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Original Research Article

Prevalence of iron deficiency anaemia in patients of cholelithiasis undergoing laparoscopic cholecystectomy

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ABSTRACT

Background: Gallstone disease (GSD) is a very common condition worldwide and the key event in the cholesterol stone formation is the supersaturation of bile with cholesterol. The role of trace elements like iron, calcium has been suggested in the pathogenesis of gallstones. Both iron deficiency and GSD are more prevalent in India. With this background, we studied the frequency of iron deficiency anaemia in GSD patients.
Methods: This prospective observational study enrolled 150 adult patients undergoing laparoscopic cholecystectomy for symptomatic GSD in a north-Indian tertiary care hospital. Complete hemogram, serum ferritin, iron and unbound iron-binding capacity (TIBC) were performed in all patients. To simplify interpretation, anaemia was defined as Hb <12 gm/dl; iron deficiency was defined as either ferritin value lower than the reference range, or, if the ferritin was within the reference range, reduced % transferrin saturation with normal-or-high TIBC.
Results: Anaemia was present in 66% and 77.3% were having iron deficiency; of which 84.5% were females. Iron deficiency with anaemia was present in 85.3%; therefore remaining patients had latent iron deficiency. Serum ferritin was normal or raised in 52 (68.1%) patients with iron deficiency, indicating that it is insensitive as a stand-alone test for iron deficiency.
Conclusions: At a public health level, our results may suggest that addressing the problem of endemic iron deficiency may also reduce the possible development of GSD in the community. Thus, pre-operative assessment of iron status appears to be a cautious choice in all patients planned for cholecystectomy as indirectly it will address the problem of anaemia in the population.

Keywords: Laparoscopic cholecystectomy, Iron deficiency anaemia, Gall stones, Anaemia

INTRODUCTION

Gallstone disease (GSD) is a very common condition worldwide with variable prevalence according to geographic location and ethnicity, with prevalence of 4.3% in India.[1-3] Clinical presentations ranges from asymptomatic states, flatulent dyspepsia and acute cholecystitis to complications like chronic cholecystitis, empyema, gangrene, bilio-enteric fistula, choledocholithiasis, pancreatitis or malignancy. Cholesterol is the major component of most gallstones; and the key event in the cholesterol stone formation is the supersaturation of bile with cholesterol. Pigment stones containing mainly calcium bilirubinate and <20% cholesterol are seen secondary to haemolytic disorders.[4,5]

The role of iron, calcium and other trace elements like zinc and copper has been evaluated in the pathogenesis of gallstones.[6-9] Iron is required by various intracellular and hepatic enzymes involved in cholesterol metabolism. It also acts as a coenzyme for the nitric oxide synthetase (NOS) enzyme which is involved in nitric oxide (NO) synthesis. Decreased NO formation in iron deficiency has been postulated to impair gallbladder smooth muscle relaxation and contraction of the sphincter of Oddi leading to gallbladder stasis and an increased risk of gallbladder stone formation.[10-12] Iron deficiency also leads to increased serum and bile concentrations of transferrin, which is a cholesterol pro-nucleator and increases risk of gallstones. Iron deficiency additionally leads to alterations of liver enzymes involved in cholesterol metabolism, like cholesterol7α-hydroxylase which is involved in cholesterol metabolism and synthesis of bile acids. Defective 7α-hydroxylase leads to decreased bile salts and increased biliary cholesterol leading to supersaturation of bile, promoting cholesterol crystal formation.[6]

The prevalence of iron deficiency anaemia (IDA) in India approaches 53%. Iron deficiency per se (with or without anaemia) is nearly 2.5 times more prevalent than IDA; rendering it the commonest nutritional deficiency.[13] Adolescent girls and women of childbearing age are more commonly affected in developing countries due to increased iron demand because of menstrual blood losses, poorer overall nutrition and healthcare access. IDA is also commoner in multiparous women who also show higher prevalence of GSD.[13,14] Insights into factors that contribute to gallstone formation can therefore have public health implications, and can aid institution of preventive measures. With this background, we studied the frequency of iron deficiency anaemia in GSD patients.

METHODS

This prospective observational study was conducted in the departments of General Surgery and Haematology, Post Graduate Institute of Medical Education and Research, Chandigarh, from June 2019 - December 2020. We enrolled 150 patients (18 to 80 years) who underwent laparoscopic cholecystectomy for symptomatic GSD after obtaining informed written consent and institutional ethical committee approval (NK/5643/MS/982). ethical committee approval (NK/5643/MS/982). GSD was diagnosed on abdominal ultrasonography. Patients with a history of oral iron supplementation, oral contraceptives, clofibrate, ceftriaxone, octreotide, those who had terminal ileal Crohn disease, had undergone ileal resection, ileostomy, vagotomy, or had any known iron storage disorders were excluded.

Complete hemogram (DxH900 analyser, Beckman Coulter, FL, USA), serum ferritin (Cobas e411 chemiluminescence analyser, Roche, Switzerland), iron and unbound iron-binding capacity (UIBC), lipid profile and liver function tests [EM Destiny 180 biochemical analyser, Transasia, Mumbai, India] were performed in all patients. Total iron binding capacity (TIBC = serum iron + UIBC) and transferrin saturation percentage (serum iron x 100 /TIBC) were calculated.

