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Original Research Article.

An Observational Study on Association of Gall Stone Disease and Iron Deficiency in the Population of Kolhan Region of Jharkhand

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ABSTRACT

Background: Gallstone disease is common gastrointestinal problem encountered in day to day practice. Super saturation of bile in cholesterol, enhanced nucleation of cholesterol, impaired gallbladder emptying and intestinal hypo motility favors the formation of gallstones. Consumption of diet rich in carbohydrates but deficient in iron alters hepatic metabolism of cholesterol and promotes cholesterol crystal formation. **Objective:** To correlate iron deficiency anemia with gallstone disease in Kolhan region of Jharkhand.

Materials & Methods: A prospective study was conducted during period of one year in department of surgery Mahatma Gandhi Memorial Medical College Hospital, Jamshedpur. 50 patients with ultrasonographically proven gallstone disease admitted in surgery department during this period were included in the study. 50 individuals admitted in surgery department, not suffering from gall stone diseases were taken as control group. Subjects were divided into two groups anemic and non-anemic based on Hemoglobin% and serum iron. Serum cholesterol of both the groups was estimated.

Results: Female was affected more in case and control group with mean age 39.72±15.382.

Conclusion: Iron deficiency anemia plays a significant role in super saturation of bile with cholesterol leading to gallstone formation.

Key Words: Iron Deficiency, Anemia, Gall Stones, Serum Iron, Serum Cholesterol.

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INTRODUCTION

Gallstone disease is one of the most common causes of gastrointestinal morbidity and mortality throughout the world. Stone present in gall bladder is called cholelithiasis. It's derived from the Greek word chol- (bile) + lith- (stone) + iasis- (process). In India prevalence of gallstones is around 4%whereas in western world it is 10%.[1] There are many risk factors for gallstone disease. Family history of gallstone, genetic predilection, ethnic background, female sex and age are non-modifiable risk factors. As shown by several studies showed Obesity, diabetes mellitus, dyslipidaemia, drugs, diet and underlying diseases – cirrhosis, crohn's disease are modifiable risk factors. Important geographical and racial variations have been observed by several workers in the incidence of cholelithiasis in various parts of the world. It is uncommon in Negro and rare among the Chinese and Japanese. It is 7 times higher in North India as compared to South India. South Indian diet is mainly vegetarian with less fat and spices while research done in Chandigarh and New Delhi region shows that inadequate physical activity, truncal obesity together with excessive consumption of PUFA and fat from non-vegetarian sources cause extra utilization of bile salts which are lost in stool. This causes decrease in bile salt and comparative increase in cholesterol in bile leading to bile super saturation and gallstone formation.[2,3]

Gallstones can occur in one large or hundreds of small stones combination. Cholesterol and calcium bilirubinate are the two main substances in the formation of gallstones. It is obtained from bile and contains a mixture of cholesterol and bilirubin with or in addition to calcium. Gallstones found in the gallbladder are

classified based on their chemical composition such as cholesterol, black or brown pigmented or mixed stones. Some factors must be met to refer the formation of cholesterol gallstones. 1. Bile must be supersaturated with cholesterol. 2. Cholesterol crystals due to enhanced nucleation 3.Gall bladder dysmotility 4. Intestinal hypo motility.[4] Recent studies have defined the role of trace elements (Fe, Ca, Zn and Cu) and defective pH in the formation of gallstones.[5,6]

Several researches have established the role of iron in bile supersaturation. It has a vital role in the underlying biochemical changes, leading to gallstones formation and high incidence among female population than in male population. Iron deficiency alters the activity of several hepatic enzymes. In the present study we have tried to find out a correlation between iron deficiency anemia and gallstone disease in Kolhan division of Jharkhand. This study was approved by Local Research Advisory committee of Department of Health Research, ICMR, Ministry of Health & Family welfare, New Delhi.

OBJECTIVE

To assess any association between gall stone formation and iron deficiency anemia in patients presenting with cholelithiasis.

MATERIALS AND METHODS

Study Design

A prospective study was conducted during period of 05 September 2018 to 10 October. 2019. The study was conducted in Department of Surgery, Mahatma Gandhi Memorial Medical College, Hospital, Jamshedpur, Jharkhand.

Study Part Divided Into 2 Groups:

A total of 100 subjects were enrolled in this study.

Case Group: A group of 50 patients with ultrasonographically proven gallstones disease admitted in the surgery department, who completed the inclusion and exclusion criteria.

Control Group: 50 matched individuals admitted in surgery department, not suffering from gall stone diseases were taken as control group

Haemoglobin percentage, Serum iron and Cholesterol contents of both groups were analyzed and compared with each other.

