to be differentiated from those of other gastrointestinal disorders like dyspepsia and irritable bowel syndrome.(69,70) With the current rise in surgical procedures, it is critical to prevent needless cholecystectomies.

Functional (acalculous) gallbladder disease:

An increased intraluminal pressure seems to be associated to biliary pain, particularly when the gallbladder contracts against an obstruction. This obstruction is typically evident in cases of gallstone disease, frequently as a result of a stone that has been stuck in the cystic duct. The pain mechanism, however, may be caused by problems such as obstructions at the gallbladder outlet, a insufficient synchronization between gallbladder contractions and the relaxation of the sphincter of Oddi, or

heightened visceral sensitivity in instances of functional gallbladder disorders, or biliary dyskinesia. Compromised gallbladder emptying, which is frequently evaluated with cholecystokinin-cholescintigraphy, may be a sign of this disease.(71)

The frequency of acalculous gallbladder disease and the best ways to manage it are still unclear despite developments. There are difficulties in choosing LC as a treatment, particularly in identifying the best candidates. A greater reliance on cholecystectomy for biliary dyskinesia could have a substantial impact on surgical trends, especially since the prevalence of this disorder is unknown. As a result, cholecystectomy is not strongly supported by the available data in situations of functional gallbladder disease.(71)

Gallstones become more common as people age, with a significant rise observed starting at around 40 years old, and older adults face a risk that is four to ten times higher. Gallstone composition also changes with age, developing a higher concentration of black pigment stones in later years after originally being predominantly composed of cholesterol (suggesting an increase in cholesterol secretion and bile saturation). Furthermore, cholecystectomies are more common as people age due to an increase in symptoms and complications.(71)

Between 5% and 30% of pregnant women may experience biliary sludge, which consists of cholesterol, calcium bilirubinate, and mucus, due to elevated levels of female sex hormones. This biliary sludge usually goes away in the postpartum phase; in two-thirds of cases.(72,73) Moreover, definitive gallstones are established in around 5% of cases, whereas minor gallstones (microlithiasis) vanish in approximately one-third of cases. (74)

Gallstone-Associated Complications in Patients with MetS

1. Cholecystitis

Gallbladder inflammation, or cholecystitis, is usually brought on by a gallstone obstructing the cystic duct.

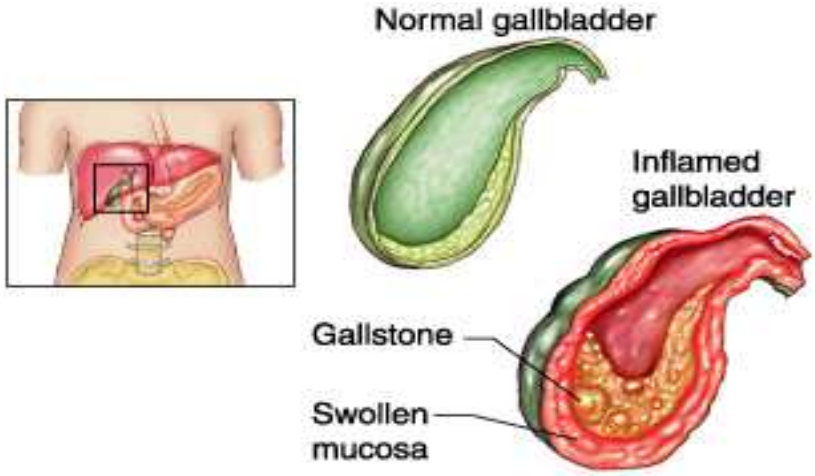


Figure 7. – Gallstone induced Acute calculous cholecystitis

The subsequent factors elevate the likelihood of cholecystitis in individuals with MetS:

Elevated cholesterol: Often associated with MetS, elevated cholesterol causes bile to become supersaturated with cholesterol, which encourages the formation of gallstones.

Insulin resistance: It alters the bile composition and hindering the movement of the gallbladder. Excess weight elevates the likelihood of developing gallstones and cholecystitis, respectively.

2. <u>Gallstone Pancreatitis</u>

When a gallstone blocks the ampulla of Vater or the pancreatic duct, it causes gallstone pancreatitis, which is an inflammation of the pancreas.

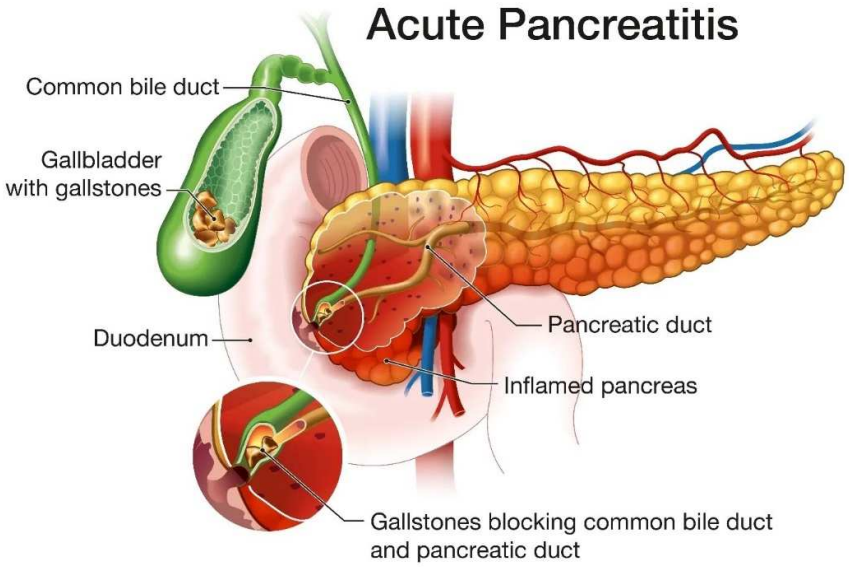


Figure 8. – Gallstone induced Acute Pancreatitis

Several factors increses the risk in patients with MetS:

Dyslipidemia: Gallstones are a result of abnormal lipid levels, which are common in MetS.

Central obesity: A higher incidence of gallstone pancreatitis is linked to excess fat, especially around the belly.

Hyperglycemia: When gallstones are present, elevated blood sugar levels can cause pancreatic injury and raise the risk of pancreatitis.

3. Post-Cholecystectomy Complications

Gallstones are frequently treated by cholecystectomy, which involves surgically removing the gallbladder. However, following surgery, patients with MetS may experience particular difficulties and complications:

- Higher risk of encountering surgical complications is seen in individuals with metabolic disorder, including infections, an extended recovery period, and anaesthetic difficulties, as a result of their obesity and other comorbidities.
- A range of GI symptoms, such as nausea, diarrhoea, and dyspepsia, are part of post-cholecystectomy syndrome. Because of pre-existing IR and impaired lipid metabolism, MetS may make these symptoms worse.

Metabolic Syndrome:

In 2001, the "National Cholesterol Education Program's Adult Treatment Panel III" (ATP III) (75) incorporated MetS as an additional risk factor alongside increased LDL cholesterol. One of the primary reasons for incorporating MetS into the cholesterol guidelines was the increasing prevalence of obesity in the United States. Multiple factors contribute to MetS, with insulin resistance (IR) and obesity—especially visceral fat—being the key risk factors. These frequently coexist, and it's unclear how much each of them contributes to the illness. However, most people agree that the primary cause of the syndrome's rising incidence is the rising trends of obesity in the US and around the world. Age, hormonal imbalances, genetic predisposition, and lack of physical activity are additional elements that can exacerbate MetS. To support routine clinical practice, straightforward diagnostic criteria were established for identifying the condition. The diagnosis requires "the presence of at least three out of five risk factors: high blood pressure, increased

glucose levels, low levels of HDL cholesterol, high serum triglycerides, and expanded waist circumference (central obesity)."

