

Association between Gallstone Disease and Metabolic Syndrome

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ABSTRACT

Introduction: Gallbladder stone disease is common and a leading cause of inpatient admissions for gastro-intestinal problem in modern world. Metabolic syndrome is slowly assuming shape of a global epidemic. There is currently only minimal data regarding the relationship between cholelithiasis and Metabolic syndrome in Indians. This study aims to assess if there is an association between the presence of gallstones and Metabolic Syndrome.

Material and methods: At a tertiary care centre in Mumbai, 100 patients with cholelithiasis were compared with 100 controls to assess the profile with respect to Metabolic Syndrome.

Result: 36% cases had Metabolic syndrome as against 16% controls. Of the components of Metabolic syndrome, obesity was the only one found to have a positive association.

Conclusion: In our study, gallstone disease showed a statistically significant association with metabolic syndrome, however this association was positive only in female patients.

Keywords: Gallstones, Metabolic Syndrome, Cholelithiasis

4. Serum Hypertriglyceridemia
5. Decreased Serum High Density Lipoprotein (HDL) Levels

Over the past two decades, a striking increase in the number of people with the metabolic syndrome worldwide has taken place. With the elevated risk not only of diabetes but also of cardiovascular disease from the metabolic syndrome,¹⁰ there is urgent need for strategies to prevent the emerging global epidemic.¹¹

Gallbladder takes precedence over all other sites in the biliary system in formation of stone, owing to its physiological function of concentration of bile.¹² Though bile super saturation is necessary for gallstones to form, not all people with supersaturated bile form gallstones.¹³ It is widely believed that diabetes mellitus and cholelithiasis are closely linked diseases, therefore an altered glucose metabolism may increase the risk of developing cholelithiasis in certain subjects.¹⁴ In recent years, a great deal of effort has been devoted to defining the pathophysiological basis of gallstone formation. The role of serum lipids in the etiology of cholelithiasis is very important and in cholesterol gall stones serum lipids are altered which is suggestive of metabolic syndrome. Research suggests that metabolic syndrome may be a risk factor for gallstones.¹⁵

INTRODUCTION

Gallstones (GS) occur commonly in the western world¹⁻⁶, however in recent years, increased incidence in India is noticed, attributed partly to widespread use of ultrasonography in the last two decades and partly to changing socioeconomic structure and changes in various other epidemiological factors including diet. Gallstone disease contributes substantially to health care costs and its complications are sometimes life threatening. If promptly diagnosed and treated appropriately, a great deal of highly morbid and potentially lethal complications can be prevented. It is of our interest to identify these patients early in the course of natural history of the disease to prevent greatly morbid complications. Most patients are unaware and remain asymptomatic for life. Only a minority of patients develop symptoms, necessitating treatment.

Towards the end of the 20 century, the clustering of risk factors for cardiovascular disease was first described, most notably the concurrent presence of obesity, type 2 diabetes, hyperlipidemia, and hypertension.^{7,8} The term "Metabolic syndrome (MS)" has now taken hold in the medical literature. The most useful clinical definition is given by National Cholesterol Education Programme (NCEP) Adult Treatment Plan (ATP III), 2001⁹ and states metabolic syndrome is present if any 3 out of the following 5 are present:

1. Abdominal Obesity
2. Diabetes
3. Hypertension

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The association between Gallstone disease and Metabolic syndrome has been a focus of some recent studies.¹⁶⁻¹⁸ but not yet fully elucidated. Moreover, there is currently only minimal data regarding the relationship between cholelithiasis and Metabolic syndrome in Indians. This study aims to assess if there is an association between the presence of gallstones and the presence of Metabolic Syndrome. Metabolic Syndrome is known to be strongly associated with lifestyle, and so, the prevalence of gallstones can be reduced through lifestyle interventions.

Study aimed to check for an association between development of Gallstone disease and presence of Metabolic syndrome and to compare Patients having cholelithiasis to general population with respect to

Abdominal Obesity, Diabetes, Hypertension, Serum Triglycerides, Serum HDL and Gender-wise comparison between cases and controls.

