



AN EPIDEMIOLOGICAL STUDY TO EVALUATE THE ASSOCIATION OF RISK FACTORS FOR GALLSTONE FORMATION

Surajit Lahiri*	Professor, Department of Surgery, ESI-PGIMSR & ESIC Medical College, Joka. *Corresponding Author
Subham Roy Choudhury	Intern ESI-PGIMSR & ESIC Medical College, Joka.
Subhajit Shyam	Assistant Professor, Department of Community Medicine, ESI-PGIMSR & ESIC Medical College, Joka.

ABSTRACT Gallstone disease and its complications are a major public health issue, equally affecting both the developed and the developing countries across the globe. The unmodifiable risk factors are universally same. The modifiable risk factors however, can vary from place to place depending upon social customs, lifestyle, food habits and preferences. This justifies the need for regional studies to look for association of risk factors that can precipitate gallstone disease so that preventive programmes can be undertaken to reduce its incidence.

The project was an institution-based observational cross-sectional study on 96 subjects to look for the risk factors associated with gallstone formation. The patients were chosen using simple random sampling technique as per the pre-decided inclusion and exclusion criteria. The data was collected through a pre-designed and pre-tested semi-structured questionnaire. For all the tests for the study, a p-value of < 0.05 was considered significant. All the statistical significance of the project was evaluated at a confidence interval of 95%. Based on the objective of the study, further descriptive and inferential statistics was drawn.

Our study showed a strong association between gallstone disease and the time elapsed between waking up in the morning and taking breakfast, with 88 subjects (91.66%) out of the possible 96 taking their breakfast over 2 hours (120 minutes) after waking up. Thus reduction in overnight fasting by advising people to take their breakfast within 2 hours (120 minutes) of waking up, can bring down the incidence of gallstone disease significantly. Thus we propose awareness programmes to highlight this issue amongst the population at risk.

KEYWORDS : Gallstones; Risk factors; Overnight fasting; Diet therapy; Food habit

INTRODUCTION

Gall stone disease is one of the most common surgical ailment throughout the world, requiring both OPD as well as in-house treatment. Every year in USA alone, over 7,00,000 cholecystectomies are performed at an annual cost of ~\$ 6.5 billion.^[1] Similarly in United Kingdom, the annual incidence of gall stones is around 5.5 million needing over 50,000 cholecystectomies a year. Thus gall stones are the most common abdominal reason for admission to hospital in developed countries and account for an important part of healthcare expenditure.^[2] Though the exact figure of the disease burden in India is yet to be ascertained, gall stone disease is undoubtedly a major cause of inpatient admission to surgical wards needing operation.^[3] Gall stone disease and its complications are a major public health issue thus contributing substantially to health care cost. Hence we see that gallstone disease holds a substantial share in the total disease burden of both developed and developing nations.^[1,2,3,4]

The four F's namely fat, fertile, female of forty are the common risk factors for cholelithiasis. Newer risk factors like changing food habits with irregular timings, recurrent oral and gastrointestinal infections, worm infestations, rapid voluntary weight loss, recurrent parenteral nutrition, decreased physical activity, chronic haemolysis and smoking are gaining importance in the etiopathogenesis.^[5,6,7,8,9]

The etiopathogenesis of gallstone is multifactorial and can be broadly classified into modifiable and unmodifiable causes that leads to lithogenesis.^[10] Different studies conducted in different parts of the world shows that although the unmodifiable risk factors for gallstone formation are more or less the same across the world, the modifiable risk factors vary from place to place based on culture, food habits and lifestyle. This justifies the need for regional study to look for the region-specific modifiable risk factors of lithogenesis so that the clinician can not only treat the patient more ably but also can formulate preventative measures to curb the disease onset.

Increasing association between gallstone and gallbladder malignancy^[11] further necessitates the urge to explore deeper into the associated risk factors that lead to gallstone formation. Although most of the gallstones are asymptomatic, complicated gallstone disease is an important cause of morbidity and mortality across the globe. The high cost of medical care associated with it make prevention of gallstone formation highly desirable.^[12]

The above observations justify the need to relook into the probable risk factors that precipitate gallstone disease in this part of the world. Apart from the well-known unmodifiable risk factors, we wanted to find out if there are any less studied modifiable causes so that we can propose preventive programs that can in the long run help in reducing the incidence of gallstone disease and thus drastically lowering the healthcare cost incurred in treating gallstone disease and its complications.