The reliability of the diagnostic criteria and the necessity of clinical intervention to reduce the risk for diabetes and cardiovascular disease (ASCVD) were questioned by communities (both cardiovascular and diabetes) following the release of the ATP III. In response, the "American Heart Association (AHA) and the National Heart, Lung, and Blood Institute (NHLBI)" jointly hosted a clinical definition workshop. The American Diabetes Association (ADA), NHLBI, and AHA then sponsored a seminar focused on the clinical management of MetS. In 2004, summaries of these seminars were released. The NHLBI and AHA then formed a writing group to analyse the new data on MetS and Integrate the outcomes of these workshops to revise the ATP III report with a scientific statement. A circular was issued by AHA/NHLBI containing an update on the ATP III MetS.(76,77). Table 1. displays the clinical criteria for MetS diagnosis that were suggested in the ATP III update. The original ATP III report has only been slightly altered by these criteria.(75)

Diagnostic Criteria for Metabolic Syndrome

Measure (any 3 of the 5 criteria below constitute a diagnosis of metabolic syndrome)	Categorical Cutpoints
Elevated waist circumference*†	≥102 cm (>40 inches) in males
	≥88 cm (>35 inches) in females
Elevated triglycerides	≥150 mg/dL (1.7 mmol/L) or
	On drug treatment for elevated triglyceride‡
Reduced HDL cholesterol	<40 mg/dL (0.9 mmol/L) in males
	<50 mg/dL (1.1 mmol/L) in females or
	On drug treatment for reduced HDL-C‡
Elevated blood pressure	≥130 mm Hg systolic blood pressure or
	≥85 mm Hg diastolic blood pressure or
	On drug treatment for hypertension is an alternate indicator
Elevated fasting glucose	≥100 mg/dL or
	On drug treatment for elevated glucose

Table 1. – Components of Metabolic Syndrome.

A diagnosis of MetS is indicated by “the presence of at least three out of five criteria: abdominal obesity, hypertension, high fasting glucose levels, increased triglyceride levels, and low HDL cholesterol levels.” Both diabetes mellitus and MetS are associated with a higher risk of developing gallstone disease, and MetS has been linked to complications related to gallstones.

WC thresholds remain consistent, except for lower thresholds recommended for individuals with clinical signs of IR or those from ethnic groups with high IR prevalence. Triglyceride and HDL Cholesterol cutoffs stay unchanged, though those on lipid-lowering medications likely have these risk factors. Elevated blood pressure is defined as “systolic ≥130 mm Hg, diastolic ≥85 mm Hg, or being on hypertension medication”.

Obesity:

China and developing countries are experiencing pandemic levels of prevalence of obesity. Obesity, especially abdominal obesity, is a known risk factor for gallstone disease.(78,79) Gallstone disease affects about 25% of morbidly obese individuals. Underweight individuals have lower risk, while overweight adolescents face higher risk. Obese women, especially those with BMI > 32 kg/m², are 2% more likely to develop gallstones. This is partly due to increased activity of the liver enzyme HMG-CoA reductase, which raises cholesterol production and secretion into bile (80).

Waist circumferences:

Obesity is defined as "abnormal or excessive fat accumulation that may impair health" by WHO. The BMI is acknowledged in this document as an approximate indicator of the level of adiposity. It is possible for people with normal BMI to have more than 30% body fat. This fat is closely linked to cardiometabolic risk, if it is

mainly distributed as visceral or central fat.(81) These individuals are more susceptible to diabetes and cardiovascular disease because to their aberrant adipose tissue distribution and function. According to the World Health Organization, these abnormally functioning fat deposits qualify as obesity, which can lead to mechanical, dysmetabolic, and atherosclerotic issues that deteriorate health. Since the 1980s, North America's obesity rates have been steadily increasing. The proportion of obese adults in the US and Canada as of 2015 was 38.2% and 25.8%, respectively.(4). Ischemic heart disease rates decreased by 55% in the US and 60% in Canada between 1990 and 2015, but the US decline has stopped off since 2011, while Canadian rates are still declining. (82,83)

The normal-weight metabolically obese phenotype may range from 13% to 38% in prevalence based on direct measurements of fat distribution or metabolic traits.(84,85) Metabolic issues are more common with truncal fat, measured by WC, waist-to-hip ratio, or waist-to-height ratio (Table 2). Subcutaneous fat, especially in the hip and thigh area, may protect against harmful fat buildup in the abdomen.(86,87)

Table 2: Measures of Body Fat Distribution: A) Mass-Based and B) Distribution-Based (88,89)

A)		
MASS-BASED MEASURE	**DEFINITION**	**COMMENTS**
Body mass index[11]	Weight in kg divided by the square of the height in m	Does not distinguish between lean and fat tissue mass
• Underweight	< 18.5 kg/m^2	Associated with higher mortality
• Normal weight	18.5-24.9 kg/m^2	Lowest mortality associated with these categories
• Overweight	25.0-29.9 kg/m^2	
• Obesity class 1	30.0-34.9 kg/m^2	No consistent association with increased mortality
• Obesity class 2	35.0-39.9 kg/m^2	Direct association with increased mortality
• Obesity class 3	≥ 40.0 kg/m^2	
B)		
DISTRIBUTION-BASED MEASURES	**VALUES REPRESENTING INCREASED RISK**	**SURROGATE MEASURES OF CENTRAL OR VISCERAL ADIPOSITY**
Waist circumference	Females ≥ 80 cm Males ≥ 95 cm	Cut points vary according to ethnicity, sex, and age[12]
Waist-to-hip ratio	Females ≥ 0.85 Males ≥ 0.95	Cut points not well established for ethnicity[13]
Waist-to-height ratio	Increased risk 0.50-0.60 Substantial risk > 0.60	Cut points the same for ethnicity, sex, and age[12] Best predicts visceral fat mass[14,15]

According to WC, abdominal obesity is rising faster than overall obesity.(90,91)

In the U.S., some non-Asian adults with slightly elevated waist circumference (94–101 cm for men, 80–87 cm for women) may have a genetic predisposition to IR and benefit from lifestyle changes. For Asians, lower thresholds (≥90 cm for men, ≥80 cm for women) are more suitable. Fibrates and nicotinic acid are often prescribed for high TG and low HDL cholesterol, indicating patients on these medications likely have high TG and low HDL levels. The "International Diabetes Federation" recently released similar criteria for the MetS, which needs proof of abdominal obesity to be clinically diagnosed. The criteria for abdominal obesity differ by ethnicity.(92) Otherwise, the diagnosis requires three of the five risk factors, with abdominal obesity being a necessary one.

The criteria for identifying abnormalities and risk factors align with those of ATP III. The updated ATP III guidelines emphasise lifestyle changes, as primary strategies for managing MetS and drug therapy is recommended for addressing specific risk factors like obesity, lipid disorders, HTN, and diabetes, following established guidelines from the "AHA, ADA, and NHLBI". However, MetS is not a tool for determining absolute risk; instead, well-established risk-assessment methods should guide clinical care and medication decisions. (76,77)

In comparison to treatments that target individual risk factors, proper management of the MetS presents a chance to lower risk for both type 2 diabetes and ASCVD. The AHA/NHLBI update, and a recent ADA paper, all emphasize the need for additional research to fully comprehend the pathophysiology of the MetS (92). All of these findings are anticipated to raise awareness of the disease and encourage further investigation. Due to the intricacy of the condition, there are numerous

possible study directions that could improve our knowledge of the control and pathophysiology of the syndrome. (92)

Dyslipidemia:

Although there is no conclusive evidence of a clear association between elevated levels of total cholesterol (hypercholesterolemia) and gallstone disease, elevated homocysteine levels may also be suggestive of a possible association with gallstone disease. (93) Cholesterol gallstone disease is inherently associated with metabolic factors. Interestingly, those with hypertriglyceridemia and lower HDL cholesterol are at a higher risk of gallstones.

IR is a major risk factor for cholesterol gallstones, as it disrupts cholesterol and bile salt metabolism. Hepatic IR can increase cholesterol secretion, reduce bile salt production, and impair gallbladder motility, contributing to gallstone formation.(94,95)

Hypertension and Gallstone Disease:

It's unclear exactly how high blood pressure contributes to gallstone disease. Nonetheless, the fact that people with hypertension frequently show elevated sympathetic nervous system activity is a likely reason. Bile stasis may result from this elevated sympathetic tone's inhibition of bowel movements and slowing of gastrointestinal motility. Biliary stasis plays a crucial role in gallstone formation by causing bile to become oversaturated with cholesterol. Hypertension is often associated with MetS, IR, and obesity, all of which are key factors in the development of gallstones [96,97].

Moreover, systemic inflammation and endothelial dysfunction caused by hypertension may change the composition of bile by promoting oxidative stress and lipid peroxidation. These alterations may increase the likelihood of gallstone development by causing cholesterol in bile to crystallize [98]. Furthermore, alterations in the composition of bile have been linked to antihypertensive drugs like diuretics, which may make bile more lithogenic. According to studies, long-term use of thiazide diuretics in particular may increase bile cholesterol levels, making people more susceptible to gallstone disease [23].