MATERIAL AND METHODS

The study was carried out on patients with cholelithiasis admitted at a tertiary care centre in Mumbai. This is a prospective study conducted over a period of 2 years in the department of General surgery at a tertiary centre. 100 patients and 100 controls in the age group of 25-65 years were included in the study. Among the cases, 72 were females and 28 were males and among the controls, 70 were females and 30 were males. Informed written consent of the patient was obtained before enrolment in the study. The study was commenced after due approval from the Ethics Committee. Patients with acute cholecystitis, renal failure, nephrotic syndrome, malignancies, liver diseases and pregnant women were excluded even if they had cholelithiasis. 100 patients with with no evidence of cholelithiasis on ultrasonography in the age group of 25-65 years were selected as controls.

After the ultrasonography confirmed presence of gallstones, a detailed history was elicited with particular attention to hepato-biliary system and to find out the risk factors. Besides this, history relevant to the components of metabolic syndrome was also obtained, specifically about presence of Diabetes and hypertension. Medication related history was documented.

Physical examination

Waist circumference was measured at the midpoint between the lower border of the rib cage and the iliac crest.

Three blood pressure readings were obtained at 1-min intervals, and the second and third systolic and diastolic pressure readings were averaged and used in the analyses.

Blood samples were drawn from the antecubital vein from participants after they had fasted for more than 12 hours. Serum triglyceride levels, serum HDL levels and fasting serum glucose levels were measured.

Diagnosis of metabolic syndrome⁹

Participants were defined as having the metabolic syndrome if they fulfilled three or more of the following:

1. Waist circumference greater than 102 cm for men, greater than 88 cm for women;
2. Diagnosed with hypertension or receiving antihypertensive medication, or mean of two blood pressure measurements exceeding 130/85 mmHg
3. Diagnosed with diabetes mellitus or receiving antidiabetic treatment, or a fasting blood glucose level of greater than 110mg/dL
4. Serum HDL level lower than 40 mg/dL for men, lower than 50mg/dL for women
5. Serum Triglyceride levels above 150mg/dL.

Statistical analysis was done using Chi-Square test

RESULTS

With respect to age and gender, both the groups were comparable and difference was not statistically significant. Among the cases, 72 were females and 70 controls were females. Comparison of prevalence of metabolic syndrome between the two groups was done using Chi-Square test (Table 1). A further analysis of these two groups was done based on the gender (Table 2). In addition to this, prevalence of components of metabolic syndrome was compared between the cases and controls. The comparison for Waist circumference, Diabetes, Hypertension and Serum Triglycerides is shown in table 3. Similarly, gender wise comparison of these components of metabolic syndrome was also done (Table 4). As the qualifying criteria for serum HDL is different for males and females, it is tabulated separately in table 5.

As seen in table 1, of the 100 patients with cholelithiasis, 36 patients were found to have Metabolic syndrome as against the control group wherein only 16 had Metabolic syndrome. With a p value of 0.023, this difference was statistically significant.

The mean age of the cases was 56.18 years which was comparable to 54.42 years in the control group. 40% of cases fell in the 60-70 years bracket as against 36% among the controls.

Criteria fulfilled ≥3/5	Controls (N= 100) No.	Cases (N= 100) No.
Yes	16	36
No	84	64
P value	0.023	

Table-1: Comparison of prevalence of Metabolic syndrome levels between the two groups

Criteria fulfilled ≥3/5	Controls (N= 100)		Cases (N= 100)	
	Male (N=30) No.	Female (N=70) No.	Male (N=28) No.	Female (N=72) No.
Yes	06	10	10	26
No	24	60	18	46
p values (Control Vs Cases)	0.59	0.03		

Table-2: Comparison of prevalence of Metabolic syndrome between the two groups as per the gender

Sr. no.	Component	Criteria fulfilled	Control (N=100) No.	Cases (N=100) No.
1	Waist circumference: Criteria fulfilled >102cm for men > 88cm for women	Yes	38	78
		No	62	22
2	Criteria fulfilled Known diabetic/ On medications/ FBS >110mg/dl	Yes	42	44
		No	58	56
3	Criteria fulfilled Known Hypertensive/ On medications/ BP >130/85mm Hg	Yes	40	44
		No	60	56
4	Criteria fulfilled Serum Triglycerides > 150mg/dl	Yes	16	24
		No	84	76