Inclusion Criteria

All consented female & male patients suffering from cholelithiasis and confirmed by ultrasonography.

Exclusion Criteria

Pregnant women gall stones patients with hematological disorder. Patients on long term NSAIDS therapy.Patients on drug causing gall stones eg- Oestrone, clofibrate, cholesterol lowering agents. Patient from outside Kolhan Region. Acalculus Cholecystitis. Primary CBD Stones.

Method of Collection of Data

Patients with gall stone to be included in the study were explained about the study, and informed consent was obtained, followed by a detailed history with clinical examination with more emphasis on the parameters of serum iron level, Hb%, serum cholesterol.

Laboratory Investigation

The numbered samples were sent to the Multi-Disciplinary Research laboratory Unit of MGMMC, Jamshedpur for analysis. Serum iron was estimated by the ERBA Mannheim System pack method. The normal reference values were supplied with the kit 65-175 mg/dl. Serum cholesterol was estimated by the Erba Mannheim System pack kit based on the cholesterol oxidase/ peroxidase method. The normal reference values were supplied with the kit ie.<200mg/dl. Based on the haemoglobin of the patients and control group, all cases were divided into two groups: Non-anaemic: (i.e., haemoglobin > 11 gm %), and Anemic (i.e., haemoglobin ≤11gm%).

Statistical Analysis

Research data was entered into Microsoft Excel 2007 and analysed with statistical software SPSS. Prevalence was expressed in percentage. Chi-square tests were used to find out the association with factors. Independent sample "t" test was used to show the significance of Haemoglobin, Serum iron, serum cholesterol levels between cases and controls. Correlation and association of parameter was obtained from Pearson's correlation. $P < 0.05$ was set as significant.

Table: 1 Distribution of anemia according to age

Age group	Case		Control	
	Anemic no. (%) (Hb<11)	Non-Anemic no. (%) (Hb>11)	Anemic no. (%) (Hb<11)	Non-Anemic no. (%) (Hb>11)
14-24	7(14%)	1(2%)	1(2%)	7(14%)
25-35	8(16%)	9(18%)	4(8%)	13(26%)
36-46	5(10%)	3(6%)	2(4%)	6(12%)
47-57	6(12%)	4(8%)	4(8%)	6(12%)
58-68	3(6%)	1(2%)	2(4%)	2(4%)
69-79	2(4%)	0(0%)	1(2%)	1(2%)
80and older	1(2%)	0(0%)	0(0%)	1(2%)
Total	32	18	14	36
Mean			39.72	
Standard Deviation			15.382	

Table: 2 Distribution of serum iron according to anemia

Serum Iron	Case		Control	
	Anemic no.(%) (Hb<11)	Non-Anemic no.(%) (Hb>11)	Anemic no.(%) (Hb<11)	Non-Anemic no.(%) (Hb>11)
<Normal	29(58%)	8(16%)	8(16%)	11(22%)
>Normal	3(6%)	10(20%)	6(12%)	25(50%)
Total	32	18	14	36
Pearson Chi-Square: 20.641, df: 1, P-Value: <0.01				

Table 3: Distribution of serum Iron according to sex

Serum Iron	Case		Control	
	Male no.(%)	Female no.(%)	Male no.(%)	Female no.(%)
<Normal	4(8%)	33(66%)	5(10%)	14(28%)
>Normal	2(4%)	11(22%)	4(8%)	27(54%)
Total	6	44	9	41

Table 4: Distribution of serum cholesterol according to anemia

Serum Cholesterol	Case		Control	
	Anemic no. (%) (Hb<11)	Non-Anemic no. (%) (Hb>11)	Anemic no. (%) (Hb<11)	Non-Anemic no. (%) (Hb>11)
Normal	31(62%)	14(28%)	14(28%)	36(72%)
>Normal	1(2%)	4(8%)	0(0%)	0(0%)
Total	32	18	14	36

Table 5: Distribution of serum cholesterol according to sex.

Serum Cholesterol	Case		Control	
	Male no.(%)	Female no.(%)	Male no.(%)	Female no.(%)
Normal	6(12%)	39(78%)	9(18%)	41(82%
>Normal	0(0%)	5(10%)	0(0%)	0(0%)
Total	6	44	9	41

Table 6: Mean value of Serum iron, Hemoglobin and serum cholesterol of study subject.

Parameters	Case(n=50); Control(n=50)	Mean	Std. Deviation
Serum Iron (mg/dl)	Case	63.2920	39.31084
	Control	78.8600	38.71403
Hemoglobin (gm %)	Case	10.182	1.8073
	Control	12.424	1.8162
Serum cholesterol (mg/dl)	Case	150.84	40.306
	Control	145.10	32.482

Table: 7 Correlation between serum Iron and hemoglobin in study subject.

