

Study of Iron Deficiency Anemia and its Association with Cholelithiasis

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Abstract

Introduction: The incidence of gall stones is in increasing trend. The old axiom that a typical gall stone sufferer is a fat, fertile, female of 50, is only partially true, as the disease is found in women soon after their first delivery, in underweight and thin people. Hence, while searching for other parameters, iron deficiency was found to be a new parameter of interest in the etiology of gall stones.

Methods: Around 50 cases of cholelithiasis and 40 cases of anemia with low serum ferritin levels from October 2018 to September 2020 were studied. Serum iron was estimated by carbonyl metallo-immunoassay method. Serum cholesterol was estimated by the cholesterol oxidase-peroxidase (CHOD-POD) Enzymatic method. Biliary cholesterol was estimated after extraction of biliary lipids from bile from the gallbladder specimen of the patients by the method of Folch *et al.* which was followed by the procedure similar to the analysis of serum cholesterol by CHOD-POD enzymatic method. Fischer's Chi-square exact test was used as statistical method.

Results: It was observed that 70% of the group A, study group with cholelithiasis had normal serum ferritin levels, and 30% had low serum ferritin levels. It was observed that 95% had normal sonographic findings and 5% had cholelithiasis with normal ferritin levels in group B.

Conclusions: In our study, low serum ferritin levels with cholelithiasis was associated with raised bile cholesterol levels and so it can be concluded that low serum ferritin level is causing biliary stasis and hence leading to increase in the incidence of cholelithiasis.

Key words: Anemia, Cholelithiasis, Cholesterol, Gall stones

INTRODUCTION

Gallstone disease is a common clinical entity affecting the adult population of both sexes. The earliest known gallstone dates back to the 21st Egyptian dynasty discovered in the mummy of priestess of Amenemhat (1085-945 BC). There are also descriptions of stones in the biliary system in Greeks in the 5th century anno domini (AD), as well as Persians in the 10th century AD. Vesalius (1514-1564) established the teaching that gallstones were evidence of disease and he associated them with jaundice.^[1,2]

Open cholecystectomy first performed by Carl Langenbuch in 1882, has been the primary treatment for gallbladder disease through the early 1990s. In 1985, the first endoscopic cholecystectomy was performed by Erich Muhe of Boblingen, Germany.^[3] Swedish epidemiologic study found that the incidence of gall stones was 1.39/100 person-years. In an Italian study, 20% of women had gall stones, and 14% of men had stones.^[4]

The prevalence of gallstones varies widely in different parts of the world. In India it is estimated to be around 4%. An epidemiological study restricted to rail road workers showed that north Indians have 7 times higher incidence of gallstones as compared to south Indians.^[5] Women are more likely to develop cholesterol gallstones than men, especially during their reproductive years, when the incidence of gallstones in women is 2–3 times that in men. The difference appears to be attributable

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Month of Submission : 09-2021
Month of Peer Review : 10-2021
Month of Acceptance : 11-2021
Month of Publishing : 11-2021

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mainly to estrogen, which increases biliary cholesterol secretion.^[6]

Risk of developing gallstones increases with age. Gallstones are uncommon in children in the absence of congenital anomalies or hemolytic disorders. Beginning at puberty, the concentration of cholesterol in bile increases. After age 15 years, the prevalence of gallstones in the US women increases by about 1% per year; in men, the rate is less, about 0.5% per year. Gallstones continue to form throughout adult life, and the prevalence is greatest at advanced age. The incidence in women falls with menopause, but new stone formation in men and women continues at a rate of about 0.4% per year until late in life.

The old axiom that a typical gall stone sufferer is a fat, fertile, female of 50, is only partially true, as the disease is found in women soon after their first delivery and also in underweight and thin people. Hence, while searching for other parameters, iron deficiency was found to be a new parameter of interest in the etiology of gall stones.^[7]

Other factors contributing to formation of gallstones impaired gallbladder function, supersaturated bile, cholesterol nucleating factors, absorption/enterohepatic circulation of bile acids.^[8] Iron deficiency, that is, low serum ferritin levels has been shown to alter the activity of several hepatic enzymes, leading to increased gall bladder bile cholesterol saturation and promotion of cholesterol crystal formation.^[9,10] Iron acts as a coenzyme for nitric oxide synthetase, which synthesizes nitric oxide and that is important for the maintenance of basal gall bladder tone and normal relaxation.^[11,12] It was found that iron deficiency (low serum ferritin levels) resulted in altered motility of gall bladder and sphincter of Oddi, leading to biliary stasis and thus increased cholesterol crystal formation in the gall bladder bile.^[13]

The present study was done to test the hypothesis that iron deficiency (low serum ferritin levels) is an etiological factor in the formation of gall stones.

