Cholelithiasis (Gall stones) : Causes, Pathophysiology, Symptoms and Treatment

Cholelithiasis (gall stones) is the presence of one or more gallstones known as calculi in the gallbladder. Cholelithiasis is caused by precipitation of substances contained in bile, mainly cholesterol and bilirubin.

There are three main factors contributing to the formation of gallstones:

- Abnormalities in the composition of bile,
- Stasis of bile, and
- Inflammation of the gallbladder.

The gallbladder is a small pear-shaped organ that is located next to the liver. The major function is to act as a store and to concentrate the bile produced in the liver. When fat is consumed in the diet the gallbladder contracts to release bile back into the digestive tract for fat digestion. Conditions affecting the biliary system are;

- **Cholelithiasis** is the presence of gallstones in the gallbladder.
- **Choledocholithiasis** is the presence of one or more gallstones in the common bile duct
- **Cholecystitis** is inflammation of the gallbladder from obstruction of the cystic duct or common bile duct (choledocholithiasis or common bile duct stone)
- **Cholangitis** is an infection of the biliary tree.

After the appendix, the gall bladder is the second intra-abdominal organ that most commonly requires surgery.

Gall stones are more common in females than in male counterparts. Its prevalence increases with increasing age.

Stages of development

Gall stones have four stages of development

1. The lithogenic stage when the conditions that favor gallstone formation are present,
2. Asymptomatic stage
3. Symptomatic stage
4. Complicated cholelithiasis

You may have heard of gallbladder colic. This is a kind of pain caused by a stone temporarily obstructing the cystic duct or common bile duct (CBD).

Pathophysiology of cholelithiasis:

Three types of gallstones exist.

- Cholesterol (most common),
- Pigment-calcium bilirubinate and,
- Mixed stones.

Cholesterol gallstones

These account for about 80 percent of all the cases of cholelithiasis.

They comprise of either **pure cholesterol stones** or **mixed cholesterol stones** which have cholesterol and calcium.

In a normal person, cholesterol is brought to the liver from chylomicrons or from other tissues in the form of low-density lipoproteins.

One of the functions of the liver is to regulate plasma cholesterol by either synthesizing it when it's low or eliminating it from the body when it accumulates to excess levels.

Cholesterol synthesis is from acetate under the influence of an enzyme known as *HMG CoA (3-hydroxy 3-methylglutaryl coenzyme A*

Like we have already mentioned, the liver regulates cholesterol levels by elimination. This elimination takes place in three different ways.

- As cholesterol
- As bile salt or as
- Cholesterol esters.

Once the cholesterol has been brought to the gallbladder it is kept in a soluble form in the vesicles.

During some instances such as extreme fasting the concentration of this cholesterol in the gall bladder exceeds its solubility limit. As a result of this supersaturation, crystals start forming. Together with the stasis in the gallbladder, it forms a biliary **sludge** which is **a** thickened gallbladder mucoprotein with tiny trapped cholesterol crystals

Biliary sludge is often a precursor of gallstones. It consists of Calcium bilirubinate (a polymer of bilirubin), cholesterol microcrystals, and mucin. Over time the crystals grow, aggregate and fuse to form microscopic stones.

Most of the sludge is does not result in any symptoms and disappears when the primary condition resolves.

This process is exacerbated by **mucin** and inhibited by **ursodeoxycholic** acid which is a bile salt, drugs such as NSAIDs and caffeine. This is the reason a dose of aspirin with a cup of coffee can help in cholelithiasis.

> An increase in the cholesterol concentration or a decrease in the bile salt concentration results in supersaturation of bile with cholesterol, and the formation of a liquid crystalline phase of cholesterol.

Normally, bile salts (ursodeoxycholic and chenodeoxycholic), lecithin, and phospholipids help to maintain cholesterol as a solute in the bile. When bile is supersaturated with cholesterol, it crystallizes and forms a nidus for stone formation.