Table-3: Comparison between the two groups for first four components of Metabolic syndrome

Component of Metabolic syndrome	Criteria	Control (N= 100)		Cases (N= 100)	
		Male (N=30) No.	Female (N=70) No.	Male (N=28) No.	Female (N=72) No.
Waist circumference	Yes	6	32	14	64
	No	24	38	14	08
	P value	0.089	0.001		
Diabetes	Yes	16	26	10	34
	No	14	44	18	38
	P value	0.3	0.39		
Hypertension	Yes	10	30	14	30
	No	20	40	14	42
	P value	0.36	0.92		
Triglycerides	Yes	04	12	08	16
	No	26	58	20	56
	P value	0.31	0.77		

Table-4: Comparison between the two groups for first four components of Metabolic syndrome as per the gender

Control		Cases		P Values Control Vs Cases
Criteria	No.	Criteria	No.	
Male (N=30) < 40 mg/dl	04	Male (N=28) < 40 mg/dl	06	0.93
Female(N=70 < 50mg/dl	04	Female(N=72) < 50 mg/dl	08	0.69

Table-5: Comparison of serum HDL levels between the two groups as per the gender

The mean age for cases positive for metabolic syndrome was 59.05 years which was significantly higher as compared to mean age for cases negative for Metabolic syndrome which was 54.96 years. Also, out of the 20 cases in the 60-70 years age group, 10 (50%) were found to have Metabolic Syndrome, thereby suggesting prevalence of Metabolic syndrome increases with age.

Of the 72 female cases, 26 i.e. 36.1% fulfilled the criteria for the metabolic syndrome and 10 of the 28 males, i.e. 35.7% were positive for Metabolic syndrome. When compared with the other group, 14.3% women fulfilled the criteria for Metabolic syndrome and 20% men were positive for Metabolic Syndrome. On testing this data statistically using Chi- Square test (p value 0.03), it was concluded that female patients with cholelithiasis had an increased prevalence of Metabolic Syndrome. The test was not statistically significant for males in the study as seen in table 2.

The other 4 components viz. Diabetes, Hypertension, Serum Hypertriglyceridemia and decreased HDL levels did not show any statistically significant difference between the two populations as seen in table 3.

Out of the five components of Metabolic Syndrome, only abdominal obesity is found to be significantly associated, but when considered as a single unit, Metabolic syndrome was found to be a risk factor for gallstone disease as compared to general population.

DISCUSSION

Gallbladder stone disease is common and a leading cause of inpatient admissions for gastro-intestinal problems in modern world. Metabolic syndrome is slowly assuming shape of a global epidemic. Gallstone formation being multifactorial, certain risk factors for gallstones are immutable: female gender, increasing age and ethnicity/family (genetic traits). Other factors

like obesity, dyslipidemia, diabetes and other components of metabolic syndrome can be modified by timely interventions. Amongst the 5 components of Metabolic Syndrome, only the waist circumference criteria was found to be statistically significant using the Chi-Square test (Table 3), and on analysing further, the difference was found significant only in the female population with a p value of 0.001 (table 4). This observation was in accordance to conclusion by Méndez-Sánchez N et al¹⁶ who in their study 'Metabolic syndrome and gallstone' found obesity is an important risk factor for gallstone disease, more so for women than for men.

The prevalence of Metabolic syndrome amongst controls in our study was comparable to 19.52%, the prevalence found in a study conducted in Mumbai by Sawant et al¹⁹

Of all the components of metabolic syndrome, the presence of obesity is the most important factor associated with the risk of having gallstones. Obese women are more likely to develop gallstones than are obese men.²⁰ The bile in obese persons have a high ratio of cholesterol to solubilizing lipids (bile acids and phospholipid). This high ratio predisposes to crystallization of cholesterol and gallstone formation. The primary reason for lithogenic bile in obese persons is an increase in total body synthesis of cholesterol. A likely prime mechanism is overloading of tissues with fatty acids, which provide precursors for cholesterol synthesis. Other adipose tissue – derived substances, which are produced in excess in obesity, may further contribute to overproduction of cholesterol. As a result of this overproduction, cholesterol secretion into bile increases. In many obese individuals, the amounts of cholesterol entering the bile exceed the solubility capacity of the bile acids and phospholipids. Both obese women and men synthesize increased amounts of cholesterol and secrete more cholesterol into bile than do nonobese persons.²¹ Obese men generally secrete more bile acids and phospholipids into bile, hence their bile is less lithogenic.

