Relationship between iron deficiency and gall stones formation

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Abstract

The old axiom that a typical gall stone sufferer is a fat, fertile, female of fifty, is only partially true, as the disease is found in women soon after their first delivery and also in underweight and thin people. So while searching for other parameters, iron deficiency was found to be a new parameter of interest in the etiology of gall stones. The aim of the study was aimed at establishing the role of iron deficiency in the supersaturation of bile with cholesterol and thus formation of gallstone. 50 patients of cholelithiasis, confirmed by ultrasonography (USG) were divided into anemic and non-anemic groups, based on serum iron levels. Serum cholesterol and gall bladder bile cholesterol of both the groups were estimated. Data amongst the two groups were subjected to statistical analysis using students t-test. The *P* -value <0.05 was considered significant. Total serum cholesterol was not different in gall stone formers from that of the general population. Gall bladder bile cholesterol was significantly higher in anemic, than in non-anemic individuals. The present study conclude that low serum iron levels lead to bile supersaturation with respect to cholesterol, which leads to gallstone formation.

Keywords: Iron deficiency, gallstones, biliary cholesterol

Introduction

The old axiom, that a typical gall stone sufferer is a fat, fertile, female of fifty, is only partially true, as the disease has been found in women soon after their first delivery and also in underweight and thin people[(1)]. So while searching the literature for different factors, Iron deficiency was found to be new and interesting etiological factor in the formation of gall stones. Gallstones may produce symptoms, or may remain asymptomatic. Over ha0lf the cases are asymptomatic, usually detected by abdominal ultrasound[(2)] .

Today the incidence of gallstone disease has increased considerably with the invention of ultrasonography [(1)].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 gall bladder long enough to agglomerate into stones [(2)].

Iron deficiency 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[(3)]. Iron acts as a coenzyme for nitric oxide synthetase (NOS), and that is important for the maintenance of basal gall bladder tone and normal relaxation [(4, 5)]. It was found that iron deficiency resulted in altered motility of gall and sphincter of oddi (SO), leading to biliary stasis and thus increased cholesterol crystal formation in the gall bladder bile[(6)].

The present study was conducted on the randomly selected individuals of the Tikrit population, suffering from gall stone formation, to study the role of iron deficiency anemia in gall stone formation.

Patients and Methods

This is a prospective study of 50 patients with gallstone, over a period of one year, from May 2007- April 2008 in Tikrit Teaching Hospital. The patients were selected, based only on the

ultrasound confirmation of their gall stones, irrespective of their age, sex, physique, parity, etc. Only those patients were included, whose serum as well as bile could be procured for analysis. Patients who underwent laparoscopic cholecystectomy were excluded, as their bile could not be procured. Patients who underwent open cholecystectomy, but whose bile sample was not available for analysis, and those with empyaema gall bladder were excluded from the study. All the patients, who were included in the study given a serial numbers from 1 to 50, in the order of their admission to the Surgery Department for cholecystectomy. Thus their bile and serum samples were also labeled 1 to 50 accordingly. The numbered samples were sent to the Biochemistry Department for analysis.

All the numbered samples with normal serum iron (n=27) were put in the non anemic group, Group A, and all the samples less than normal serum iron (n=23) were put in the anemic group, Group B.

Serum iron was estimated by FER kit method for determination of iron. This kit was procured from REACTIFS BIOLABO. The normal reference values supplied with the kit, for males (60-160 ug/dl) and for females (35-145 ug/dl), were used to label the patients as anemic and non-anemic i.e. males with serum iron < 60 ug/dl and females with serum iron <35 ug/dl were labeled as anemic. During the operation for open cholecystectomy, bile was aspirated with a needle mounted on a sterilized syringe. The aspiration needle was passed obliquely into the fundus of gall bladder and as much of bile as possible, was withdrawn from the gall bladder. Bile was kept in a sterile labeled container and carried to the Biochemistry Department for analysis. Serum cholesterol and gall bladder bile cholesterol of all the patients were estimated. Bile was first subjected to the Folch method to extract lipids and then the cholesterol contents were estimated as for serum cholesterol. In the Folch method, lipids from bile were extracted by using water, Methanol and Chloroform mixture in the ratio of 3:4:8 v/v and from the extracted lipids, cholesterol was estimated by Enzopak kit, based on the cholesterol oxidase/peroxidase method. The enzymes used only the cholesterol as substrate and hence Bilirubin is automatically eliminated, from the procedure of cholesterol estimation. Data amongst the two groups were subjected to statistical analysis using students' t-test. The *P* -value <0.05 was considered significant.

