Original Research Article

Correlation of serum iron and ferritin levels in patients of cholelithiasis and comparison with healthy individuals

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ABSTRACT

Background: Gall stones have afflicted man kinds since antiquity. Gall stone disease is prevalent, major source of morbidity and costly health problem. Presence of stones in the gallbladder is referred to as cholelithiasis, from the Greek chol-(bile)+lith (stone)+iasis-(process). If gallstones migrate into the ducts of the biliary tract, the condition is referred to as choledocholithiasis.

Methods: It is case control study. Inclusion criteria were, patients aged above 18 years suffering from cholelithiasis confirmed by USG. The exclusion criteria were, patients having hematological disorder, having any systemic disease leading to iron deficiency, on drugs causing gallstones and pregnant females.

Results: Study shows females were affected more in case (64%) and control (76%) group with mean age was of case (42.84 years) and control (40.64 years) group. 24% of patients was anaemic in cases. The mean serum cholesterol between cases and control was statistical insignificant (p=0.252). The mean serum ferritin between cases and control was statistical insignificant (p=0.800).

Conclusions: The study of 100 cases, based on serum iron, serum cholesterol, serum ferritin and hemoglobin, concludes that the disease is more prevalent in female gender. Serum ferritin association is insignificant as it increases other condition with inflammation also. Low serum iron level associated with high risk of cholelithiasis as this may lead to super saturation of bile.

Keywords: Cholelithiasis, Cholecystitis, Serum ferritin, Serum iron

INTRODUCTION

Gall stones have afflicted man kinds since antiquity, being found by Egyptians in their dead, used as charms, potions and paints. Now gall stone disease is prevalent, major source of morbidity and costly health problem. Presence of stones in the gallbladder is referred to as cholelithiasis, from the Greek *chol-* (bile) + *lith-* (stone) + *iasis-* (process). If gallstones migrate intothe ducts of the biliary tract, the condition is referred to as choledocholithiasis, from the Greek *chol-* (bile) + *docho-* (duct) + *lith-* (stone) + *iasis-* (process).

In pigment stone formation mainly, infection plays role. Ideally biliary tract infection should be defined by organism count in bile. Therefore 10^5 organisms/ml in over 90% of peroperative bile culture is taken as diagnostic.[1,2]

The presentation may range from flatulent dyspepsia and acute cholecystitis to its complications like empyema, chronic cholecystitis, gangrene, fistula and gallbladder carcinoma.[3] Today, the incidence of gallstone disease has increased considerably due to frequent use of ultrasonography.[4] Recent studies have defined the role of

trace elements (Fe, Calcium , Zn and Cu) and defective pH in the formation of gall stones.[5]

Aim of this study was to find out any association of serum iron and ferritin levels in patients of cholelithiasis.

METHODS

Study design

Case control study conducted during period of 1st February 2017 to 30th April 2018.

Study area

Department of General Surgery, SMS Medical college and Hospital, Jaipur, Rajasthan.

Sample size

Sample size was calculated to be 41 subjects in each group at an alpha error 0.05 and power 80% assuming proportion of subjects with iron level less than normal range in gall stone cases and control 78% and 46%. So, for the study purpose 50 gall stone cases and 50 normal healthy matched control were taken.

Inclusion criteria

Inclusion criteria were patients aged above 18 years suffering from cholelithiasis confirmed by USG; those patients who have given written and informed consent.

Exclusion criteria

Exclusion criteria were patients having hematological disorder; patients having any systemic disease leading to iron deficiency; patients on drugs causing gallstones; pregnant females.

Source of data

Cases

Patients reporting to SMS Hospital Jaipur with ultrasonographically proven gall stone and meeting inclusion and exclusion criteria.

Control

Matched control will be taken for study. Apparently healthy individual without cholelithiasis will be the control.

Method of collection of data

Patients with gall stone to be included in the study. After explaining about the study to the subjects, an informed consent will be obtained, followed by a detailed history with clinical examination with more emphasis on the parameters given below in outcome variable (ultrasonography finding, serum iron level, serum ferritin level, serum cholesterol).

