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Review Article

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A REVIEW ON EFFECT OF LIPID METABOLISM IN GALLSTONE DISEASE

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INTRODUCTION

Gallstone diseases are the leading cause for hospital admissions related to gastrointestinal problems. They are most common and costly. Gallbladder is a gastrointestinal organ that concentrates and stores hepatic bile for delivery into the intestinal lumen during the food intake cycles for lipid digestion and absorption, and that it is the organ where gallstones (GS) form, producing GB disease (GBD).[1] Cholesterol gallstone formation is based upon supersaturated bile formation and pigment stones are formed in bile rich in bilirubin. Thus, defects of hepatic metabolism of lipids and organic anions lead to biliary stones.[2]

Cholesterol (CH) GS are present in approximately 80% of patients with GBD. The remaining GS patients harbor black pigment stones, mainly composed of calcium bilirubinate, and brown pigment or mixed stones.[1] Most of the risk factors for cholesterol gallstone formation are not modifiable such as ethnic background, increasing age, female gender and family history or genetics. Conversely, the modifiable risk factors for cholesterol gallstones are obesity, rapid weight loss and a sedentary lifestyle. The rising epidemiology of obesity and the metabolic syndrome predicts an escalation in the frequency of cholesterol gallstone. Risk factors for biliary sludge include pregnancy, drugs like ceftriaxone, octreotide and thiazide diuretics, and total parenteral nutrition or fasting. Diseases like cirrhosis, chronic hemolysis and Crohn's disease are risk factors for black pigment stones.[3] The major purpose of this article is, to review some of the metabolic links between abnormalities of lipid metabolism commonly found in GB functions and GBD.

Biliary Cholesterol

Cholesterol is an insoluble molecule that is critical for cellular structure and function. Homeostasis of this compound is kept by biliary elimination from the liver, where it is catabolized to bile salts for a regulation of pool size.[2] Free cholesterol represents the least concentrated lipid in bile. Like bile acids, the principle source of biliary cholesterol appears to be lipoprotein free cholesterol coupled with a modest contribution from the newly synthesized pool of cholesterol. Biliary cholesterol and lecithin have their immediate origins within the hepatocyte and depend on bile salts for their secretion into bile. Most of the biliary lecithin is synthesized by the process of de novo within the hepatocytes however, some may be derived from the surface coat of serum lipoproteins.

Gallbladder

Gallbladder epithelium can absorb lipid from Bile. Bile is the only significant pathway for elimination of excess cholesterol from the body, either as free cholesterol or as bile salts. The GB plays a central role in the digestion and absorption of lipids present in the diet. It stores and concentrates hepatic bile secreted by the liver during periods of fasting and then sends it to the intestine during food intake.

Physical and Chemical events in Gallbladder

In normal individuals, differential absorption of bile salts, cholesterol and phospholipid functions to reduce the saturation of bile with cholesterol. Impaired lipid absorption can lead to sustained supersaturation of bile with cholesterol and therefore predispose to cholesterol crystallization. Defective gallbladder motility also plays a key role in cholesterol cholelithiasis. Abnormalities in both filling and emptying, defects in contractility are attributable to excess membrane accumulation in gallbladder smooth muscle cells of biliary cholesterol. This will result in diminished gallbladder relaxation. Further more, the enhanced synthesis and hypersecretion of mucin in the gallbladder enhance the cholesterol crystallization and growth and macroscopic gallstones form eventually under the circumstance of gallbladder dysfunction.[2,3]

Bile Secretion

Bile consists of cholesterol, phospholipids and bile salts. Bile secretion is stimulated by food intake. The presence of food in the duodenum (especially fat) induces

secretion of cholecystokinin (CCK) by mucosal endocrine cells which, in turn, causes contraction and release of bile by the gallbladder. The failure of gallbladder contraction can result in stasis of gallbladder bile and can enhance the formation of biliary "sludge" characterized by the accumulation of a lipid-mucin -proteinaceous debris with calcium bilirubinate salts that generally precedes gallstone formation.

Physiological events associated with digestion and absorption stimulate hepatic bile synthesis and secretion to effectively increase the concentration of biliary micelles, i.e. phospholipid, bile acid, and free cholesterol, and decrease the relative biliary cholesterol concentration.

Gallstones

Gallstones are the common cause of Biliary tract dysfunction. A history of gallstones appears to carry the highest risk for gallbladder cancer,but not all people with gallbladder cancer have cholelithiasis.[4] The pathogenesis of cholesterol gallstones involves a complex set of variables affecting the relative concentration of bile acid, phospholipid, free cholesterol, and protein during their collective flux through the biliary system. The stones with cholesterol concentrations higher than 50% are considered to be cholesterol stones and 70% to 80% of gallstones are cholesterol stones.