Weight loss:

Diet with low calorie or surgery that results in rapid weight loss are linked to gallstone development in a significant proportion of people, ranging from 30% to 71%. Notably, the risk of getting stones is significantly increased and stones show up within 6 weeks of surgery if you lose more than 1.5 kg per week following bariatric surgery. Gallstones brought on by weight reduction are usually asymptomatic; approximately 7% to 16% of individuals develop symptoms. (94)

Diet and total parental nutrition:

Aside from the fact that eating excessive number of calories contributes to obesity, the role of dietary composition is still uncertain and difficult to identify

Research indicates that consuming foods high in fats, cholesterol, refined carbs, or certain plant-based proteins may elevate the risk of gallstone. In contrast, incorporating healthy fats, beverages like coffee, dietary fiber, nutrients such as vitamin C, calcium, and consuming alcohol in moderation may help lower the likelihood of gallstones. Notably, the main cause of the significant rise in cholesterol gallstones among American Indians and the post-World War II trend in European

nations is the adoption of a more Western diet, It is characterized by low fibre levels and high levels of fat (triglycerides) and processed carbs.

In Asian nations, the switch from pigment to cholesterol stones may also be attributed to this nutritional change. (95). Some people may develop cholesterol gallstones in response to dietary changes because of genetic differences.

Total parenteral nutrition is a recognized risk factor for gallstone disease, microlithiasis, and acute acalculous cholecystitis in critically ill patients. In an intensive care unit, these issues usually appear 5–10 days following fasting. According to studies, almost half of patients experience gallbladder sludge as shown by ultrasonography after four weeks of TPN; by six weeks, the prevalence rises to all patients. Surprisingly, most sludge patients do not exhibit any symptoms. (99). Fortunately, sludge typically resolves within four weeks after stopping TPN and resuming oral intake, similar to patterns seen during pregnancy or rapid weight loss, where sludge disappears once the underlying cause is addressed. Gallbladder stasis, caused by reduced intestinal stimulation during fasting, may contribute to this condition. Additionally, ileal conditions often require TPN, can disrupt bile acid cycling, potentially increasing bilirubin absorption and liver excretion (100).

Lifestyle factors and socioeconomic status:

There is ongoing discussion over the exact correlation between gallstones and socioeconomic class. Gallbladder illness is negatively correlated with socioeconomic position in a previous study that involved Mexican Americans and non-Hispanic whites. But it's also likely that socioeconomic status is just a stand-in for other risk factors. It's yet unclear how smoking affects cholelithiasis.

Low levels of physical activity make people more prone to gallstone disease, while high levels of physical activity can help prevent cholelithiasis regardless of its implications for weight loss. (101). Gallstone disease incidence may be significantly reduced by performing moderate endurance workouts or vigorous exercises for less minutes per week. (102)

MATERIALS AND METHODS

Source of Data: Patients of age 18-60 years with Metabolic Syndrome having cholelithiasis at KLE Dr. Prabhakar Kore Hospital, Belagavi

Study Design: A Cross-sectional study

Study Period: 1st September 2023 – 31st August 2024

(One year study)

Sample Size:

In this study, 120 individuals with gallstone disease were compared with various components of Metabolic Syndrome.

Inclusion Criteria:

All patients admitted in General surgery ward of KLE's Dr Prabhakar Kore hospital & MRC with history of gallstone disease.

- Patients of 18-60 years of age group
- All patients with or without Metabolic syndrome having gallstone disease.
- Patients who are willing to participate in the study

Exclusion Criteria:

- Patients with diagnosed acute pancreatitis
- Complicated gallstone disease like mucocele, empyema and perforation of gallbladder
- Pregnant females
- Immunocompromised patients
- History of any major gastrointestinal surgeries
- Malignancy or carcinomas

Data collection procedure:

Every patient admitted in General Surgery ward, who meets the inclusion criteria. All patients will provide written informed consent prior to the start of the study. By taking a full history, conducting a comprehensive clinical examination, and collecting laboratory and radiographic studies in accordance with the proforma, patients' demographic and clinical data will be assembled. Physical examination will be performed on the paticipants as per diagnostic criteria of Adult Treatment Panel III.

Participants will undergo a head to toe general physical examination. Waist circumference is taken at umbilicus in standing position. The BP readings are obtained after subject had sat down and rested for 15 mins.

Complete workup of the patients will be done which includes -

1. Routine Blood Investigations
2. Urine Routine Microscopy
3. Electrocardiograph

Radiological Imaging: Chest X ray, Ultrasound of abdomen and pelvis ± CECT (Abdomen + Pelvis).

Appropriate Medical treatment will be given for the patients with MetS:

- Oral hypoglycemic agents or insulin for Diabetes mellitus patients depending on individual glycemic control
- Oral antihypertensives for Hypertensive patients
- Proper diet counseling.
- Exercise and lifestyle modifications.

- Patients with high cholesterol levels will be managed on statins with medical consultation.

Based on the evaluation, patients fitting into the criteria of MetS were subjected to surgery.

Appropriate surgical management with Laparoscopic Cholecystectomy with option for conversion to open procedure was performed.

Post operatively, patient will be given appropriate treatment with antibiotics (eg. Inj XONE 1g, Inj. METRONIDAZOLE 400mg), analgesics (eg. Inj. DOLO 1g, Inj INAC 75mg), and other supportive treatment (like Inj. EMESET 4mg, Inj. PANTOPRAZOLE 40mg) as required.

Dressing was changed on post operative day 3 and suture line were checked. Sutures removal was done on post operative day 10 or later.

STATISTICAL ANALYSIS –

Statistical Software:

Analysis were performed using R version 4.3.3. A p-value of less than 0.05 was considered statistically significant for all tests.

Data Presentation:

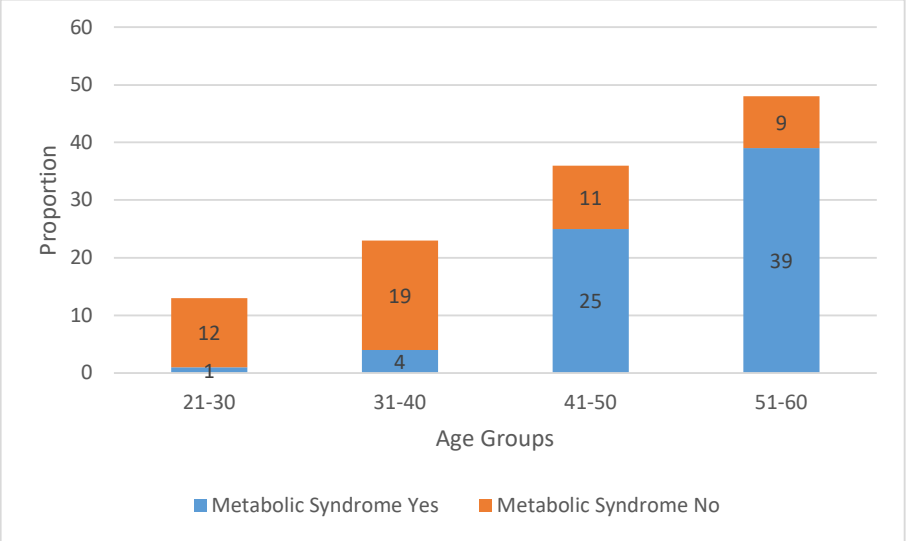
Results were presented in tables and figures that included means (SD), medians (IQR), frequencies, and percentages. Graphical representations, such as bar charts, pie charts, and box plots, illustrated key findings. Tables provided detailed summaries of demographic characteristics, clinical profiles, and laboratory findings.

