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A Study on Correlation of Serum Ferritin Levels with Biliary Cholesterol Levels in Patients with Cholelithiasis Undergoing Cholecystectomy

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Introduction

Gallstones afflict 10% to 20% of adults residing in Western countries in the Northern Hemisphere, 20% to 40% in Latin American countries, and only 3% to 4% in Asian countries. In the United States, about 1 million new cases of gallstones are diagnosed annually, and two thirds of persons so affected undergo surgery, with retrieval of as much as 25 to 50 million tons of stones! There are two main types of gallstones: cholesterol stones, containing crystalline cholesterol monohydrate (80% of stones in the West), and pigment stones, made of bilirubin calcium salts.

Risk Factors for Gall Stones

Cholesterol Stones

Demography: Northern Europeans, North and South Americans, Native
Americans, Mexican Americans
Female gender
Pregnancy
Obesity and insulin resistance
Female sex hormones
Oral contraceptives
Advancing age
Rapid weight reduction
Gallbladder stasis
Dyslipidemia syndromes
Inborn disorders of bile acid metabolism

Pigment Stones

Demography: Asian more than Western, rural more than urban
Biliary infection
Chronic hemolysis (e.g., sickle cell anemia, hereditary spherocytosis).
Gastrointestinal disorders: ileal disease (e.g., Crohn disease), ileal resection or bypass, cystic fibrosis with pancreatic insufficiency. There are many risk factors for gall stone disease this study identifies the correlation of serum ferritin with biliary cholesterol level in formation of gall stones.

Aims and Objectives

To evaluate the correlation of Low level Serum Ferritin with elevated biliary cholesterol in formation of Gall stones.

Methodology

Design of Study: Non randomized prospective study

Sample Size: 50 CASES admitted in General Surgery ward for Laparoscopic/Open Cholecystectomy for the period of 8 months (January 2018 to August 2018)

Inclusion Criteria

- Patients of age group >12years and both sex with sonographic evidence of gall stones admitted for

cholecystectomy • Patients with positive/elevated CRP

- Patients with sonogram showing features of cholecystitis
- Patients on Hypolipidemic drugs, OCPs
- Patients with obstructive jaundice/choledocholithiasis
- Patients with negative CRP
- Patients with sonogram showing no evidence of cholecystitis

Exclusion Criteria

Methodology

- Patients with CHOLELITHIASIS who are admitted in my department are chosen(by criteria mentioned above), who may undergo either LAP or OPEN CHOLECYSTECTOMY.
- Written and informed consent will be sought.
- Preoperative blood sample taken for SERUM FERRITIN.
- By calculating Serum Ferritin mean value, they are divided into two groups
  - GROUP A- Patients with above mean value
  - Group B- Patients with below mean value
- As they undergo surgery, intraoperative bile sample taken for BILIARY CHOLESTEROL analysis.
- Biliary Cholesterol levels are correlated in above two groups.

Review of Literature

Pathogenesis of Gall Stone Formation

Bile formation is the only significant pathway for elimination of excess cholesterol from the body, either as free cholesterol or as bile salts. Cholesterol is rendered water-soluble by aggregation with bile salts and lecithin. When cholesterol concentrations exceed the solubilizing capacity of bile (super saturation), cholesterol can no longer remain dispersed and crystallizes out of solution. Cholesterol gallstone formation is enhanced by hypo mobility of the gallbladder (stasis), which promotes nucleation, and by mucus hyper secretion, with consequent trapping of the crystals, thereby enhancing their aggregation into stones. Formation of pigment stones is more likely in the presence of unconjugated bilirubin in the biliary tree, as occurs in hemolytic anemias and infections of the biliary tract. The precipitates are primarily insoluble calcium bilirubinate salts.

Up to 80% of people with gallstones, however, have no identifiable risk factors other than age and gender

Some elaboration on these risk factors follows:

• Age and gender. The prevalence of gallstones increases throughout life. In the United States, less than 5% to 6% of the population younger than age 40 has stones, in contrast with 25% to 30% of those older than 80 years. The prevalence in women of all ages is about twice as high as in men.

• Ethnic and geographic. Cholesterol gallstone prevalence approaches 50% to 75% in certain Native American populations—the Pima, Hopi, and Navajos—whereas pigment stones are rare; the prevalence seems to be related to biliary cholesterol hyper secretion.