MATERIALS AND METHODS

The project is an institution-based observational cross-sectional study to look for the risk factors associated with gallstone formation among patients who presented with ultrasound proved gallbladder stone at the OPD or were admitted in IPD under the Department of Surgery at ESI-PGIMSR & ESIC Medical College, Joka, Kolkata during a study period of two months.

The ethical approval was taken from the Institutional Ethical Committee and the identity of the patients were kept strictly confidential. Informed consent was also taken from each selected patient.

The patients were chosen using simple random sampling technique and the inclusion criteria were patients of either sex, above 13 years of age, whose vitals are stable, having gallstone disease confirmed by trans-abdominal ultrasound. Whereas the exclusion criteria were patients below 13 years of age, who are not clinically stable and those who were unwilling to participate in the study.

Based on a study by Sayeed Unisa et al. to estimate the prevalence of gallbladder disease in rural Gangetic basin of North India^[13], the prevalence of gallstones was taken as 6.20%. The sample size for the study was then calculated using the formula given by Lwanga SK and Lemeshow S in their study on sample size determination in health studies.^[14] The required sample size came as 89. A non-response of 10% is expected for any study and thus the sample size was fixed at 98 for the present study. Out of the 98 selected patients, 2 patients turned noncompliant and were excluded from the study. Thus the final study size was 96 patients.

The data was collected through a pre-designed and pre-tested semi-structured questionnaire. The data of the study was analyzed using

appropriate statistical tests by using R (version 3.5.0). For proportions, Pearson's Chi square test was applied to find out significant association between independent and dependent variables. For all the tests for the study, a p-value of <0.05 was considered significant. All the statistical significance of the project was evaluated at a confidence interval of 95%. Based on the objective of the study, further descriptive and inferential statistics was drawn.

RESULTS AND ANALYSIS

A total of 96 patients were examined and their data were analyzed in this study. Out of 96 patients, there were 23 males (24%) and 73 females (76%). This matches with almost all literatures reviewed as all of them identified female sex as an unmodifiable risk factor for gallstone disease.

The minimum age of our study group was found to be 14 years while the maximum age was 76 years. The study population was divided into 3 (three) equal classes each having an equal class interval of 20 years. In the age group 14 – 34 years there were 20 patients (20.8%). In the age group 35 – 55 years there were 63 patients (65.6%). Finally, in the age group 56 – 76 years there were 13 patients (13.5%). The mean age of the study population was 43.4 years. This finding again matches with the fact that gallstone disease is more common in females during their child-bearing age with maximum prevalence when they are in their forties.

All the participating patients were asked whether they took their daily major meals at more or less the same time or not. Depending on their answer, they were divided into 3 (three) categories. Firstly, those who took their meals regularly at almost the same time. Secondly, those who were sometimes irregular and lastly those who were mostly irregular in taking their major meals. The regularity of meals is shown in Figure 1.

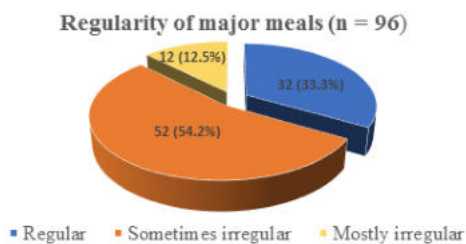


Fig. 1: Pie chart showing the distribution of gallstone patients according to the regularity of intake of daily major meals.

It is clearly seen in Figure 1 that only 32 patients (33.3%) took their daily major meals regularly at more or less the same time, thus leaving 2/3rd of the patients in the study group taking meals irregularly. This finding matches with most of the articles reviewed as it is repeatedly asserted that irregular meals lead to increased incidence of cholesterol stones. The patients were also asked regarding their food preference. The food preference is depicted in Figure 2.

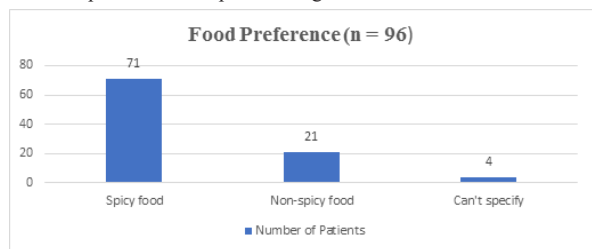


Fig. 2: Bar diagram showing the frequency distribution of gallstone patients according to their preference for spicy or non-spicy food.