METHODS

Study Design

This was a prospective study of minimum 90 patients of either sex admitted to our hospital (a tertiary level center) with cholelithiasis or anemia with low serum ferritin levels. The study was prospective, observational, and analytical study.

Selection of Patient

Inclusion criteria

Inclusion criteria were all patients with sonographic findings of cholelithiasis. All patients with low serum ferritin levels.

Exclusion criteria

Exclusion criteria were patients with empyema of gall bladder. Patients with mucocoele of the gall bladder, Immunocompromised patients and patients not willing for the study were excluded. The present study will comprise of 50 cases of cholelithiasis (group A) and 40 cases of anemia with low serum ferritin levels (group B) from October 2018 to September 2020. Detailed clinical history and examination of the 90 selected cases was done. Estimation and tabulation of the lipid profile, serum ferritin level and bile cholesterol in the 50 cases of cholelithiasis were done and the outcome was analyzed. 40 cases of anemia with low serum ferritin levels were studied and evaluated for the presence cholelithiasis and association with lipid profile.

As all cholelithiasis cases with low serum ferritin levels were not fit for surgery so to test the reverse hypothesis and to look for cholelithiasis in a known case of anemia with low serum ferritin levels these 40 cases were taken into our study. The study protocol was approved by the review board of our institute for ethical research.

Serum iron was estimated by carbonyl metallo-immunoassay method. The normal reference values for our laboratory were, for males (15–220 ug/dl) and for females (10–124 ug/dl), that is, males with serum ferritin <15 ug/dl and females with serum iron <10 ug/dl were labeled as anemic. Serum cholesterol was estimated by the cholesterol oxidase-peroxidase (CHOD-POD) enzymatic method.^[14] Biliary cholesterol was estimated after extraction of biliary lipids from bile from the gallbladder specimen of the patients by the method of Folch *et al.*, which was followed by the procedure similar to the analysis of serum cholesterol by CHOD-POD enzymatic method. The reference values were taken with respect to the standard reference values for our laboratory. For males and females, the normal range was 130–200 mg/dl.

For serum ferritin, serum lipid profile 5 ml of intra venous blood sample was drawn and sent to the laboratory for investigation and for the estimation of bile cholesterol if the operative procedure was open then bile was directly aspirated from the gall bladder after cholecystectomy and if the operative procedure was laparoscopic then bile was aspirated from one of the 5 mm ports.

RESULTS

In group A, it was observed that 72% of the study group were females and 28% were males. Cholelithiasis occurs most commonly in the age group 35–45 years. 68% of the group A study group with cholelithiasis had normal

Table 1: Ferritin levels in comparison to cholesterol

Variables	Normal (%)	High (%)	Total
Ferritin Group			
Normal	34 (68)	0 (0)	34
Low	16 (32)	2 (100)	18
Total	50	2	52

Chi-square (df)=6.5546 (1), $P < 0.05$ (significant)**Table 2: Ferritin level in comparison to cholelithiasis**

Variables	Cholethiasis (%)	Cholethiasis (%)	Total
Ferritin Group			
Normal	34 (66.03)	0 (0)	34
Low	19 (35.84)	37 (100)	56
Total	53	37	

Chi-square (df)=41.8531, $P < 0.05$ (significant)**Table 3: Serum cholesterol (rows) versus biliary cholesterol (columns)**

Cholesterol Group	Normal	Abnormal	Total
Normal	47 (94%)	0 (0%)	47
Low	3 (6%)	4 (100%)	7
Total	50	4	

Chi-square (df)=0.1273, $P > 0.05$ (not significant)

serum ferritin levels and 32% had low serum ferritin levels. 94% had normal serum cholesterol levels and 6% had high serum cholesterol levels. 92% had normal bile cholesterol and 8% had high bile cholesterol. These 4% had low serum ferritin level and normal serum cholesterol levels. In group B, it was observed that 92.5% had normal sonographic findings and 7.5% had cholelithiasis with normal ferritin levels [Tables 1-3].

DISCUSSION

Recent studies have defined the role of trace elements (Fe, Ca, Zn, and Cu) and defective pH in the formation of gall stones. Iron deficiency, that is, low serum ferritin levels has been shown to alter the activity of several hepatic enzymes, leading to increased gall bladder bile cholesterol saturation and promotion of cholesterol crystal formation.^[10,11] In our study, 90 cases constituted the study population. In group A, 50 cases of cholelithiasis were taken and in group B 40 cases of anemia with low serum ferritin levels were taken.