• Heredity. In addition to ethnicity, a positive family history imparts increased risk, as do a variety of inborn errors of metabolism such as those associated with impaired bile salt synthesis and secretion.

• Environment. Estrogenic influences, including oral contraceptives and pregnancy, increase hepatic cholesterol uptake and synthesis, leading to excess biliary secretion of cholesterol. Obesity, rapid weight loss, and treatment with the hypocholesterolemic agent

clofibrate also are strongly associated with increased biliary cholesterol secretion.

• Acquired disorders. Any condition in which gallbladder motility is reduced predisposes to gallstones, such as pregnancy, rapid weight loss, and spinal cord injury. In most cases, however, gallbladder hypomotility is present without obvious cause.

Role of Iron in Gallstone Formation

As per the popular belief that a typical gallstone sufferer is a fat, fertile, female of forty, is only partially true, as the disease has been found in women soon after their first delivery and also in underweight and thin people. So while searching the literature for different factors, iron deficiency was found to be new and interesting etiological factor in the formation of gallstones. Gallstones may produce several symptoms or may remain asymptomatic. Over half the cases are asymptomatic, usually detected by abdominal ultrasound. Today, the incidence of gallstone disease has increased considerably with the invention of Ultrasonography.

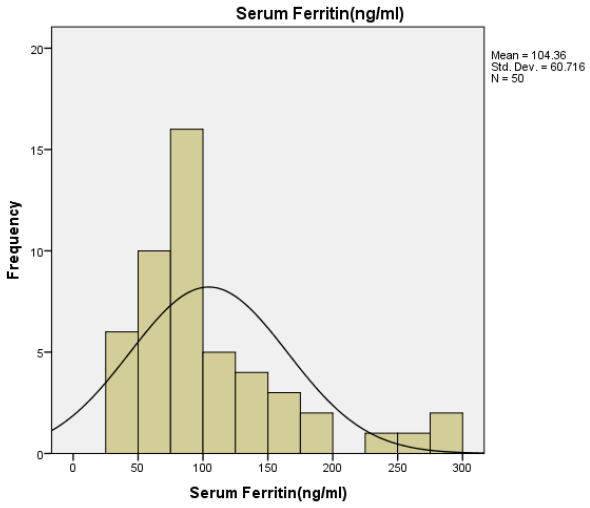
Three conditions must be met to permit the formation of cholesterol gallstones:

1. Bile must be supersaturated with cholesterol.
2. Nucleation must be kinetically favorable.
3. Cholesterol crystals must remain in the gallbladder long enough to agglomerate into stones.

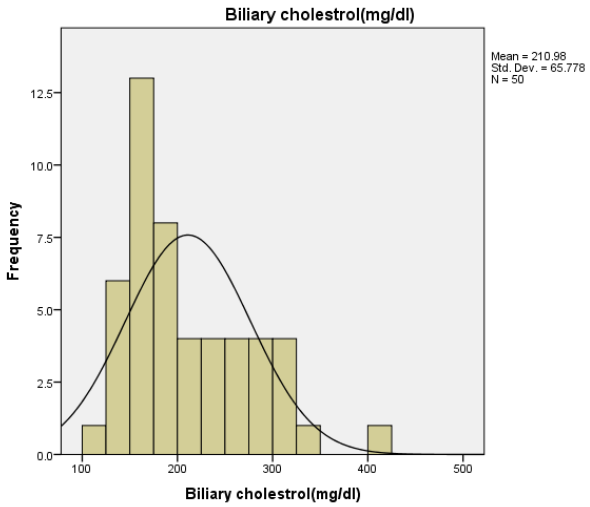
Iron deficiency has been shown to alter the activity of several hepatic enzymes, leading to increased gallbladder bile cholesterol saturation and promotion of cholesterol crystal formation. Iron acts as a coenzyme for Nitric Oxide Synthetase (NOS), which synthesize Nitric Oxide (NO) and that is important for maintenance of basal gallbladder tone and normal relaxation. It was found that iron deficiency resulted in altered motility of gallbladder and sphincter of Oddi leading to biliary stasis and thus increased cholesterol crystal formation in the gallbladder bile.