RESULTS

RESULTS AND OBSERVATION

Table 3. Association of age of the patients with presence of MetS (N=120)

Age group (in years)	MetS	
	Yes	No
	n	n
21-30 (10.8%)	1	12
31-40 (19.2%)	4	19
41-50 (30)	25	11
51-60 (40%)	39	9
n = 120	**69**	**51**

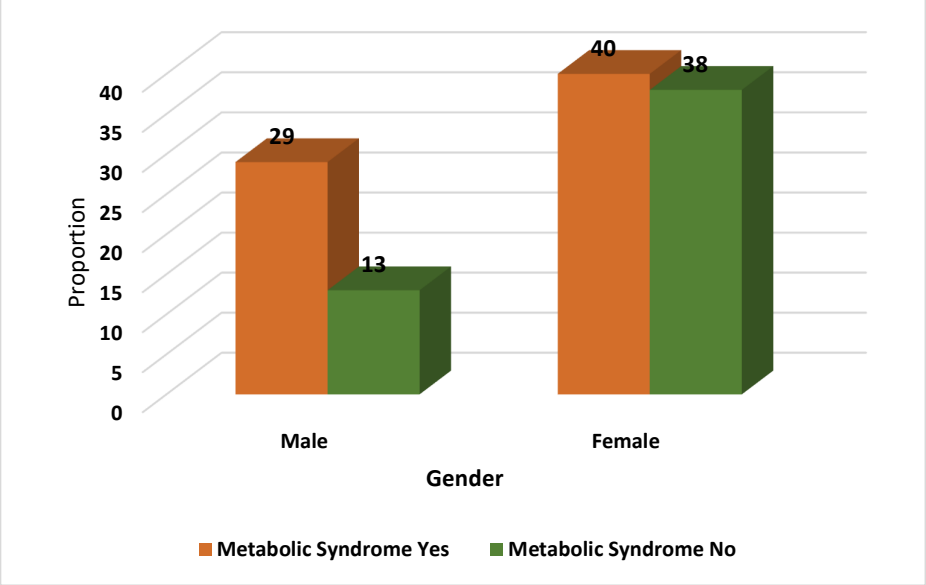


Graph 1. Association of age of the patients with presence of MetS in patients with GSD

Table 3 (Graph 1.) presents the association between age and the presence of MetS in a cohort of 120 patients of gallstone disease. Of the 69 individuals with MetS, the highest prevalence was observed in the 51-60 age group, where 39 patients had MetS, followed by 40–50 age group accounting for 25 patients. The data reveals a clear age-related increase in the prevalence of MetS in patients with GSD.

Table 4. Association of gender of the patients with presence of MetS (N=120)

Gender	MetS	
	Yes	No
	n	n
Male (35%)	29	13
Female (65%)	40	38
n = 120	**69**	**51**

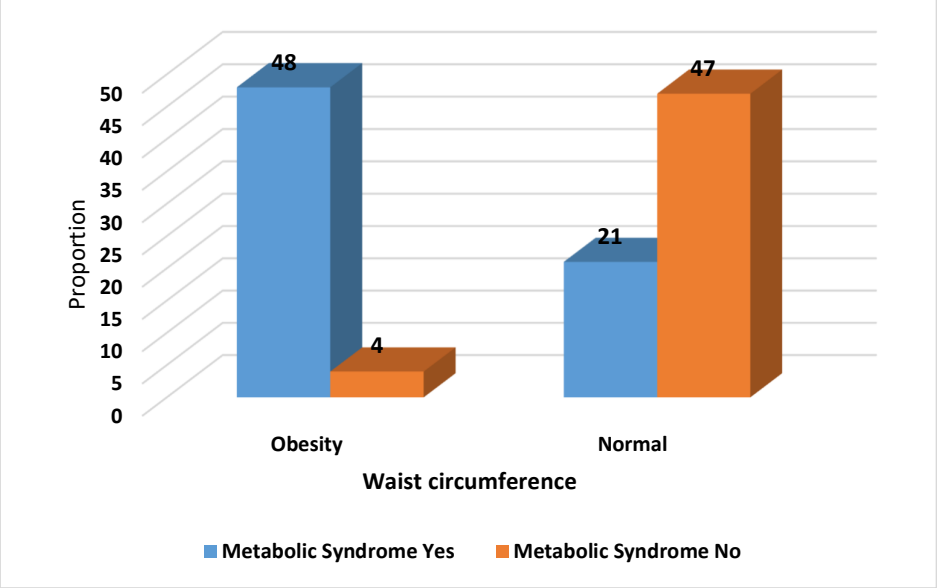


Graph 2. Association of gender of the patients with presence of MetS in patients with GSD

Table 4 (Graph 2) illustrates the association between gender and the presence of MetS. Of the 120 patients, 29 men had MetS whereas 40 were women. Our study found that GSD in presence of MetS was fairly common in men in equal proportion to female population.(29 & 40).

Table 5. Association of waist circumference (obesity/normal) of the patients with presence of MetS (N=120)

Waist circumference	MetS	
	Yes	No
	n	n
Obesity (43.3%)	48	4
Normal (56.7%)	21	47
n = 120	**69**	**51**

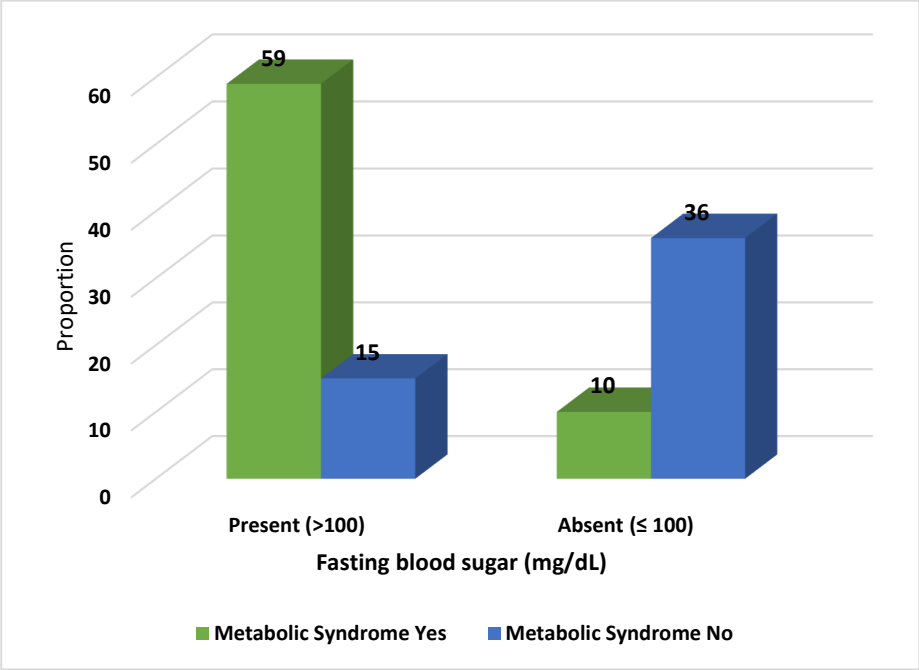


Graph 3. Association of waist circumference (obesity/normal) of the patients with presence of MetS in patients with GSD

Table 5 (Graph 3) shows the (as an indicator of obesity or normal weight) and the presence of MetS. Among patients with obesity, 48 had MetS, while only 21 patients with normal waist circumference had MetS. The data reveals a clear association between waist circumference and the prevalence of MetS in patients with GSD.

Table 6. Association of fasting blood sugar of the patients with presence of MetS (N=120)

Fasting blood sugar (mg/dL)	MetS	
	Yes	No
	n	n
Present (>100) (61.7%)	59	15
Absent (≤ 100) (38.3%)	10	36
n = 120	**69**	**51**

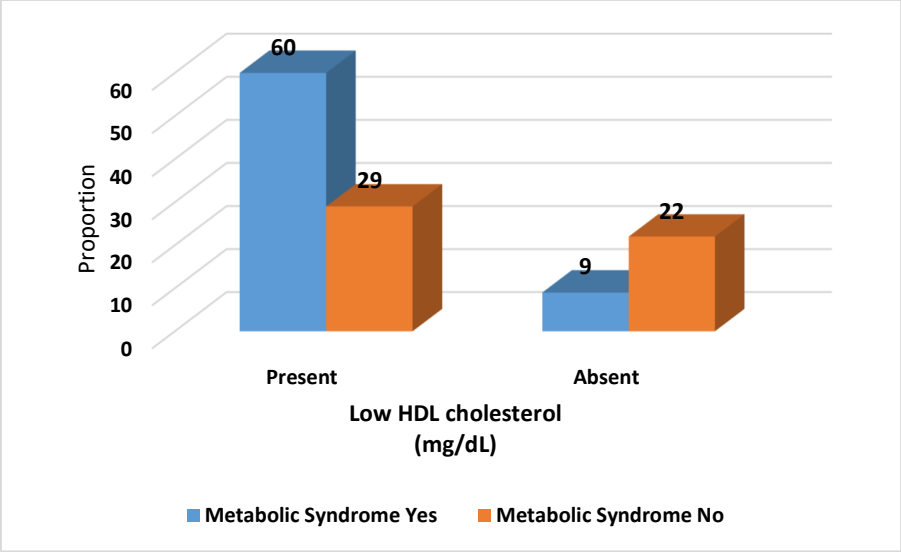


Graph 4. Association of fasting blood sugar of the patients with presence of MetS in patients with GSD

Table 6 (Graph 4) shows the association between fasting blood sugar levels and the presence of MetS. Among patients with fasting blood sugar levels greater than 100 mg/dL, 59 had MetS, while among those with fasting blood sugar levels of 100 mg/dL or less, 10 patients had MetS. The data reveals a strong association between fasting blood sugar levels and the prevalence of MetS in patients with GSD.