Figure 2 shows that the food preference of the patients in the study group. 71 (74%) patients preferred spicy food. This finding corroborates with the finding of Chandran AP et al. They too observed that spicy food intake increased risk of gallstone disease in South Indian population.^[15]

Review of literature showed that stasis of bile in gallbladder often lead to supersaturation of bile and subsequent cholesterol deposition and stone formation. Achalovschi M in his review article on cholesterol gallstones observed that gallbladder stasis is an important risk factor

for gallstone formation. He also proposed that gallbladder stasis can be prevented by a regular eating pattern, avoiding long periods between meals, by a bedtime snack to reduce overnight fasting or by small fatty meal during rapid weight loss.^[10] Keeping this in mind, in our study we specifically asked the subjects regarding the time elapsed between waking up and taking breakfast to get an idea about the length of their overnight fasting. Based on the time elapsed between waking up and taking breakfast, the 96 subjects in the study group were further subdivided into five sub-groups. The timing of breakfast is displayed in Figure 3.

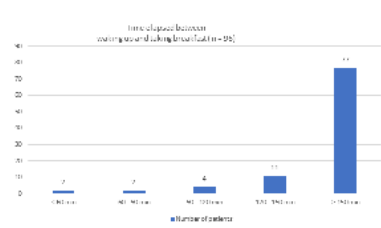


Fig. 3: Bar diagram showing frequency distribution of gallstone patients according to the time elapsed between their waking up in the morning and taking their first meal of the day

Table 1. Association of gender of subjects with the time elapsed between waking up in the morning and taking their breakfast

Time	Gender		Total (%)	Fishers exact test statistics value	95% Confidence Interval (CI)	Mean	Standard Error
	Male (%)	Female (%)					
Less than 120 min	6 (26.08)	2 (2.74)	8 (8.33)	0.0021	(158.4, 175.6)	167	4.3
More than 120 min	17 (73.92)	71 (97.2)	88 (91.66)				
Total	23	73	96				

On careful study of Figure 3 we see that only 8 subjects out of the total of 96 used to take their breakfast within 2 hours (120 minute) of waking up while 88 subjects (91.66%) used to take their breakfast after 2 hours from waking up. This is a very interesting fact. Probably, increased overnight fasting lead to biliary stasis resulting in cholesterol deposition that ultimately ended up with gallstone formation.

Table 1 shows that Fishers exact test statistics value is 0.0021. This is statistically significant as the p-value is < 0.05. Moreover, the 95% confidence interval is (158.4, 175.6). Confidence interval (CI) enable researchers to estimate population values, from trends shown in study group, without having data from all members of the population. In most cases, CIs are based on 95% confidence level.^[16] It indicates a 95% probability that the true mean in the source population will be within the calculated range.^[17] This means that if our study is extended from the study group to the general population in the society, it is 95% certain that the true mean will lie within the interval of 158.4 to 175.6 minutes with a mean of 167 minutes and a standard error of 4.3.

From the above findings we can infer that if the breakfast is taken within 2 hours of waking up in the morning, then there could be a drastic reduction in the incidence of gallstones. This is the most important modifiable risk factor that our study has revealed. Hence, based on the above finding, we can propose preventive measures to bring down the incidence of gallstone formation significantly. This in turn will drastically reduce the healthcare cost incurred in treating gallstone disease and its complications.

Another very important question asked was about the fertility status of the female subjects in the study group. The fertility status of the 73 female subjects in our study group is depicted in Figure 4.

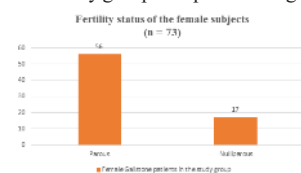


Fig. 4: Bar diagram showing the frequency distribution of female subjects according to their fertility status

Figure 4 clearly shows that out of the possible 73 female subjects in the study group, 56 (76.7%) were parous while the remaining were nulliparous. This finding, too, matches with most of the literatures, which clearly shows that parity increases the risk of gallstone formation due to increased concentration of cholesterol in bile because of increased level of oestrogen in blood.^[18,19]

Next we recorded the history of oral contraceptive pill (OCP) intake in our female subjects. There was almost equal distribution with 34 subjects (46.6%) out of the possible 73 having a history of OCP intake while 39 subjects (53.4%) having no history of OCP intake. Though many literatures identify OCP intake as an important risk factor for gallstone formation, our study does not show any such clear association. This finding can be explained by the fact that newer and newer brands of OCP are coming in the market with very low dosage of oestrogen, with less chance of interaction with cholesterol synthesis in the body.