Results

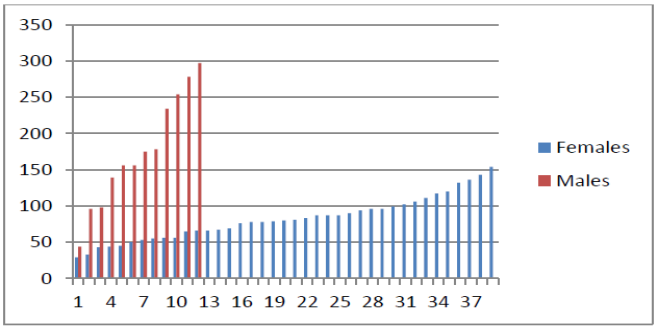
The following figure illustrates the serum ferritin levels of the participants with mean of 104.36ng/ml (S.D=60.718).



The following figure illustrates the biliary cholesterol levels of the participants with mean of 210.98 mg/dl (S.D=65.778).



The serum ferritin levels have a mean value of 175.14 ng/ml (S.D=77.794, n=12) in males while females have a mean of 81.92 ng/ml (S.D=30.466, n=38).



Using mean of Serum ferritin values study sample is divided into two groups A and BThus, Group A - above mean (n=22) and Group B - below mean (n=28)Biliary Cholesterol is divided into four quartilesIt was assumed that given the high range of bile cholesterol, some of the values might affect the mean values; hence a quartile-wise distribution will take care of the extreme values.In Group A, maximum number of subjects had bile cholesterol values in the second quartile whereas in Group B, maximum number of subjects had bile cholesterol values in the third quartile. In Group A, minimum number of subjects had bile cholesterol values in fourth quartile whereas in Group B minimum number of subjects had values in first quartile.More than 75% of Group A fall within first and second quartile whereas in Group B more than 75% fall within third and fourth quartile.

Both values are compared as shown in table below

Biliary Cholesterol(quartiles) mg/dl	Group A(n=22)		Group B(n=28)	
	No.	%	No.	%
First(<151)	6	27.3	2	7.2
Second(152-187)	11	50	5	17.8
Third(187-296)	5	22.7	14	50
Fourth(>296)	-	-	7	25

Correlation test between serum ferritin and biliary cholesterolThe correlation test between serum ferritin and Biliary cholesterol levels shows a negative correlation of -0.537 with $p<0.005$ (N=50). Low ferritin levels leads to high biliary cholesterol.

Conclusion

The study was performed in 50 individuals admitted in our department for lap/open Cholecystectomy by fulfilling inclusion criteria for the period of 8 months. The results showed negative correlation between mean serum ferritin and biliary cholesterol level($p<0.005$). The association between serum ferritin levels and bile cholesterol levels was also traced by dividing the bile cholesterol in four quartiles and then comparing the proportion of subjects in two groups in these four quartiles. It was assumed that given the high range of bile cholesterol, some of the values might affect the mean values; hence a quartile-wise distribution will take care of the extreme values. Distributions among those were tabulated in table . The study by Roslyn et al (1987) suggested that dietary factors may be responsible for the increasing incidence of gallstones. Although iron deficiency alters the activities of several hepatic enzymes, its effect on biliary lipid metabolism is not known. This study indicates that consumption of diets rich in carbohydrates but deficient in iron alters hepatic metabolism of cholesterol and may be an important etiologic factor in gallstone formation. Iron supplementation may prevent gallstones in certain high-risk groups. Iron is known to be necessary in the functioning of many intracellular enzyme systems, including hepatic enzymes involved in cholesterol and bile salt regulation. Iron also may play a role in normal gallbladder and sphincter of Oddi functions because of its interaction with nitric oxide, which, in turn, affects

smooth muscle function. Iron deficiency is further associated with raised serum transferrin. Therefore, iron deficiency may enhance cholesterol gallstone formation by altering hepatic enzyme function, biliary motility, cholesterol crystal nucleation, or some combination of the three. Iron deficiency and low serum ferritin are probably independent risk factors operating for the causation of gallstones. In the study correlation between serum ferritin deficiency and increase in cholesterol level in bile was established. This result gives impression that in reference to serum cholesterol, deficiency of serum ferritin will lead to increase in saturation of biliary cholesterol which may enhance Gallstone formation. The scope of this study can be further advanced in the field of enzymes controlling gall bladder tone, motility and relaxation and cofactors affecting these enzymes. The study also raises a question if serum levels of ferritin can be used as a marker for lithogenic bile with high levels of biliary cholesterol level which cannot be measured in a normal healthy person, do prevention of iron deficiency anemia also prevents the possible development of gallstones in a healthy person.

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