Table 7. Association of Low HDL of the patients with presence of MetS (N=120)

Low HDL cholesterol (mg/dL)	MetS	
	Yes	**No**
	n	n
Present (74.2%)	60	29
Absent (25.8%)	9	22
n = 120	**69**	**51**

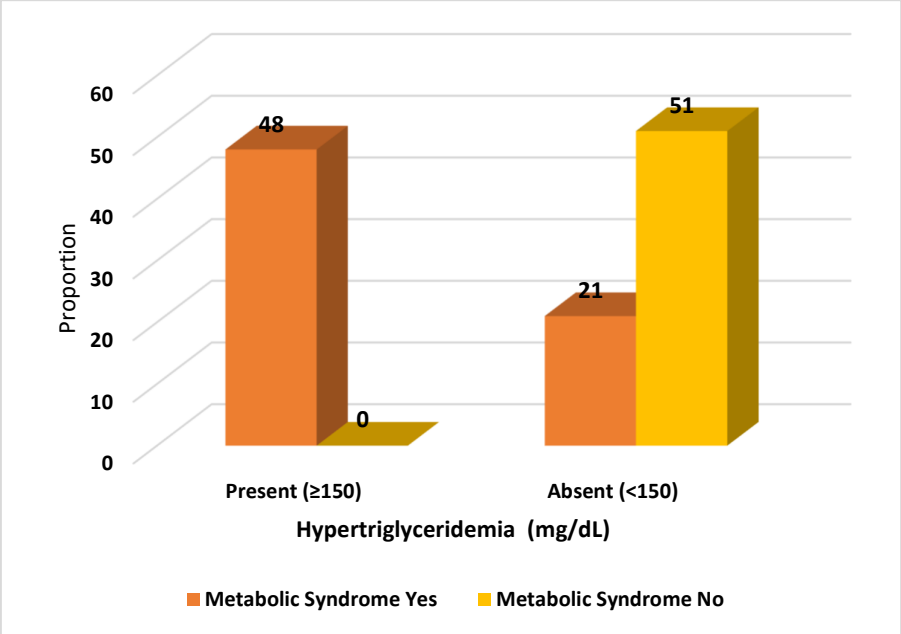


Graph 5. Association of Low HDL of the patients with presence of MetS in patients with GSD

Table 7 (Graph 5) presents the association between low HDL cholesterol levels and the presence of MetS. Among patients with low HDL cholesterol, 60 had MetS, while those without normal HDL cholesterol, 9 patients had MetS. The data reveals a clear association between low HDL cholesterol levels and the prevalence of MetS in patients with GSD. It appears through this study that HDL appears to be a protective factor in preventing MetS.

Table 8. Association of hypertriglyceridemia of the patients with presence of MetS (N=120)

Hypertriglyceridemia (mg/dL)	MetS	
	Yes	No
	n	n
Present (≥150) (40%)	48	0
Absent (<150) (60%)	21	51
n = 120	**69**	**51**

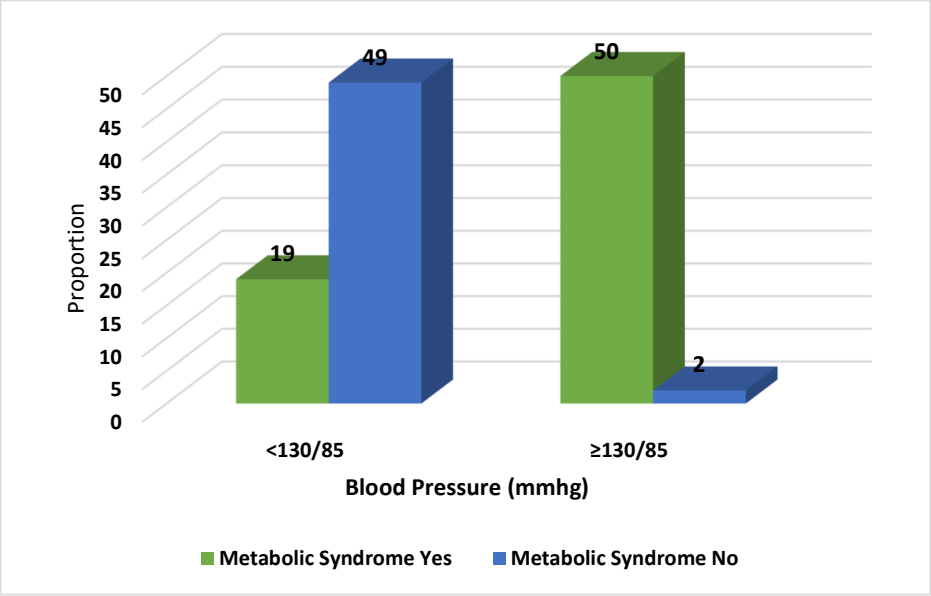


Graph 6. Association of hypertriglyceridemia of the patients with presence of MetS in patients with GSD

Table 8 (Graph 6) illustrates the association between hypertriglyceridemia and the presence of MetS in patients with gallstone disease. Among patients with hypertriglyceridemia (defined as triglyceride levels ≥150 mg/dL), 48 had MetS, while among patients without hypertriglyceridemia (triglyceride levels <150 mg/dL), 21 patients had MetS. The data shows a significant association between hypertriglyceridemia and the prevalence of MetS in patients with GSD.

Table 9. Association of blood pressure of the patients with presence of MetS (N=120)

Blood Pressure (mmhg)	MetS	
	Yes	No
	n	n
<130/85 (56.6%)	19	49
≥130/85 (43.4%)	50	2
n = 120	**69**	**51**



Graph 7. Association of blood pressure of the patients with presence of MetS in patients with GSD

Table 9 (Graph 7) presents the association between blood pressure levels and the presence of MetS. Among patients with blood pressure levels <130/85 mmHg, 19 had MetS, while among patients with blood pressure levels ≥130/85 mmHg, 50 had MetS. The data reveals a clear association between high blood pressure and the prevalence of MetS in patients with GSD.

DISCUSSION

This study assesses the relationship between MetS and gallstone disease. Gallstone disease often leads to cholecystitis, pancreatitis, and biliary colic (103). The increased prevalence of gallstone disease has been related to several metabolic conditions (104). MetS is recognized as a significant risk factor for chronic illnesses, mainly diabetes mellitus & ASCVD (6) Nonetheless, research on its role in gallstone formation is still ongoing. This study supports the idea that MetS is a major factor in gallstone formation, showing a strong connection between components of MetS and gallstone disease (105). Understanding the association may aid in lowering the gallstones incidences and related complications through early detection and MetS-focused treatments (106).

Age and Occurrence of Gallstone Disease:

The findings indicate that the prevalence of gallstone disease increases with age, with the largest incidence occurring in those aged 51 to 60 years. (107). These results align with earlier studies suggesting that ageing could contribute to the formation of gallstones due to prolonged exposure to metabolic risk factors (108). Furthermore, the physiological changes that accompany aging also promote the development of gallstones, like decreased bile acid production, increased cholesterol release in bile, and decreased gallbladder motility (109). This strong correlation further supports the role of aging in gallstone development and emphasizes the importance of early metabolic health interventions.(110).

Gallstone disease tends to be significantly more prevalent among older individuals with MetS compared to younger individuals, as indicated by multiple studies (111). This connection may be due to chronic metabolic problems that arise from prolonged exposure to dietary and lifestyle risk factors. (112). Additionally,

hormonal changes associated with aging may lead to higher bile cholesterol saturation, which would facilitate the production of gallstones (113). Lifestyle changes and MetS management are necessary to reduce the incidence of gallstone disease (114).