Obesity is identified as an important risk factor for prevalence of gallstones in many literatures reviewed.^[12,20] Figure 5 shows the obesity status of the subjects based on their BMI.

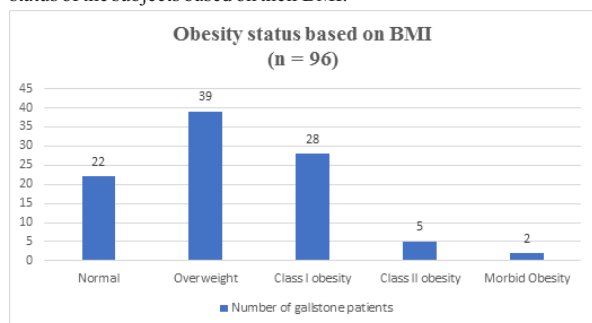


Fig. 5: Bar diagram showing the frequency distribution of study subjects according to their obesity status based on body mass index (BMI)

Figure 5 clearly indicates that only 22 subjects (22.9%), in our study, had normal weight based on their BMI. The remaining 74 subjects (77.1%) were either overweight or had varying degrees of obesity. This absolutely corroborates with the literatures which clearly states that increased BMI alters cholesterol synthesis making the bile supersaturated with higher risk of cholesterol stone formation.

Our study did not find any association between gallstones and history of weight loss as only a few subjects gave history of weight loss in the recent past and that too none of them had rapid weight loss. Moreover, our study also did not find any co-relation between gallstone formation and history of TPN administration or history of pancreatitis or patients suffering from chronic haemolytic anaemia or diabetes. This can again be justified by the fact that we excluded all ill patients from our study resulting in elimination of many patients with serious co-morbidities. Perhaps a more extensive study with inclusion of all gallstone patients irrespective of their physical health is required before we can make any conclusion regarding association of the above co-morbidities with gallstones.

CONCLUSION

Gallstone disease is a very common ailment in the present day world affecting both the developed and the developing countries alike. It is probably the most common cause of indoor admission in surgical wards across the world. Thus every country is incurring a huge expenditure on healthcare cost for treating gallstone diseases and its complications. Studies have been carried out in various corners of the world to identify the risk factors associated with gallstone disease so that effective preventive programmes can be chalked out and implemented to reduce cost incurred on gallstone disease.

Our study is also an endeavor to find out the probable risk factors associated with gallstone disease. We found strong association between gallstone disease and female sex, increasing age, parity, obesity, irregular meal intake, preference for spicy food and increased interval between waking up in the morning and taking breakfast thus increasing the duration of overnight fasting.

Our study was inconclusive in establishing any strong association between gallstone disease and history of TPN administration,

haemolytic anaemia, OCP intake, weight loss, pancreatitis and diabetes.

The most significant finding that our study has revealed is that there is a strong association between gallstone disease and the time elapsed between waking up in the morning and taking breakfast with 88 subjects (91.66%) out of the possible 96 taking their breakfast over 2 hours (120 minutes) after waking up. Delayed breakfast increases overnight fasting and thus reduces gallbladder motility and promotes biliary stasis resulting in supersaturation of bile with increased cholesterol deposition and subsequent cholesterol stone formation. This is a modifiable risk factor that can be easily addressed by increased awareness regarding gallstone disease and the probable complications that it can precipitate.

Keeping the above finding in mind we would like to propose that healthcare strategy makers should seriously consider incorporating awareness programmes that highlight the fact that by taking breakfast within 2 hours (120 minutes) of waking up, we can avoid gallstone disease and its complications to a great extent.

To implement the above awareness programmes, we need not require starting fresh campaigns at high costs but instead can include such awareness programmes (in the form of posters, videos, awareness camps, door-to-door visits, counselling etc.) in our already running welfare programmes of the Government of India (like National Health and Family Welfare Programmes, National Family Planning Programmes, National Nutrition Programmes, Programmes implemented through Anganwadi workers who do home-to-home visits, National Programmes on prevention of Diabetes, Obesity etc.).