		Serum Iron	Hemoglobin
Serum Iron	Pearson Correlation	1	.454**
	Sig. (2-tailed)		.000
	N	100	100
Hemoglobin	Pearson Correlation	.454**	1
	Sig. (2-tailed)	.000	
	N	100	100

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Table: 8 Correlation between serum Iron and cholesterol in study subject.

		Serum Iron	Cholesterol
Serum Iron	Pearson Correlation	1	.074
	Sig. (2-tailed)		.465
	N	100	100
Serum cholesterol	Pearson Correlation	.074	1
	Sig. (2-tailed)	.465	
	N	100	100

Table: 9 Correlation between serum cholesterol and Hemoglobin in study subject

		Serum cholesterol	Hemoglobin
Serum cholesterol	Pearson Correlation	1	.120
	Sig. (2-tailed)		.236
	N	100	100
Hemoglobin	Pearson Correlation	.120	1
	Sig. (2-tailed)	.236	
	N	100	100

RESULTS

Table 1 shows that the mean age of case and control group are found to be 39.72±15.382 (ranging from 14-80years). As far as age distribution is considered , highest number of cases are found in the age group (25-35) which is 34% and 20% are found in the age group (47-57).

Table 2 shows that: The patients in the case group who had the value of serum iron <normal (normal value: 64-164µg/dl) was 74% in which 58 % were anemic and 16% were non-anemic. The patients in the control group who had value of serum iron <normal (normal value: 64-164µg/dl) was 38% in which 16 % were anemic

and 22 % were non-anemic. Most of the patient found with gall stone had serum irons levels <normal and they were anemic.

Table 3 shows that: There were 66 % female patients in the case group whose serum iron level was < normal value. There were 28% of female patients in the control group whose serum iron level was <normal value. Most of the patient with gall stone disease whose serum iron levels were not meeting the standard value was in the females group. Table 4 shows that: In the case group there were 62% of anemic and 28% of non-anemic patients who had normal serum cholesterol level whereas in the control group there were 28% anemic and 72% non-anemic such patients.. Hence we can say that there is no effect of anemia and gall stone disease on the level of serum cholesterol levels.

Table 5 shows that: 12% of male and 78% female patients in the case group had normal serum cholesterol level. As far as control group was considered 18% of male and 82% of female patients had normal serum cholesterol levels. Hence we found that serum cholesterol had no effect on the sex of the patients regarding the formation of gall stones.

Table 6 shows that: the mean serum iron level was <normal in cases (63.2920 ± 39.31084mg/dl) than in controls (78.8600 ± 38.71403mg/dl). The mean hemoglobin level was also <normal in cases (10.182 ± 1.8073 gm %) than controls (12.424 ± 1.8162 gm %). The mean serum cholesterol level was found to normal in cases to be 150.84mg/dl ± 40.306 mg/dl, whereas in controls, it was found to be 145.10 ± 32.482 mg/dl.

Table 7 showed that strength of association between the serum iron and Hemoglobin are statistically highly significant ($p<0.01$).

Table 8 showed that strength of association between the serum iron and cholesterol are statistically not significant ($p>0.01$).

Table 9 showed that strength of association between the serum iron and cholesterol are statistically not significant ($p>0.01$).

DISCUSSION

Biochemical Aspect of Derangement

It has been suggested that iron deficiency alters the activity of several hepatic enzymes. Consumption of diet rich in carbohydrate but deficient in iron alters hepatic metabolism of cholesterol which in turn increased gall bladder bile cholesterol and promoted cholesterol crystal formation. Diminished gall bladder neuronal nitric oxide synthase contributed to gall bladder stasis that occurred with iron deficiency. Iron acts as a co-factor for Nitric oxide synthase, which plays a key role in normal relaxation of gall bladder. Iron deficiency resulted in altered motility of gall bladder and sphincter of oddi and thus increased cholesterol crystal formation in gall bladder bile. Nitric oxide (NO) is a major inhibitory non adrenergic, non-cholinergic neurotransmitter in the gastrointestinal tract. NO released in response to nerve stimulation of the myenteric plexus causes relaxation of the smooth muscle. NO is synthesized by the activation of neuronal NO synthase. NO synthase is a haemoprotein. It acts on L-Arginine inside vascular endothelial cells to produce Nitric oxide by 5 electron oxidation of amide nitrogen of L arginine. Function of NO is mediated through activation of soluble Guanylate Cyclase present in most cell types. NO is lipophilic and can readily permeate in another cell type. Inactive form of soluble Guanylate Cyclase enzyme is present in the cytoplasm in good amount. It has penta-coordinate haem bound to histidine on beta chain. NO binds to Fe2+ as sixth ligand to form a hexa-coordinate heme and causes breakage of heme-histidine bond producing conformational change. This active penta co-ordinate nitrosyl complex of soluble guanylate cyclase causes 400 fold increases in rate of cGMP formation. Accumulation of cGMP in smooth muscle cells triggers rapid and sustained relaxation of contractile apparatus. The mechanism of smooth muscle relaxation includes Increased intracellular cGMP inhibits Ca++ ion entry into the cells and decreased intracellular Ca++ concentration. Activates K+ channels, which leads to hyper polarization & relaxation. Stimulates cGMP dependent protein kinase G that activates myosin light chain phosphates. This enzyme dephosphorylates myosin light chain leading to smooth muscle relaxation. The reduction of nNOS expression associated with impaired local production of NO, may be responsible for motility disorders in gallbladder.[6-11]