Gender and Occurrence of Gallstone Disease:

Gallstone disease was diagnosed in females (40 cases) more than males (29 cases) (115). This finding is consistent with previous research that indicates hormonal factors, specifically oestrogen, may contribute to bile cholesterol saturation and gallstone formation, even though the connection was not statistically significant.(116) Studies have shown that oestrogen increases cholesterol secretion from the liver and decreases bile acid production, causing bile to become oversaturated and contributing to stone formation (117). Another important hormone, progesterone, is also known to decrease gallbladder mobility, which raises the risk of gallstone development and causes bile stasis (118). Gallstone disease occurs more frequently in women, particularly in those who have MetS, which may be explained by these hormonal factors (119).

Additionally, changes in the movement of gallbladder and the bile composition during pregnancy can increase the likelihood of gallstones in women. (120). Increased cholesterol secretion during pregnancy is caused by increasing oestrogen levels, whereas bile stasis is the result of progesterone-induced gallbladder relaxation (121). Moreover, the likelihood of developing gallstones rises due to components of MetS that are more prevalent among women, such as obesity and IR (122). These results emphasize on how crucial it is to take gender-specific risk factors into account when developing preventative and treatment strategies for gallstone disease, especially when MetS is included (123).

Obesity, Waist Circumference, and Gallstone Disease :

There are numerous research that support the well-established association between obesity and gallstone disease. Gallstone production is strongly correlated with increased body fat, as indicated by the fact that a significant number of people with gallstone disease are obese (124,125). Research has demonstrated a significant relationship between central obesity, and the incidence of gallstone disease, making it an independent risk factor (126). The fundamental mechanism is that obese people secrete more hepatic cholesterol, which causes bile supersaturation (123). Additionally, obesity hinders gallbladder movement, which exacerbates gallstone development through promoting cholesterol crystallization and bile stasis (127).

Epidemiological studies indicate that individuals with elevated BMI and waist circumference are at a greater risk of developing gallstones. The relationship between these factors involves a complicated process that includes persistent inflammation, IR, and changes in lipid metabolism. (128,116). A pro-inflammatory state brought on by obesity alters the composition of bile and damages gallbladder function, which raises the risk of gallstones (129). Furthermore, MetS, which is quite common in obese people, increases this risk by aggravating IR and dyslipidaemia, two conditions that are linked to the development of gallstones (130).

Fasting Blood Sugar and Occurrence of Gallstone Disease:

A significant correlation has been observed between gallstone disease and hyperglycaemia (>100 mg/dL),observed in 59 patients with MetS (131). IR, a major factor in metabolic syndrome, contributes to gallstone formation by boosting liver cholesterol secretion and reducing gallbladder movement, causing bile buildup and cholesterol crystallization.(116). Gallstones form when the gallbladder's ability to contract reduces, which slows bile emptying, leading to the accumulation of cholesterol-rich bile.(132).

Gallbladder function is further hampered by chronic hyperglycaemia, which is associated with oxidative stress and systemic inflammation (131). According to research, people with diabetes and chronic hyperglycaemia are more likely to develop gallstone disease because autonomic neuropathy impairs gallbladder contractions, making bile stasis worse (133). Furthermore, chronic hyperglycaemia impairs the metabolism of bile acids, raising cholesterol saturation and increasing bile's lithogenicity (114). These findings emphasize the importance of managing blood sugar levels, particularly among individuals with MetS.

Blood Pressure and Occurrence of Gallstone Disease:

Studies have reported a significant correlation between gallstone disease and hypertension (134). While it is still unclear how exactly hypertension and gallstone formation are related, some theories suggest that gallstone development is related to chronic hypertension, which causes oxidative stress, systemic inflammation, and vascular dysfunction (135). The gallstones occurrence is also strongly linked to IR and abnormal lipid metabolism, both of which are common in people with hypertension (136).

Additionally, studies indicate that hypertensive patients have heightened sympathetic nervous system activity that may decrease gallbladder motility, resulting in bile stagnation and a higher risk of cholesterol crystallization (137). Additionally, MetS and hypertension usually coexists, which elevates the risk factors associated with the development of gallstones (138). These findings highlight the importance of taking measures to reduce the occurrence of gallstone disease, blood pressure control is essential in addition to other components.

Dyslipidemia and Occurrence of Gallstone Disease:

There is a significant relationship between gallstone disease & low HDL cholesterol, which is seen in 60 patients with MetS (74). HDL cholesterol helps eliminate surplus cholesterol from bile and is crucial for the process of reverse cholesterol transport. (139). Decreased HDL levels disrupt this protective mechanism, imbalance in bile composition promotes cholesterol supersaturation and gallstone development (140).

According to the study, 48 patients of gallstone disease with MetS have hypertriglyceridemia (triglycerides ≥150 mg/dL) (141). By modifying metabolism of bile acids and raising hepatic cholesterol output, elevated triglyceride levels promote the development of gallstones (142). This change in metabolism raises the likelihood of cholesterol crystallization and gallstone development by promoting bile that contains a high level of cholesterol. (118). Moreover, IR hinders gallbladder movement and encourages bile stasis, is intimately linked to hypertriglyceridemia (143).

CLINICAL IMPLICATIONS

The findings of the study carry significant clinical importance. Due to the strong relationship between MetS and gallstone disease, healthcare providers ought to regularly assess the components of MetS in patients at risk for developing gallstones. The results highlight the importance of early identification and management of metabolic risk factors to potentially reduce the incidence of gallstone disease, especially given the rising rates of MetS in the Indian population. By recognizing and addressing issues such as obesity, dyslipidaemia, hypertension, and hyperglycaemia, the occurrence of gallstones and their associated complications can be minimized.

Promoting lifestyle changes, including dietary changes and increased physical activity, should be prioritized as key preventive strategies. In conjunction with consistent exercise, a diet rich in fibre while low in refined carbohydrates and saturated fats can aid in decreasing IR and obesity, thereby reducing the likelihood of gallstone development. Additionally, people with severe metabolic disorders will require medical management. antihypertensives, insulin-sensitizing drugs, and lipid-lowering medicines may all help reduce the risk of gallstones. In order to promote early intervention and avoid complications, clinicians should also take into account gallstone screening in patients with MetS, especially those who have several risk factors.

LIMITATIONS

There are some limitations to this study. Gallstone incidence and MetS cannot be causally linked according to the cross-sectional methodology. To validate these relationships, longitudinal research is required. Furthermore, variables that may also affect the formation of gallstones, such as dietary habits, use of medications, and genetic susceptibility, were not taken into account.

CONCLUSION

This research shows a strong correlation between various parameters of MetS and the development of gallstone disease with hypertension, hyperglycaemia, obesity, and dyslipidaemia emerging as major contributing factors. Focused preventative strategies, including lifestyle modifications and adequate medical treatment, are essential for minimizing the impact of gallstone disease. To establish the cause and determine appropriate interventions for lowering the risk of gallstones in vulnerable populations is important, future research should concentrate on longitudinal studies. Gallstone disease and its related complications can be avoided by early detection and treatment of MetS components. To decrease the growing incidence of gallstone disease, public health campaigns should also stress the significance of lifestyle modifications and metabolic health education. The entire burden of gallstone disease and the risks associated with its complications can be greatly minimized by tackling the root causes of MetS, which will improve patient outcomes and the effectiveness of the treatment.

SUMMARY

An observational study was conducted among 120 patients diagnosed with gallstone disease to evaluate for the presence of metabolic abnormalities, including obesity, dyslipidemia, hypertension, and glycemic status. The findings indicate that several metabolic factors are prevalent among individuals with gallstone disease, suggesting a possible link between metabolic dysfunction and gallstone formation.

1. A higher prevalence of gallstone disease was observed in individuals aged 41–60 years compared to younger age groups.

2. A greater number of females were diagnosed with gallstone disease compared to males. While the study did not assess the role of hormonal factors, the predominance of female patients is consistent with known epidemiological trends.

3. Patients with gallstone disease exhibited a higher prevalence of increased waist circumference. This finding suggests a possible link between central obesity and gallstone disease, though further investigation is required to establish causality.

4. Dyslipidemia, particularly low HDL cholesterol levels and hypertriglyceridemia, was observed in a substantial proportion of patients with gallstone disease. These results align with previous studies that have reported a connection between lipid metabolism disturbances and gallstone formation.

5. Notable proportion of patients with gallstone disease exhibited elevated fasting blood sugar levels. While this suggests a potential association between glycemic dysregulation and gallstone disease, additional studies are needed to clarify the nature of this relationship.