Statistical analysis

For data comparison in different groups for categorical data chi-square test, for quantitative data, mean, standard deviation student t-test were used. For probality p value were calculated.

RESULTS

The study shows in the case group 64% of patient was female and 36% was male and in the control group 76% of patient was female and 24% was male (Table 1).

Table 1: Distribution of cases according to sex (n=50).

	Group C		Group N	
	No.	%	No.	%
Male	18	36	12	24.00
Female	32	64	38	76.00
Total	50	100	50	100.00

The mean age in the case group (gallstones present) is 42.84 years (ranging from 0-60 years), as compared to the control group (healthy volunteers) the mean age is 40.64 years (ranging from 20-60 years), Both groups are comparable as far as age distribution is considered. (Table 2).

Table 2: Distribution of cases according to age.

Age group	Case		Control	
	Anaemic (Hb<11)	Non anaemic (Hb>11)	Anaemic (Hb<11)	Non anaemic (Hb>11)
0-20	0	2	1	5
21-40	11	11	3	12
41-60	5	14	7	19
>61	0	7	2	1
Total	16	34	13	37
Mean±SD	42.84±14.23		40.64±14.36	

Table 3: Distribution of serum iron according to anemia.

Serum iron	Case		Control	
	Anaemic (Hb<11)	Non anaemic (Hb>11)	Anaemic (Hb<11)	Non anaemic (Hb>11)
<Normal	12	24	2	8
Normal (>40)	4	10	11	29
Total	16	34	13	37

Table 4: Distribution of serum iron according to sex.

Serum iron	Case		Control	
	Male	Female	Male	Female
<Normal	8	28	2	8
Normal (>40)	10	4	10	30
Total	18	32	12	38

Table 5: Mean serum iron (n=50).

	Mean	SD	P value
Group C	50.80	31.62	0.010
Group N	69.18	38.38	

Table 6: Distribution of cholesterol according to anaemia.

Serum iron	Case		Control	
	Anaemic (Hb<11)	Non anaemic (Hb>11)	Anaemic (Hb<11)	Non anaemic (Hb>11)
Normal (<200)	12	24	9	27
>Normal (>200)	4	10	4	10
Total	16	34	13	37

In this study 36 (72%) patients with gallstones have the value of serum iron less than normal (normal value: >40 µg/dl), 12 (24%) patients in the case group whose value is less than normal are anemic, 10 (20%) of the healthy volunteers have value of serum iron less than normal, 2(4%) of the healthy volunteers who have value of serum iron less than normal are anemic (Table 3).

Our study shows, there are 28 (56%) female patients with gallstone disease who have serum iron levels below the normal value, 8 (16%) females in the healthy volunteer group whose serum iron levels are below normal, only 4 (8%) female patients with gallstones whose serum iron levels are normal which is 30 (60%) females in the healthy control group. Most of the patients with gallstone disease whose serum iron levels are subnormal are females (Table 4).

Our study shows that the mean serum iron between cases and control was statistically significant (p=0.010) (Table 5).

In this study, 12 (24%) of anaemic and 24 (48%) of non-anaemic patients with gallstones have normal serum cholesterol levels, which is 9 (18%) and 27 (54%) in normal healthy individuals, respectively. 4 (8%) of anaemic and 10 (20%) of non-anaemic patients with gallstones have more than normal serum cholesterol level which is 4 (8%) and 10 (20%) in normal healthy individuals, respectively. There is no effect of anemia on serum cholesterol (Table 6).

Table 7: Distribution of cholesterol according to sex.

Serum iron	Case		Control	
	Male	Female	Male	Female
Normal (<200)	10	26	10	26
>Normal (>200)	8	6	2	12
Total	18	32	12	38

This study shows, 10 (20%) of male and 26 (52%) of female patients with gallstones have normal serum cholesterol levels, which is 10 (20%) and 26 (52%) in normal healthy individuals, respectively. 8 (16%) of male and 6 (12%) of female patients with gallstones have more than normal serum cholesterol levels, which is 2 (4%) and 12 (24%) in normal healthy individuals, respectively. Serum cholesterol has no effect on sex in the formation of gallstones (Table 7).