People with diabetes are at higher risk for gallstones and have a higher than average risk for acalculous gallbladder disease. Gallbladder disease may progress more rapidly in patients with diabetes, who tend to have worse infections. In diabetic subjects, the biliary saturation index is increased. Moreover, in subjects with gallstones high levels of insulin have been described, such as occur in patients with insulin independent diabetes. The hepatic insulin resistance provides a crucial link between the metabolic syndrome and increased cholesterol gallstone susceptibility. High insulin level elevates the risk of nucleation (during the formation of a gallstone). Increase in insulin level may increase the activity of methyglutaryl-coenzyme A reductase, the rate limiting step in the cholesterol synthesis and increasing hepatic uptake of LDL cholesterol.²² Insulin resistance is also associated with lower serum levels of HDL cholesterol, a known risk factor for prevalent gallstones.²³

Scragg et al.²⁴ were among the first to evaluate the relationship between plasma insulin levels and gallstone risk. In a 1984 hospital-based case control analysis, they determined the fasting insulin means to be higher in gallstone cases of both

sexes, regardless of age and triglyceride levels. Heaton et al.²⁵ determined that nondiabetic British men with the highest levels of insulin had twice the risk of gallstones as those with low levels, but the relationship proved insignificant after the subjects were matched for waist-to-hip ratio. Chang et al.²⁶ from Korea presented the conclusion that even in an Asian, non-diabetic male population, insulin resistance appears to be an independent predictor of gallstones, regardless of obesity. Therefore, gallstones appear to be a marker for insulin resistance, even in non-diabetic, non-obese men. Chung-Jyi Tsai et al.²⁷ in their study 'Prospective study of abdominal adiposity and gallstone disease in US men' found of a significant association between abdominal adiposity and the incidence of symptomatic gallstone disease. Our study concluded the same. N Ata et al.¹⁷ conducted a study on 217 patients in Turkey and concluded that Metabolic Syndrome was associated with complicated gallstone disease. Devaki R N²⁸ concluded that triglyceride levels are elevated in both males and females with gallstones. Their study also found that decreased HDL levels in females with cholelithiasis compared to controls. However, our findings did not correlate with this association reported. They also concluded oral glucose tolerance, a surrogate marker for Diabetes, showed no significant difference between cases and controls. This observation is in accordance with the observation in our study that prevalence of Diabetes is not significantly increased in cholelithiasis. Chen LY et al.¹⁸ found a higher prevalence of cholelithiasis in males. They reported waist circumference as a significant component in cholelithiasis, which supports our observation. A study by Nagraj et al.²⁹ from Karnataka 'Risk Factors and the biochemical evaluation of Biliary Calculi in Rural Kolar, Karnataka' India found 64% of patients with cholelithiasis to have altered lipid profile which is higher than what we found.

CONCLUSION

In conclusion, as with cardiovascular disease and diabetes mellitus, gallstone disease appears to be strongly associated with metabolic syndrome. These results are also consistent with the hypothesis that insulin resistance plays an important role in the pathogenesis and that gallstone disease may be a part of metabolic syndrome.

Gallstone disease is a common condition worldwide. Because of its high prevalence and elevated health costs, it is an important condition for which further research is needed.

In our study, we found

- Cholelithiasis is more prevalent in females (72%) as against (28%) in males.
- The incidence of Metabolic syndrome in control group was 16% and that in cases was 36%.
- Abdominal obesity was significantly prevalent among patients with cholelithiasis.
- Difference in prevalence of diabetes between cases and controls was not significant.
- Difference in prevalence of hypertension between cases and controls was not significant.
- Differences in serum triglyceride levels between cases

and controls were not significant.

- Differences in serum HDL levels between cases and controls were not significant.
- Overall Gallstone disease is associated with Metabolic Syndrome.
- This difference is statistically significant in females.

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