6. A higher proportion of patients with gallstone disease had elevated blood pressure. While this study did not determine a direct causal link, the coexistence of hypertension and gallstone disease warrants further research.
7. Gallstone disease was the primary diagnosis among study participants, with many patients also exhibiting metabolic abnormalities such as obesity, dyslipidemia, and hypertension. The concurrent presence of these factors highlights the need for comprehensive metabolic assessments in patients with gallstone disease.

The findings suggest that gallstone disease is frequently associated with metabolic risk factors such as obesity, dyslipidemia, hyperglycemia, and hypertension. While these associations do not imply causation, they underscore the importance of routine metabolic evaluations in patients diagnosed with gallstone disease. Further research could help to understand this relationship and guide preventive and management strategies.

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ANNEXURE 1 : CONSENT FORM

KLE ACADEMY OF HIGHER EDUCATION AND RESEARCH.

BELAGAVI, KARNATAKA

INFORMED CONSENT FORM

"A STUDY OF ASSOCIATION OF METABOLIC SYNDROME WITH THE OCCURRENCE OF GALLSTONE DISEASE –A ONE YEAR CROSS-SECTIONAL STUDY AT TERTIARY CARE HOSPITAL, BELAGAVI**"**

Introduction: To study the relation between metabolic syndrome and its components (such as obesity, type II diabetes mellitus, hypertension and a complete cholesterol panel) with gallstone disease.

Explanation of procedure: Demographic data**,** detailed history, clinical examination and laboratory and radiological investigation will be recorded as per the proforma.

Withdrawal from participation in the study: Participation in this study in voluntary. You will be free to decide whether to participate in this study or continue participation once enrolled. In case you decide to withdraw your participation, you are free to do so. However, please convey the decision to the principal investigator.

Possible benefits from participating in the study: You will/will not get any benefits by participating in this study. The data gathered will help population at large.

Possible risks from participating in the study: There are no risks involved in participating in this study

Privacy and confidentiality: The information collected from you will be coded, to prevent any person to identify you. Your identity will never be revealed. The data collected from you will be kept confidential and only processed or aggregated data will be used for publication.

Financial incentives: You will not receive any payment for participating in this study.

Cost of investigations which are not routinely done, during the course of study will be paid by the **principal investigator.**

Authorization for publication of aggregated data: Results obtained after processing of the aggregated data will be published for scientific purpose and or presented to scientific groups. However, your identity will never be revealed.

Questions: In case of any questions with regard to this study, you are free to contact:

If you have any question or complaints with regard to your right as study participant you may contact Dr Harsha Hegde, Chairperson, Ethical committee of JNMC, 0831-2473777 Extn 4052.

Legal rights: By signing this consent form, we are not waving any of your legal rights

CONSENT STATEMENT

I am making a voluntary decision to participate in the study "**A STUDY OF ASSOCIATION OF METABOLIC SYNDROME WITH THE OCCURRENCE OF GALLSTONE DISEASE –A ONE YEAR CROSS-SECTIONAL STUDY AT TERTIARY CARE HOSPITAL, BELAGAVI**". My signature below indicates that I have decided to participate and I have read the information provided above or the information provided above has been read to me in the language that I understand best. I was given the opportunity to ask questions and that they have been answered to my satisfaction.

Name of the participant:

Signature or left thumb impression of the participant:

Name of the witness:

Signature or left thumb impression of the witness:

Name of the investigator:

Signature of the investigator:

ANNEXURE 2: PROFORMA

PROFORMA

S.No.: OP/IP No.:

Name: Age/sex:

Date of Admission:

Address:

Date of Discharge:

1. Chief Complaints

2. History of Present Illness:

- Pain:

  Duration

  Onset
  Site of pain
  Character
  Radiation
  Aggravating factors
  Relieving factors
  Associated symptoms
  Any other

3. Past History

History related to medical disorders
History of similar illness in past
History of any surgery in the past

4. Personal History:

Diet
Appetite
Sleep
Bowel &Bladder habits
Habits: Smoking/Alcohol/tobacco or pan chewing

5 Menstrual History (females): Menarche-
Cycles-
LMP:
H/o dysmenorrhea
H/o menorrhagia
H/o passage of clots

6 Obstetric History (females): Obstetric score-

H/o cesarean section:
H/o Tubectomy:

7 Family History:

History of similar illness in family

8 General Physical Examination

Conscious, co-operative and oriented
Built and Nourishment
Pallor/Icterus/Cyanosis/ Clubbing / Edema/ Lymphadenopathy

Vital Data:

Pulse: Temperature: Blood Pressure: Respiratory Rate:

9 Systemic Examination:

PER ABDOMEN:

Inspection

• Shape: Distension:
• Movements with Respiration:
• Engorged veins/Scars/sinuses:

• Any skin changes:

• Any visible mass:

• Hernial orifices:

• Umbilicus :

Palpation

- Soft/firm:
- Guarding/rigidity:
- Tenderness:
- Any palpable mass:
- Any palpable organomegaly:
- Other findings:

Percussion: Whole abdomen: resonant/dull:

Free fluid: if present, shifting dullness/fluid thrill:

Auscultation:
Bowel Sounds present/absent/ present &sluggish:

CARDIOVASCULAR SYSTEM:

RESPIRATORY SYSTEM:

CENTRAL NERVOUS SYSTEM:

Provisional Diagnosis:

Investigations
Routine:
Blood
Hb% :
TC :
DC: N/L/E/M -
LFT- TP:
TB/DB/IB:
Serum Albumin:
Serum Globulin:

A:G-
SGOT- SGPT- ALP-

FBS/PP/HBA1C:

Blood urea:

Serum Creatinine:

PT/INR

Lipid profile: Cholesterol
HDL
LDL
Urine*:* Sugar: Albumin: Microscopy:

ECG:

X-ray:

USG:

<u>Surgical Treatment:</u>

ANNEXURE 3: MASTER CHART

S. No.	Age	Sex	WC	WC	BP	FBS	TG	HDL	MetS	Diagnosis
			(Normal/ Obesity)	(cm)	(mmHg)	(mg/dl)	(mg/dl)	(mg/dl)	(Y/N)	
1	53	F	Obesity	95	150/90	155	138	48	Y	Cholelithiasis + HTN +DM
2	60	M	Normal	100	130/90	108	140	44	N	Cholelithiasis
3	55	F	Obesity	96	140/90	118	142	36	Y	Cholelithiasis + HTN + Hyperthyroidism
4	45	F	Normal	84	120/70	104	136	48	N	Cholelithiasis
5	59	F	Normal	82	140/90	150	154	40	Y	Cholelithiasis + HTN +DM
6	60	M	Normal	90	130/80	100	138	42	N	Cholelithiasis
7	54	M	Obesity	104	140/94	161	148	38	Y	Cholelithiasis + DM + IHD
8	60	F	Obesity	92	144/90	170	144	43	Y	Cholelithiasis + HTN
9	53	M	Normal	92	110/70	135	165	42	Y	Cholelithiasis + DM + IHD
10	60	M	Normal	96	120/70	130	140	40	N	Cholelithiasis +DM
11	52	F	Normal	84	130/80	80	136	48	N	Cholelithiasis + HTN
12	60	M	Normal	90	120/84	82	142	44	N	Cholelithiasis + HTN
13	60	M	Normal	92	142/94	138	180	31	Y	Cholelithiasis + HTN + DM
14	59	M	Normal	96	150/90	132	150	34	Y	Cholelithiasis + HTN + DM
15	60	M	Normal	86	130/80	140	179	32	Y	Cholelithiasis + DM
16	36	F	Normal	82	110/70	79	136	49	N	Cholelithiasis
17	59	F	Obesity	92	120/80	126	172	40	Y	Cholelithiasis + HTN
18	50	M	Normal	89	120/70	112	150	42	N	Cholelithiasis
19	59	F	Obesity	94	140/90	135	139	46	Y	Cholelithiasis + DM + Hyperthyroidism
20	58	F	Normal	86	110/70	96	148	47	N	Cholelithiasis + HTN
21	39	F	Normal	82	120/80	78	132	46	N	Cholelithiasis
22	52	F	Normal	86	130/80	100	148	44	N	Cholelithiasis
23	60	M	Normal	90	140/90	140	152	40	Y	Cholelithiasis + HTN
24	35	F	Normal	85	120/70	90	144	48	N	Cholelithiasis
25	52	M	Normal	94	150/90	130	156	40	Y	Cholelithiasis + HTN
26	38	F	Normal	82	120/84	89	140	47	N	Cholelithiasis
27	59	F	Obesity	93	110/80	152	148	38	Y	Cholelithiasis + DM + Hyperthyroidism
28	53	F	Normal	86	140/94	190	146	42	Y	Cholelithiasis + HTN + DM + Hyperthyroidism
29	60	F	Normal	82	130/84	88	138	49	N	Cholelithiasis + HTN
30	58	F	Obesity	90	140/90	140	147	46	Y	Cholelithiasis + HTN + DM
31	44	M	Normal	92	120/70	130	172	35	Y	Cholelithiasis + DM
32	43	F	Normal	80	110/80	110	140	51	N	Cholelithiasis
33	38	F	Normal	85	120/70	78	144	51	N	Cholelithiasis
34	22	F	Normal	78	130/80	84	135	54	N	Cholelithiasis
35	43	M	Obesity	103	140/90	110	182	38	Y	Cholelithiasis
36	35	F	Obesity	95	150/90	80	160	40	Y	Cholelithiasis + HTN
37	42	F	Normal	84	110/70	80	146	48	N	Cholelithiasis
38	60	M	Normal	86	150/100	220	168	44	Y	Cholelithiasis + HTN + DM
39	60	F	Normal	88	140/90	94	160	38	Y	Cholelithiasis + HTN
40	53	F	Obesity	92	140/92	180	144	46	Y	Cholelithiasis + DM + HTN
41	56	F	Obesity	90	120/70	187	152	33	Y	Cholelithiasis + DM
42	46	F	Obesity	92	120/80	130	140	34	Y	Cholelithiasis + DM
43	32	M	Normal	98	110/80	150	148	44	N	Cholelithiasis
44	48	F	Obesity	90	150/90	82	214	40	Y	Cholelithiasis
45	59	M	Obesity	106	140/90	158	160	36	Y	Cholelithiasis + DM + HTN