Cholesterol gallstones composed predominantly of cholesterol crystals result from abnormalities in cholesterol metabolism. Four types of abnormalities have been considered to be responsible for cholesterol gallstone formation. 1. Super saturation of bile in cholesterol 2. Enhanced nucleation of cholesterol 3. Impaired gallbladder emptying with stasis 4. Intestinal hypomotility. First and essential requirement is bile super saturation in cholesterol. The percent saturation of cholesterol in bile is determined by the molar ratio of the three major biliary lipids: cholesterol, bile acids and phospholipids. Cholesterol super saturation, the essential requirement for cholesterol gallstone formation, might occur via excessive cholesterol biosynthesis (increased 3 – hydroxyl – 3 methyl glutaryl (HMG) coenzyme A reductase activity), which is the main lithogenic mechanism in women and obese persons. A reduced acyl – Co A cholesterol acyl transferase (ACAT) activity, inhibiting cholesterol esterification, leads to an increase a excretion of free cholesterol into the bile. In the non-obese, excessive cholesterol secretion could result from defective conversion of cholesterol to bile acids, due to a low or relatively low activity of cholesterol 7 alpha hydroxylase, the rate limiting enzyme for bile acid biosynthesis (and cholesterol elimination). Finally, interruption of the enterohepatic circulation of bile acids could increase bile saturation. Temporary interruption of the enterohepatic bile acid circulation during overnight fasting leads to a high cholesterol/ phospholipids ratio in the vesicles secreted by the liver. The second abnormality is enhanced nucleation of cholesterol crystals. Mucin and its cogeners, the major proteins act as matrix molecules to hold cholesterol crystal aggregation together to form a stone. There also must be sufficient time for nucleation to occur, for crystals to form and grow to microliths to aggregate to form gall stones, hence gallbladder stasis is a contributing factor to gall stone formation. During overnight fasting, the gallbladder does not empty so that hours of storage occur in all individuals. It should be the sum of these three factors that determines when gall stones form. If bile is highly supersaturated, hyper nucleation or prolonged stasis might result in gallstone formation. Intestinal hypo motility has been recently recognized as a fourth primary factor in cholesterol litho genesis. Having a longer exposure to intestinal microorganisms, primary bile salts are in greater proportion deconjugated and decarboxylated to more hydrophobic secondary bile salts. An increased proportion of the secondary bile acid deoxycholate, a potent down regulator of the rate limiting enzyme bile acid biosynthesis, enhances cholesterol hyper secretion into bile.[12]

This study found that iron deficiency anemia plays a significant role in super saturation of bile leading to stone formation in gall bladder. Serum cholesterol level of anemic and non-anemic group was similar.

Our observations were found in various other studies such as done by P.C. Prasad et al: 2015 in prospective study, yogendra Dadhich, Girish Bhardwaj et al 2019 case-control study and Dr. Nasim Akhtar et. Al.[13] in prospective study reported that the iron deficiency anemia play a significant role in super saturation of bile, leading to stone formation in the gall bladder. Serum total cholesterol of the patients of cholelithiasis was not different from that of general population. There were no significant variations in the serum cholesterol contents of both the groups.

CONCLUSION

Our study based on serum iron, hemoglobin and serum cholesterol we drew the following conclusions.

1. Cholelithiasis was more prevalent in females than in male in Kolhan.
2. Serum total cholesterol of the control group was not much different from that of the patients of case group. No significant variations were noticed in the serum cholesterol contents of both the groups.
3. Iron deficiency anemia plays a significant role in super saturation of bile with cholesterol leading to gallstone formation.

ETHICAL CONSIDERATIONS

This study was approved by Intuitional Ethics Committee of MGM Medical College, Jamshedpur.

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