To simplify interpretation, anemia was defined as Hb <12 gm/dl (incorporating the WHO cut-off of <12 gm/dl for non-pregnant women). Iron deficiency was defined as either ferritin value lower than the reference range (unequivocal iron deficiency), or, if the ferritin was within the reference range, reduced `transferrin saturation with normal-or-high TIBC (these patients were labelled as having iron deficiency with coexisting inflammation).[15,16]

Statistical analysis

Descriptive statistics were used to describe different variables. Quantitative variables were reported as mean±SD and range while qualitative variables were described in proportions. Means were compared by Student's t-test or variance analysis. The $\chi 2$ test was used to detect association(s) between categorical variables. All statistical tests were two sided and with a significance level of $p<0.05$. Statistical analysis was performed on Microsoft Excel 2019 (Microsoft, Redmond, WA) and Statistical Software for Social Sciences (SPSS) software version 20.0 (IBM Corp., Armonk, NY).

RESULTS

Of 150 patients, 110 (73.3%) were females. Age ranged from 18-80 years and 40% were in the 31-50 year age group.

Table 1: Comparison of demographic and laboratory parameters in patients with and without iron deficiency.

Parameter	Iron deficient patients (n=116)	Non-iron deficient patients (n=34)	P value
Age (years)	44±15.1 (19-78)	47.1±16.4 (19-80)	0.303
M:F	0.24:1	1:1	0.006
Hemoglobin (gm%)	11.4±1.3	12.4±1.8	0.002
Serum iron (µg/dl)	36.6±17.5 (9.7-110)	88.9±46.0 (41.2-285.2)	0.001
Transferrin saturation (%)	12.4±5.6 (3.0-44.7)	31.9±13.0 (20.3-73.8)	0.001
Ferritin (ng/ml)	56.81±93.1 (3.5-659)	141.3±89.1 (30.9-424.9)	0.001
TIBC (µg/dl)	298.2±57.9 (130-461.8)	282.0±64.7 (67.9-414.6)	0.165

Continued.

Parameter	Iron deficient patients (n=116)	Non-iron deficient patients (n=34)	P value
Alanine aminotransferase (IU/l)	43.5±32.3 (6-187.5)	49.0±68.7 (11-313.8)	0.514
Aspartate aminotransferase (IU/l)	30.9±16.4 (9.2-117.6)	43.5±53.0 (9-318)	0.026
Total bilirubin (mg/dl)	0.6±0.5 (0.1-4.6)	0.9±0.6 (0.3-2.3)	0.004
Conjugated bilirubin (mg/dl)	0.4±0.4 (0.04-4.5)	0.3±0.3 (0.1-1.6)	0.179
Cholesterol (mg/dl)	175.8±47.6 (80.6-509.2)	166.2±35.7 (86.7-255.5)	0.278

All p-values by paired t test, except M:F ratio by Chi-square test.

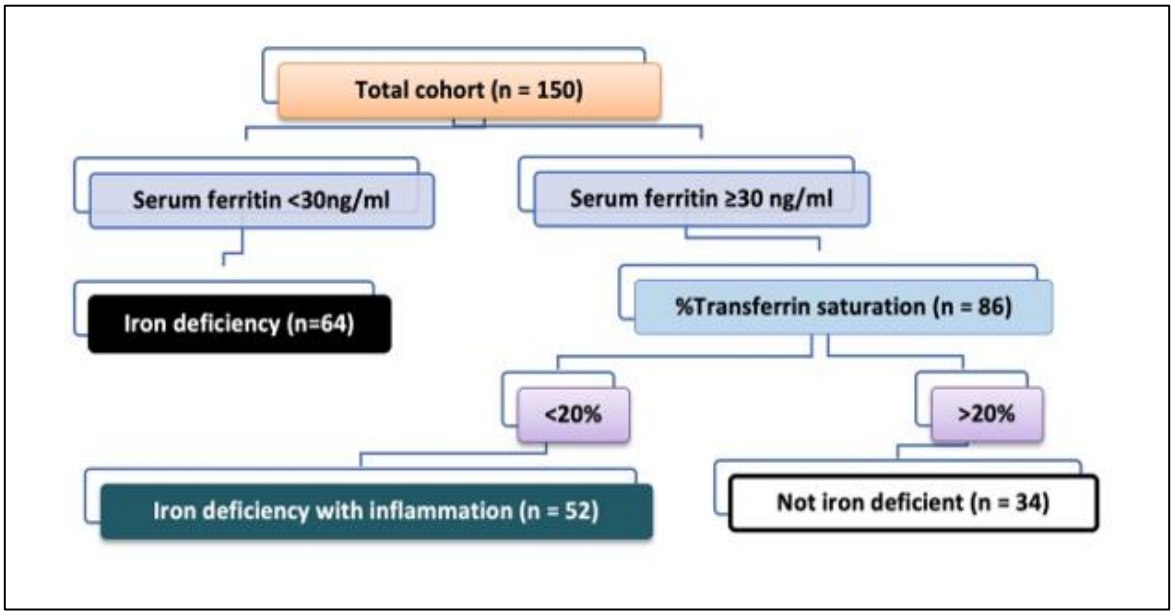

Figure 1: Distribution of patients as per iron profile parameters.