46	42	F	Normal	84	130/80	80	150	52	N	Cholelithiasis
47	30	F	Obesity	92	120/70	78	148	50	N	Cholelithiasis
48	40	F	Obesity	106	150/90	92	160	45	Y	Cholelithiasis + HTN
49	46	M	Normal	90	130/70	90	144	42	N	Cholelithiasis
50	45	M	Obesity	120	120/80	100	160	38	Y	Cholelithiasis
51	21	M	Normal	90	110/70	90	140	45	N	Cholelithiasis
52	33	F	Normal	80	120/70	80	138	52	N	Cholelithiasis
53	25	F	Normal	86	110/80	80	140	50	N	Cholelithiasis
54	32	F	Obesity	90	130/80	86	144	48	N	Cholelithiasis
55	27	F	Normal	88	120/80	82	148	40	N	Cholelithiasis
56	37	F	Obesity	93	150/90	84	160	42	Y	Cholelithiasis
57	48	M	Obesity	120	140/80	110	152	36	Y	Cholelithiasis
58	60	F	Obesity	113	130/80	92	162	36	Y	Cholelithiasis + DM
59	51	M	Normal	100	140/100	94	156	38	Y	Cholelithiasis
60	46	M	Normal	90	130/80	108	160	34	Y	Cholelithiasis
61	39	F	Normal	80	120/70	80	140	48	N	Cholelithiasis
62	50	F	Obesity	103	130/80	92	148	38	Y	Cholelithiasis
63	38	F	Normal	88	120/70	84	140	50	N	Cholelithiasis
64	47	F	Obesity	106	150/90	96	146	40	Y	Cholelithiasis + HTN + DM
65	48	M	Obesity	112	140/90	103	148	36	Y	Cholelithiasis
66	59	F	Obesity	92	130/80	159	162	51	Y	Cholelithiasis + DM
67	27	F	Normal	80	110/70	100	140	56	N	Cholelithiasis
68	47	F	Obesity	96	150/90	170	154	40	Y	Cholelithiasis + HTN + DM
69	48	F	Obesity	100	140/90	130	144	50	Y	Cholelithiasis + DM
70	45	M	Normal	98	120/70	90	140	43	N	Cholelithiasis
71	60	M	Obesity	106	130/80	148	160	34	Y	Cholelithiasis + DM
72	42	F	Obesity	102	130/80	110	144	48	N	Cholelithiasis
73	60	F	Obesity	94	150/90	137	140	50	Y	Cholelithiasis + HTN + DM
74	29	F	Normal	80	110/70	80	138	44	N	Cholelithiasis
75	34	M	Normal	94	120/80	96	146	42	N	Cholelithiasis
76	48	F	Obesity	97	140/100	108	197	35	Y	Cholelithiasis
77	58	M	Obesity	100	150/90	135	155	38	Y	Cholelithiasis + HTN + DM
78	47	F	Normal	86	130/80	88	148	40	N	Cholelithiasis
79	47	M	Obesity	110	160/90	104	168	36	Y	Cholelithiasis
80	60	M	Normal	96	140/90	140	156	36	Y	Cholelithiasis +HTN + DM
81	39	M	Normal	90	120/70	100	142	42	N	Cholelithiasis
82	60	M	Normal	94	150/90	136	180	32	Y	Cholelithiasis + HTN +DM
83	27	F	Normal	84	120/70	86	136	47	N	Cholelithiasis
84	40	M	Obesity	106	130/80	140	164	34	Y	Cholelithiasis + DM
85	53	F	Normal	86	120/70	110	140	45	N	Cholelithiasis
86	39	F	Normal	80	110/80	86	136	40	N	Cholelithiasis
87	56	M	Obesity	109	150/90	118	172	37	Y	Cholelithiasis +HTN
88	48	F	Obesity	95	140/80	103	147	43	N	Cholelithiasis
89	60	M	Obesity	112	150/100	112	159	39	Y	Cholelithiasis + HTN
90	50	F	Obesity	102	150/90	153	142	34	Y	Cholelithiasis + HTN + DM

91	46	F	Obesity	97	140/100	147	138	37	Y	Cholelithiasis + HTN + DM
92	36	F	Normal	83	120/70	79	145	40	N	Cholelithiasis
93	51	F	Normal	87	140/90	155	177	43	Y	Cholelithiasis + DM
94	50	F	Normal	80	110/70	81	137	35	N	Cholelithiasis
95	31	F	Normal	77	110/80	93	141	41	N	Cholelithiasis
96	60	M	Obesity	91	150/90	102	161	36	Y	Cholelithiasis + HTN
97	59	F	Obesity	106	140/100	142	133	31	Y	Cholelithiasis + HTN + DM
98	32	F	Normal	85	110/70	87	147	39	N	Cholelithiasis
99	60	F	Obesity	100	150/90	138	140	37	Y	Cholelithiasis + HTN + DM
100	36	F	Normal	79	110/80	97	148	42	N	Cholelithiasis
101	29	F	Normal	76	120/70	83	143	41	N	Cholelithiasis
102	50	F	Obesity	97	150/100	133	138	36	Y	Cholelithiasis + DM + HTN
103	48	F	Normal	87	150/90	126	161	46	Y	Cholelithiasis + HTN
104	55	M	Obesity	99	140/90	108	157	39	Y	Cholelithiasis + HTN
105	27	F	Normal	80	110/70	88	143	47	N	Cholelithiasis
106	48	F	Normal	86	150/90	144	165	38	Y	Cholelithiasis +HTN +DM
107	29	F	Obesity	95	140/100	114	160	41	Y	Cholelithiasis + HTN
108	60	F	Normal	83	150/90	118	153	43	Y	Cholelithiasis + HTN
109	46	F	Obesity	96	110/80	189	210	38	Y	Cholelithiasis
110	39	M	Normal	94	130/80	110	150	51	N	Cholelithiasis
111	49	M	Obesity	110	150/90	120	189	38	Y	Cholelithiasis + HTN
112	40	F	Obesity	98	140/90	97	171	30	Y	Cholelithiasis + HTN
113	56	M	Normal	99	130/70	153	168	44	Y	Cholelithiasis + DM
114	28	F	Normal	79	110/70	84	137	42	N	Cholelithiasis
115	46	F	Normal	87	140/90	107	196	32	Y	Cholelithiasis
116	49	M	Obesity	114	120/80	149	166	47	Y	Cholelithiasis
117	53	F	Obesity	96	120/80	154	157	38	Y	Cholelithiasis + DM
118	33	F	Normal	84	110/80	104	140	46	N	Cholelithiasis
119	21	M	Normal	90	130/80	79	144	51	N	Cholelithiasis
120	48	F	Obesity	100	130/70	138	176	37	Y	Cholelithiasis + DM