It should be noted that any factor that increases plasma and bile cholesterol levels exacerbates the production of sludge in the gallbladder. These conditions are for example obesity, diabetes mellitus, cystic fibrosis, female gender, and pregnancy.

> How does pregnancy lead to increased plasma and bile cholesterol?

Also, some drugs such as clofibrate and other fibrate hypolipidemic drugs can deplete bile salts and increase the hepatic elimination of cholesterol increases the risk of cholesterol cholelithiasis. Somatostatin analogs also reduce gallbladder emptying.

The sludge can be reabsorbed or continue to form gallstones over a period of 8 years to 12 years.

Another type of gallstones are pigmented stones

Pigment stones

Pigment stones result from bilirubin production. To begin with, bilirubin is a product derived from the breakdown of heme. Normally bilirubin is first solubilized by a process known as conjugation in the liver.

This conjugation leads to the formation of diglucuronide which is stable and water-soluble. But is some circumstances a small portion of bilirubin remains unconjugated and forms an insoluble salt or precipitate with calcium.

Gallstones can result through three pathways that are;

1. **Increased bilirub**in is secondary to hemolytic anemia. This causes accumulation of too much-unconjugated bilirubin.
2. The second way is by the **development of insoluble bilirubin** due to glucuronidases like in the case of obstruction allowing accumulation of glucuronidase containing bacteria.
3. The third mechanisms are **liver cirrhosis**. Cirrhotic patients have reduced glucuronidase inhibitors. This causes too much accumulation of unconjugated bilirubin because the liver has failed in its conjugation function.

Black pigment stones

Once the unconjugated bilirubin forms an insoluble salt, calcium bilirubinate it then crystallizes to form a gallstone. This deposition results in the accumulation of multiple small **black stones**. As various oxidation takes place bilirubin precipitates to form a jet-black color.

Black pigment stones are small, hard gallstones composed of Calcium bilirubinate and inorganic Calcium salts. Factors that accelerate stone development include alcoholic liver disease, chronic hemolysis, and older age.

Another kind of pigmented stone is **brown pigment stone.**

brown pigment stone.

Normally bile is sterile but if there is an obstruction like in the case of biliary stricture it may become colonized by bacteria. The colonizing bacteria, in turn, hydrolyzes the conjugated bilirubin back to unconjugated bilirubin leading to precipitation of calcium bilirubinate crystals.

Bacteria also have the ability to hydrolyze lecithin to release fatty acids that also combine with calcium to form a brown pigment stone mostly de novo in the bile duct.

The Brown pigment stones are characteristically soft and greasy. They consist of bilirubinate and fatty acids (specifically Calcium palmitate or stearate). This kind of stone forms during infection, inflammation or a parasitic infestation.

> **Black stone**s are usually common in individuals with hemolytic disorders whereas **Brown pigment stones** are common in the intrahepatic or extrahepatic duct and are associated with gallbladder infections.

Mixed stones

infection of cholesterol gallstones with bacteria elicits gallbladder mucosal inflammation. Lytic bacterial enzymes and leucocytes hydrolyze conjugated bilirubin and fatty acids. As a result, cholesterol stones may accumulate a large amount of calcium bilirubinate and other calcium salts producing a mixed stone.

On a plain x-ray film, these stones form an eggshell appearance due to the calcium rim on their surface.

Symptoms and Signs of cholelithiasis

Most gallstones are asymptomatic.

The remainder has symptoms ranging from biliary-type pain (biliary colic) to cholecystitis to life-threatening cholangitis.

Pain due to cholelithiasis is of two types

- **Obstructive pain or**
- **Inflammatory pain.**

Like its name, obstructive pain results when the neck of the gallbladder becomes obstructed by a

stone and gallbladder contraction continues under the influence of cholecystokinin and neural reflexes from the duodenum.

The bare nerve endings detect this tension and since they pass centrally