Group A

In our study, 50 cases of cholelithiasis 24% were male and 76% were females. Our findings correlated with the study done by Sarhan *et al.* in which 80% were female and 20% were males supporting the age-old axiom that gall stones

are more common in the females.^[6,15] 50% of the patients were in the 35–45 years age group.

In our study, out of 50 cases 34, that is, 68% had normal serum ferritin and 16, that is, 32% had low serum ferritin. In a study done by Muneesh *et al.*,^[16] 52% had normal serum ferritin and 48% had low serum ferritin levels.

In our study, 47, that is, 94% had normal serum cholesterol and 3, that is, 6% had high serum cholesterol. In our study, there was no significant correlation between high serum cholesterol with cholelithiasis. Our findings correlated with the findings of the study done by Muneesh *et al.*^[16] In a study done by Sarhan *et al.*,^[15] also there was no significant difference in the serum cholesterol levels of the cholelithiasis patients with low serum ferritin levels and with cholelithiasis patients with normal serum ferritin levels.

In our study, 46, that is, 92% had normal biliary cholesterol and 4, that is, 8% had high biliary cholesterol. The 4 patients with high biliary cholesterol had normal serum cholesterol and low serum ferritin levels. In a study done by Sahu *et al.* the mean bile cholesterol level in group A, that is, normal serum ferritin group was found to be 214.6 mg/dl and in group B, that is, low serum ferritin group was 375.3 mg/dl. The difference in values in both the groups was found to be statistically extremely significant ($P < 0.0001$).^[17]

We would like to continue our study with a larger study group and taking some other factors into consideration like other trace elements. As all cases of cholelithiasis with anemia with low serum ferritin levels are not fit for surgery and are not operated, so 40 cases of anemia with low serum ferritin levels were taken and studied for the findings of cholelithiasis and in a way testing the reverse hypothesis.

Group B

In our study, of 40 cases only 3, that is, 7.5% of the study group had cholelithiasis. The serum cholesterol was normal in these 7.5% of the study group. Later on, these cases were operated and their bile cholesterol was also found out to be normal. Probably anemia, obesity, and sex hormones are independent risk factors operating for the causation of gallstones and if present together, they produce synergistic effects. The scope of this study can be further advanced in the field of enzymes controlling gallbladder tone, motility and relaxation and cofactors affecting these enzymes.

We would like to continue our study further with a larger study group. Many other studies are required related to this topic as both cholelithiasis and low serum ferritin are fairly common conditions prevalent in the general population. On combining group A and group B and cross tabulating

the results of our study, our findings were 66.07% of the cholelithiasis cases had normal serum ferritin and 35.84% of the cholelithiasis cases had low serum ferritin levels. Chi-square (df) = 41.8531, $P < 0.05$ (significant). Our findings correlated with the findings of the study done by Sarhan *et al.*,^[15] 96% of the cholelithiasis cases had normal serum cholesterol and 4% had high serum cholesterol Chi-square (df) = 1.4948, $P > 0.05$ (not-significant). Our findings correlated with the findings of the study done by Muneesh *et al.*^[6] *et al.* in a study done by Sarhan *et al.*^[15] also there was no significant difference in the serum cholesterol levels of the cholelithiasis patients with low serum ferritin levels and with cholelithiasis patients with normal serum ferritin levels.^[6] 92% of the cholelithiasis cases had normal bile cholesterol and 8% had high bile cholesterol. Chi-square (df) = 6.5546, $P < 0.05$ (significant). Chi-square (df) = 0.1273, $P > 0.05$ (not significant).

CONCLUSIONS

Based on our studies the following are the conclusions, cholelithiasis is more common in females than in males and the most common affected age group is 35–45 years. Low serum ferritin level is a significant factor in the formation of gallbladder stones. No significant correlation could be found with raised serum cholesterol and cholelithiasis. In our study, low serum ferritin levels with cholelithiasis was associated with raised bile cholesterol levels and so it can be concluded that low serum ferritin level is causing biliary stasis and hence leading to increase in the incidence of cholelithiasis.

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How to cite this article: Sivakumar B, Kuthus NSA. Study of Iron Deficiency Anemia and its Association with Cholelithiasis. *Int J Sci Stud* 2021;9(8):123-126.

Source of Support: Nil, **Conflicts of Interest:** None declared.