In this study the mean serum cholesterol between cases and control was statistical insignificant (p=0.252) (Table 8).

Table 8: Mean serum cholesterol (n=50).

	Mean	SD	P value
Group C	173.1	42.71	0.252 (NS)
Group N	183.26	45.47	

In this study, 44 (88%) of patients with gallstones have normal value of serum ferritin; in this 14 (28%) are anemic whereas 47 (94%) in the control group have normal value and anemic are only 13 (26%). In both group patients with gallstones most of them are non-anemic.

Table 9: Distribution of serum ferritin according to anemia.

Serum ferritin	Case		Control	
	Anemic (Hb<11)	Non anemic (Hb>11)	Anemic (Hb<11)	Non anemic (Hb>11)
<Normal	1	0	0	1
Normal	14	30	13	34
>Normal	1	4	0	2
Total	16	34	13	37

Table 10: Distribution of serum ferritin according to sex.

Serum ferritin	Case		Control	
	Male	Female	Male	Female
<Normal	0	1	0	1
Normal	14	29	12	35
>Normal	4	2	0	2
Total	18	32	12	38

Table 11: Mean serum ferritin (n=50).

	Mean	SD	P value
Group C	150.67	118.23	0.800 (NS)
Group N	156.27	102.51	

Our study shows the mean serum ferritin between cases and control was statistical insignificant (p=0.800) (Table 11).

DISCUSSION

Gall stone disease is a very common gastrointestinal problem in day today practice. There was definite clustering of cases around 4th and 5th decade as evident from data. The 8 (16%) patients out of the whole study group presented in their 6th decade whereas 11 (22%) belonged to 3rd decade. There were 7 (14%) patients who had age more than 60 years at the time of presentation with eldest being 66 years and only 2 (4%) patient falling into 2nd decade with age of 19 years each. These findings were similar to those observed in epidemiological study of cholelithiasis.[6]

The prevalence of gallstone disease was much more in females as compared to males with 32 (64%) patients out of the total 50 being females and the rest 18 (36%) were male. This is in accordance with the previous studies which stated a high prevalence of cholelithiasis in females which may be due to the effects of estrogen and progesterone on the biliary tract. Estrogenic influences increase the effect of hepatic lipoprotein receptors and stimulate hepatic hydroxyl methyl glutaryl coenzyme A (HMG Co-A) reductase activity. Consequently, together cholesterol uptake and biosynthesis are increased leading to super-saturation of bile with cholesterol and helping in formation of gallstones. Progesterone alters the sphincter of Oddi and gallbladder function ultimately causing a derangement in bile flow dynamics. Even though, the effects of progesterone on the biliary tract have been implicated in the increased incidence of gallstones among the women, the specific effects of prolonged elevated levels of progesterone on the sphincter of Oddi and bile flow dynamics are still incompletely understood.[7,8]

This study shows, in the case group, 0% of male and 1 (2%) of female patients have less than normal serum ferritin levels. This is 0 % and 1 (2%) in the control group. In the case group, 14 (28%) of male and 29 (58%) of female patients have normal serum ferritin levels. This is 12 (24%) and 35 (70%), respectively, in the control group. In the case group, 4 (8%)of male and 2 (4%) of female patients have more than normal serum ferritin levels. This is 0 and 2 (4%), respectively, in the control group. The number of females having normal serum ferritin levels (in both case and control groups) is more (Table 10).