Pathology

Biliary Sludge is the precursor of gallstones. It consist of Calcium Bilirubinate, cholesterol microcrystals and mucin. The sludge develop during gallbladder stasis. Most of them are asymptomatic and disappears when primary condition resolves. Alternatively, a sludge can be evolve into gallstones or migrate into biliary tract, obstructing the ducts and leads to Biliary colic, cholangitis, pancreatitis. The following conditions must be present to permit the formation of cholesterol gallstones; Bile must be supersaturated with cholesterol, Nucleation must be kinetically favourable, Cholesterol crystals must remain in the gall bladder long enough to aggregate into stones.

Diagnosis

The best epidemiological screening method to accurately determine point prevalence of gallstone disease is ultrasonography. More reliable epidemiological studies now use transabdominal ultrasound to screen robust numbers in defined asymptomatic populations. Ultrasonography is an ideal means to quantitate the frequency of gallstone disease, being a noninvasive and safe imaging technique that accurately can detect the point prevalence of gallstones in a defined asymptomatic population.

The number of surgical procedures for cholelithiasis has risen markedly in developed countries since 1950.[5] The introduction of laparoscopic cholecystectomy in 1989 further increased the cholecystectomy rate.[6,7] From 1990 to 1993, there was a 28% escalation in the number of cholecystectomy performed.[8] The change in practice emanated from the laparoscopic surgical approach, which represented a less invasive, more cosmetically acceptable operation while providing a lower surgical risk compared to the then conventional or “open” procedure. This likely resulted in more surgeries being done in patients previously thought to be too high a risk, or in those with minimal symptoms. Although there is undoubtedly an element of overuse, cholecystectomy is now the most common elective abdominal surgery. [3,9]

Lipid Metabolism

Cholesterol is water insoluble and is rendered water soluble by aggregation with bile salts and lecithin secreted into bile. When cholesterol concentration exceeds the solubilising capacity of bile, cholesterol can no longer remain dispersed and nucleates into the solid cholesterol monohydrate crystals.[10] The known factors associated with cholesterol gallstones include cholesterol hypersecretion and supersaturation, bile salt and phospholipid concentrations, crystal nucleation, gallbladder dysmotility and gallbladder absorption and secretion functions. Cholesterol gallstone disease is a metabolic abnormality, which can be correlated with adiposity, diabetes mellitus and lipid abnormality.

LDL transports cholesterol from the liver to the peripheral tissues, and HDL transports cholesterol from the peripheral tissues to the liver. Triglycerides are major metabolites through which energy can be stored in adipose tissue and transported throughout the organism for maintaining energy homeostasis.

When dietary fat enters the plasma from the small intestine in the form of chylomicrons, and they then deliver Free Fatty Acids (FFA) from Triglycerides (TG) to the tissues that express lipoprotein lipase. Once approximately two thirds of their TGs are unloaded in peripheral tissues, chylomicron remnants containing the remaining TGs and CH esters are quickly taken in by the liver[8] Abnormal accumulation of hepatic lipids occurs when the amount of FFAs and CH entering the hepatocytes exceeds their exit. FFA flow between the different tissues changes according to the nutritional state of the subject. Similarly, cellular CH content will depend on the uptake from plasma lipoproteins and the level of endogenous synthesis. In the feeding stage, FFAs travel bound to albumin towards the tissues to be stored in adipose tissue. The endogenous secretion of TGs and CH to the plasma is carried out from the liver in the form of VLDL and is regulated by food intake cycles. This regulation is dependent on insulin effects that decrease the hepatic production of VLDL, which is increased in states of Insulin Resistance.[9] Serum TG concentrations after ablation of the GB, suggest that cholecystectomy and GBD disease may impact negatively on the metabolic homeostasis of the whole body.

High serum cholesterol, high serum LDL, and low serum HDL levels may be expected to increase cholesterol excretion with bile and cause cholesterol gallstone disease. The relationship between serum cholesterol, LDL, and HDL levels and cholesterol gallstone formation is multifactorial and complex and is also dependent on other individual properties. A low HDL cholesterol and hypertriglyceridemia carry an increased risk of developing stones. In contrast, various research studies does not describe a definite association with GS disease and hypercholesterolemia. High homocysteine levels may also correlate with gallstone disease.

Both the metabolic syndrome and diabetes mellitus are risk factors for gallstone disease.[11] Insulin resistance predisposes to cholesterol gallstone formation,[12,13] suggesting an altered cholesterol and bile salt metabolism. Hepatic insulin resistance may act by enhancing hepatic cholesterol secretion, depressing bile salt synthesis and/or impairing gallbladder motility. [14-16]

CONCLUSION

Recent studies have shown that hypertriglyceridaemia, hypercholesterolemia and low level of high density lipoprotein cholesterol (HDL) a common finding in patients with cholilithiasis. Bile is the only significant pathway for elimination of excess cholesterol from the body, either as free cholesterol or as bile salts. Abnormalities of lipid metabolism in GBD are related to both primary abnormalities in the regulation of biliary lipid secretion and GB function, and abnormalities of whole body lipid metabolism are commonly found in IR states, particularly obesity, Type 2 diabetes and Non-Alcoholic Fatty liver disease (NAFLD). TC, TG, LDL are risk factors, while HDL is a protective factor.

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