Results

Out of the total 50 patients, 40 (80%) were females and 10 (20%) were males. The male to female ratio was 1:4. Anemia is more common in females than males, as 22 (55%) females were observed to be anemic, as compared to 1 (10%) male Table(1).

The majority of patients 31 (62%) presented with all the three symptoms of cholelithiasis i.e. pain in the right upper quadrant, nausea/vomiting and flatulent dyspepsia. Pain was the most consistent symptom present in 49 (98%) patients.

Thirty one (77.5%) out of the total female patients was multipara. In both the non anemic and anemic groups of female gall stone formers, the number of multipara females (n=12 and n=19 respectively) was more than that of primipara (n=4 and n=2 respectively) and nullipara (n=2 and n=1 respectively) Table (2).

Forty (80%) patients had body mass index (BMI) more than normal and 10 (20%) had normal or decreased BMI. Normal BMI means values between 19.1&24.9 i.e. <25.

All non anemic gall stone sufferers (n=27) had a high average

serum iron content of 91 ± 35 microg/dl, as compared to anemic ones (n=23), where average serum iron was 26 ± 9.5 mg/dl. The corresponding values for serum cholesterol were observed to be 183 ± 36 mg% and 172 ± 49 mg% and that for gall bladder bile cholesterol were 0.70 ± 0.37 g% and 1.2 ± 0.41 g%, respectively Table(3).

Discussion

Out of the 50 gall stone patients included in the present study, 40 (80%) were females, and 10 (20%) were males, supporting the age old axiom that gall stone formation is most common in the female population [(1)]. The increased prevalence of gall stone formation in females could be attributed to the fact, that anemia is more common in females than males.

The male to female ratio of 1:4 observed in the present .This sex-related difference showing more prevalence of cholelithiasis in females could be linked to pregnancy and female sex hormones and also to iron deficiency anemia now [(7,8)].

In both the non anemic and anemic groups of female gall stone formers, the number of multipara females suffering from gall stones was more than that of primipara and nullipara, suggesting that parity plays a significant role in gall stone formation. More the number of babies delivered, more is the probability of a female suffering from gall stone formation. It could probably be attributed to advancing anemia with increase in number of deliveries. The percentage of multipara female patients was more in the anemic (86.5%) group than in the non anemic (66.7%) group, again reinforcing the fact that anemia contributes to gall stone formation[(8)].

Different workers suggested differently about the serum cholesterol levels and cholelithiasis[(9,10)]. Serum total cholesterol of gall stone formers was not different from that of the general population. There were no significant variations in the serum cholesterol contents of both groups (P =0.367, t=0.91).

Also, there was no significant variation of the above parameter in the male and female patients (P =0.082, t=1.77).The gall bladder bile cholesterol was significantly higher in the anaemic individuals, as compared to that of the non-anemic ones (P <0.0001, t=4.53) , suggesting that anemia may be contributing to the super saturation of gall bladder bile with respect to cholesterol independent of serum cholesterol levels [(11)] .

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 gall bladder tone, motility and relaxation and cofactors affecting these enzymes.

As a conclusion; Low serum iron levels lead to bile supersaturation with respect to cholesterol, which leads to gallstone formation.

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Table (1): Serum iron levels of gall stone former

Individuals	No.	%	Range (ug/dl)	Mean ±S.D
Males				
Non-anemic	9	90	90-140	119±18
Anemic	1	10	40-90	40
Total	10	100	140-40	111±30
Females				
Non-anemic	18	45	40-150	77±33
Anemic	22	55	5-35	25±9
Total	40	100	5-150	48±35

Table (2): Distribution of female patients according to parity

Parity	Group A			Group B		
	No.	%	Mean serum iron(ug/dl)	No.	%	Mean serum iron(ug/dl
Nullipara	2	11.1	77	1	4.5	30
Primipara	4	22.2	77	2	9	22
Multipara	12	66.7	77	19	86.5	25
Total	18	100		22	100	

Table (3): Serum iron, serum cholesterol and bile cholesterol of patients in both group

Groups	Sr. Iron (ug/dl)	Sr. Cholesterol (mg/dl)	Bile Cholesterol(g/dl)
A	91±35	183±36	0.7±0.37
B	26±9.5	172±49	1.2±o.41
P value	≤0.001	- 0.367	≤0.001