Pregnancy favours the formation of gallstones through the hormonal influence on bile composition (increased biliary cholesterol secretion, diminished and disturbed bile acid pool). Estrogen induces an increased input to the hepatic free cholesterol pool by up regulating the low density lipoprotein. Decreased gallbladder motility during third trimester of pregnancy and an altered function of gallbladder mucosa that may favour nucleation and growth of stones.[9] While studying the pathogenesis of gallstone formation, certain known risk factors can be enlisted like elderly age, female sex, obesity and rapid weight loss, cirrhosis and different diet linked issues. On seeking for other risk factors, latest studies have defined the role of trace elements like iron and calcium which might play a definitive role in the formation of gallstones. Iron deficiency alters the activity of several hepatic enzymes, leading to increased gallbladder bile cholesterol saturation and promotion of cholesterol crystal

formation.[10] It is also suggested that iron deficiency alters the activity of several hepatic enzymes.[11] They concluded that consumption of diet rich in carbohydrates but deficient in iron altering hepatic metabolism of cholesterol that might be important in gallstone formation.

Researchers concluded that iron deficient diet altered hepatic enzyme metabolism which in turn increased gallbladder bile cholesterol and promoted cholesterol crystal formation.[12] Researchers have observed the same parameters in their study.[13] Researchers have demonstrated that diminished gallbladder neuronal nitric oxide synthase contributed to the gallbladder stasis that occurred with iron deficiency.[14] Iron acts as a cofactor for nitric oxide synthase, which plays a key role in normal relaxation of gallbladder. It has been reported that iron deficiency resulted in altered motility of gallbladder and sphincter of Oddi and thus increased cholesterol crystal formation in the gallbladder bile.[14,15] Thus, iron deficiency was found to have a major role in gallstone formation.

Serum iron

On examination of group C and group N patients, it can be concluded that the occurrence of gall stones had greater predilection for iron deficient patients as compared to patients with normal serum iron. In group C, 72% of the patient had serum iron level below normal range whereas 28% had serum iron level normal. This was 20% and 80% respectively in group N.

A study showed 78% of patient had iron deficiency whereas 22% had normal serum iron level in patients with cholelithiasis. In control group it was 56% and 54% respectively.[16]

Another study showed 75% of patient had iron deficiency whereas 25% had normal serum iron level in patients with cholelithiasis. In control group it was 48.3% and 51.7% respectively.[17]

A study showed 78% of patient had iron deficiency were as 22% had normal serum iron level in patients with cholelithiasis. In control group it was 46% and 54% respectively.[16]

These findings were in accordance to literature.[10-12] Researchers have concluded that iron deficiency led to gall bladder stasis thus, causing increased cholesterol crystal formation in bile within the gall bladder.[14,15]

Serum cholesterol

In the study conducted by Prasad et al and Akhtar et al 96% of patient with cholelithiasis and 98% in control group had serum cholesterol normal or less than normal.[16] Kshirsagar et al showed 95% of patient with cholelithiasis

and 98% in control group had serum cholesterol normal or less than normal.[17]

In our study 72% patient in each group had normal cholesterol level whereas 28% in each group had serum cholesterol level more than normal. Thus, serum cholesterol levels in group C and N were not significantly different and the mean serum cholesterol (shown in Table 8) were normal in each group (Group C=173.1 and Group N=183.26) and statistically insignificant (P=0.252) suggesting that serum cholesterol is not a significant criterion in the super saturation of bile with respect to cholesterol and these results were comparable to the above studies.[16]

Serum ferritin

In the study conducted by Prasad et al and Nasim Akhtar et al 80% of patient with cholelithiasis and 98% in control group had serum ferritin normal or less than normal. In our study 90% of patient with gallstones had serum ferritin normal or less than normal while it was 96% in the control group.[16]

The mean serum cholesterol (shown in Table 11) were normal in each group (Group C=150.67 and Group n=156.27) and statistically insignificant (p=0.252). Thus, we can conclude that serum ferritin cannot be used as a diagnostic tool for iron deficiency in patient with gallstones.

Our study has a limitation of small sample size so a study with larger sample size is required to establish the role of iron deficiency in patient with cholelithiasis.

CONCLUSION

The study of 100 cases, based on serum iron, serum cholesterol, serum ferritin and hemoglobin, concludes that the disease is more prevalent in female gender. Serum ferritin association is insignificant as it increases other condition with inflammation also. Low serum iron level associated with high risk of cholelithiasis as this may lead to super saturation of bile.

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