Mean haemoglobin was 11.6±1.5 gm% (range 7.0 to 16.0). Ninety-nine patients (66%) had Hb<12 gm%, the majority being females (n=79). Of the total 110 female patients, 71.8% were anaemic by the WHO cut-off. Mean haemoglobin among women was 11.33±1.25 (range 7.0 to 14.8) and among men was 12.39±1.87 (range 8.6 to 16.0) gm%.

Of the 150 patients, only 31 (20.7%) had normal iron parameters, 64 (42.7%) had iron deficiency alone (i.e., reduced ferritin), 52 (34.7%) had iron deficiency with features of coexisting inflammation (i.e. normal range ferritin but with reduced transferrin saturation), one had inflammation alone (raised ferritin with reduced TIBC) and two had iron excess (high ferritin, serum iron and percentage transferrin saturation). Patient break-up based on the iron profile is shown in Figure 1.

Hence; overall, 116 (77.3%) patients had iron deficiency, either alone or in conjunction with anaemia of inflammation. Of these 116 iron deficient patients, 93 (80.2%) were women. The frequency of iron deficiency among female patients was 84.5% (93/110) and among male patients was 57.5% (23/40). Of the patients with iron deficiency, 99 (85.3%) had anaemia (i.e. Hb<12 gm%), the remainder had latent iron deficiency without anaemia (i.e in the form of decreased transferrin saturation).

On comparison of various clinical and laboratory parameters in patients with and without iron deficiency (Table 1), the iron deficient subset had significantly higher numbers of female patients and significantly lower haemoglobin, serum iron, percentage transferrin saturation and ferritin as compared to patients who were not iron deficient. Although normal serum ferritin levels also associated with latent iron deficiency in the form of decreased transferrin saturation levels due to chronic inflammation like chronic cholecystitis. The iron deficient patients also had significantly lower total bilirubin as well as AST levels, since the mean values of these parameters in both groups were within their respective normal ranges, they were not analysed further.

DISCUSSION

Both iron deficiency and gallstone disease are more prevalent in females with the latter showing male-to-female ratio of 1:4.[3] In our cohort, 73.3% were females with a majority in the 4th or 5th decades of life. Gallstones

commonly occur in fat, fertile, flatulent females around forty due to the effect of female hormones (oestrogen and progesterone) on the biliary tract. However, GSD is also seen in males, thin and young females suggesting that there must be additional mechanisms favouring gallstone formation.

We observed anaemia in 66% of gallstone patients; of which 71.8% were females. Iron deficiency was present in a 77.3% of our cases; of which 84.5% were females. Although initially astonishing, it must be viewed in light of the fact that iron deficiency is the commonest cause of anaemia in India (53%), and the patients coming to a government subsidized hospital possibly do not represent economically very well-off sections of Indian society.[14,17]

Even so, our observation that iron deficiency with anaemia was present in majority of GSD patients suggests that assessment of iron status must be performed routinely in these patients. The complete iron profile is superior to serum ferritin alone in detecting patients in whom the latter is not reduced due to co-existing inflammation. Haemoglobin concentration alone only indicates the severity of anaemia; it cannot be used to diagnose iron deficiency.

We did not find significant differences in serum cholesterol levels in our patients with or without iron deficiency. One postulated mechanism for gallstone formation in iron deficiency include alterations in the hepatic enzyme metabolism, leading to supersaturation of bile with cholesterol irrespective of serum cholesterol levels. In a prospective analysis of 100 patients of GSD; Misra et al found that in patients with iron and calcium deficiency, bile cholesterol levels were high along with a low serum-to-bile cholesterol ratio in women. They concluded that increased biliary cholesterol along with decreased serum iron and serum calcium results in supersaturation of bile with cholesterol, alteration in gallbladder motility and increased crystallisation in the gallbladder.[7] Johnston et al also showed that iron deficiency can alter hepatic cholesterol enzyme metabolism and increases gall bladder crystal formation leading to gallbladder stone formation in animal's who were given the iron-deficient diet.[6]

At a more immediate and clinical level, the presence of anaemia is an independent predictor of outcome for patients undergoing laparoscopic cholecystectomy; and is known to correlate with several compilations including increased transfusion requirement, higher rates of wound and urinary tract infections and venous thromboembolism, and increased operating time as well as hospital stay.[18] Thus, pre-operative assessment of iron status appears to be a judicious choice in all patients planned for cholecystectomy.

This study was conducted in a tertiary care centre on a small sample size in patients who came for surgery for symptomatic GSD. Therefore, further study including large population should be done which can reflect the status of iron deficiency in general population.

CONCLUSION

At a public health level, our results may suggest that addressing the problem of endemic iron deficiency may also reduce the possible development of gallstone disease in the community. Accordingly, pre-operative assessment of iron status appears to be a cautious choice in all patients planned for cholecystectomy as indirectly it will address the problem of anaemia in the population.

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