The above proposal will not only require less funding but in the long run will help a lot in bringing down the incidence of gallstone disease in our country, thus drastically reducing the healthcare cost incurred upon treating gallstone diseases and its complications that drain a huge proportion of the overall healthcare budget. Money saved is money earned. The money thus earned by saving on healthcare budget can be utilized on providing education to all and on infrastructure building to take the country several steps ahead on its journey towards being a developed country in the near future.

REFERENCES

- Shaffer EA. Epidemiology of gallbladder stone disease. *Best Pract Res Clin Gastroenterol*. 2006; 20(6):981-996
- Beckingham JJ. Gallstone disease. *BMJ*. 2001; 322:91
- Krishnasamy Narayanasamy DM, Kiranumar B, Karthick R. A Cross Sectional Study on Gallstone Disease and its Risk Factors in a Tertiary Care Hospital of South India. *JSM Gastroenterol Hepatol*; 2017; 5(3): 1090
- Gyedu A, Aday-Abogae K, Badu-Peprah A. Prevalence of Cholelithiasis among persons undergoing abdominal ultrasound at the Komfo Anokye Teaching Hospital, Kumasi, Ghana. *Afr Health Sci*. 2015 Mar; 15(1): 246-52
- Sachdeva S, Khan Z, Ansari MA, Khalique N, Anees A. Lifestyle and gallstone disease: scope for primary prevention. *Indian J Community Med*. 2011 Oct; 36(4): 263-7
- Al-Kayatt MK, Al-Youzbaki DB, Al-Zubeer AA. Sociological Risk Factors in Development of Gallstones for Childbearing Age Women. *Iraqi J. Comm. Med. Apr*. 2008; 97-103
- Chen CH, Huang MH, Yang JC, Nien CK, Etheredge GD, Yang CC et al. Prevalence and risk factors for gallstone disease in an adult population of Taiwan: an epidemiological survey. *J Gastroenterol Hepatol*. 2006 Nov; 21(11): 1737-43
- Gomati A, Elafi S, Rafe H. A study on the Risk Factors for Gallbladder diseases in El-Khoms Teaching Hospital, Libya. *IOSR-JDMS* 2014; 13(2): 1-4
- Panpimmas S, Manmee C. Risk factors for gallstone disease in a Thai population. *Journal of Epidemiology/Japan Epidemiological Association*. 2008; 19: 116-21
- Achalovschi M. Cholesterol gallstones: from epidemiology to prevention. *Postgrad Med J*. 2001; 77: 221-229
- Stinton LM, Shaffer EA. Epidemiology of gallbladder disease: cholelithiasis and cancer. *Gut and Liver*. 2012 Apr; 6(2): 172-187
- Shaffer EA. Epidemiology and risk factors for gallstone disease: has the paradigm changed in the 21st century? *Curr Gastroenterol Rep*. 2005 Apr; 7(2): 132-140
- Sayed Unisa, Palepa Jagannath, Vinay Dhir, Chianjeeva Khandelwal, Lalatendu Sarangi, Tarun Kumar Roy. Population based study to estimate prevalence and determine risk factors of gallbladder disease in the rural Gangetic basin. *HBP (Oxford)* 2011 Feb; 13(2): 117-125
- Lwanga SK, Lemeshow S. *World Health Organization. Sample size determination in health sciences: A practical Manual*. Geneva: WHO; 1991
- Chandran AP, Sivarajan R, Srinivasan V, Srinivas M, Jayanthi V. Risk profile for gallstone in southern Indian population: Is there anything new? *Indian J Gastroenterol*. 2014 May; 33(3): 254-257
- Medina LS, Zurakowski D. Measurement variability and confidence intervals in medicine: Why should radiologists care? *Radiology* 2003; 226(2): 297-301
- Patino CM, Ferreira JC. Confidence intervals: a useful statistical tool to eliminate effect sizes in the real world. *J Bras Pneumol*. 2015; 41(6): 565-566
- Novacek G. Gender and gallstone disease. *Wein Med Wochenschr*. 2006 Oct; 156(19-20): 527-533
- Valdivieso V, Covarrubias C, Siegel F, Cruz F. Pregnancy and cholelithiasis: pathogenesis and natural course of gallstones diagnosed in early puerperium. *Hepatology*. 1993 Jan; 17(1): 1-4
- Serge Erlinger. Gallstones in obesity and weight loss. *European Journal of Gastroenterology & Hepatology* 2000; DOI: 10.1097/00042737-200012120-00015