Original Article

Lifestyle and Gallstone Disease: Scope for Primary Prevention

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ABSTRACT

Objective: To study the antecedent risk factors in the causation of gallstone disease in a hospital-based case control study. **Materials and Methods:** Cases (n = 150) from all age groups and both sexes with sonographically proven gallstones were recruited over a duration of 3 months from the surgical wards of a tertiary care teaching hospital. Modes of presentation were also noted among cases. Age- and sex-matched controls (n = 150) were chosen from among ward inmates admitted for other reasons. Univariate and multivariate logistic regression analyses were performed for selected sociodemographic, dietary, and lifestyle-related variables. **Results**: Females had a higher prevalence of gallstone disease than males ($P < 0.01$). Among males, the geriatric age group (>60 years) was relatively more susceptible (28%). Prepubertal age group was least afflicted (3.3%). Univariate analysis revealed multiparity, high fat, refined sugar, and low fiber intakes to be significantly associated with gallstones. Sedentary habits, recent stress, and hypertension were also among the significant lifestyle-related factors. High body mass index and waist hip ratios, again representing unhealthy lifestyles, were the significant anthropometric covariates. However, only three of these, viz., physical inactivity, high saturated fats, and high waist hip ratio emerged as significant predictors on stepwise logistic regression analysis ($P < 0.05$). **Conclusion**: Gallstone disease is frequent among females and elderly males. Significant predictor variables are abdominal adiposity, inadequate physical activity, and high intake of saturated fats; thus representing high risk lifestyles and yet amenable to primary prevention.

Keywords: Gallstone, lifestyle, risk factors

Introduction

Once considered a disease of the Western world and the affluent, cholelithiasis has increasingly become a major cause of abdominal morbidity, leading to hospital admission in the developing world.[1,2] Its occurrence has been found to be at least 7.4% in the adult population of North India.[3] There has also been a remarkable shift in the trend of gall-stone disease from middle aged, fertile, fat females to young asthenic females in their twenties.[4] The increasing magnitude and epidemiologic shifts in the natural history of gallstone disease in India qualify for the need of research in different geographical areas, and also to explore the predictor variables. This is particularly because a majority of risk factors associated with gallstone disease are potentially modifiable. The present study is therefore aimed at quantifying the sociodemographic and lifestyle risk factors for gallstones among age- and sex-matched cases and controls. Besides, an ancillary observation is made regarding the various modes of presentation and complications of gallstone disease among different age groups.

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Materials and Methods

In the present case control study, 150 cases were recruited from cholelithiasis patients (proven by sonography) admitted in the surgical wards of JN Medical College Hospital, Aligarh, from January to April 2010. Their clinical presentations were noted from the records. Age- and sex-matched controls (n = 150) comprising of patients admitted for other morbidities and sonographically negative for

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gallstones were simultaneously recruited from the same wards. Tools for data collection were interview, clinical examination (including anthropometry), and investigations (estimation of hemoglobin, fasting blood sugar, and serum lipids). A pretested questionairre incorporating personal and sociodemographic details was administered to both groups. Modified Prasad's classification was used to categorize the social class.[5] Dietary information was derived from a semiquantitative food frequency questionnaire.[6] Participants were asked to indicate their frequency of consumption, on average, of typical servings of selected foods during the previous month. Nutrient intakes were calculated by multiplying the frequency of consumption of each unit of food from the semiquantitative food frequency questionnaire by the nutrient content of the specified portion according to food composition.[7] Anthropometric indices (weight, height, body mass index (BMI), waist circumference, and waist hip ratio) were calculated for all cases and controls. Comorbidities such as recent stress (operationally defined as a persistent physical or psychological stimulus occurring over the past 6 months and causing impairment of activities of daily living) and current smoking were looked for. Physical activity was gauged as moderate (indulgence per day of 60 min or more in activities such as brisk walking/domestic chores/carrying or moving loads up to 20 kg) and vigorous (running/cycling/swimming/carrying or moving loads above 20kg) [*www.who.int › WHO › Health topics*]. Anything short of moderate physical activity was considered sedentary. Clinical presentations and complication(s) were recorded among different age groups of cases from individual records. Binary logistic regression was used for multivariate analysis.

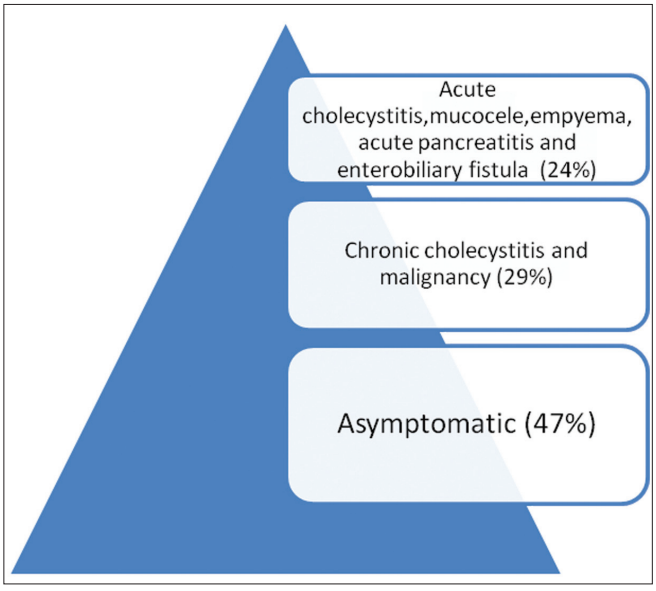

Figure 1: Disease iceberg depicting spectrum of clinical presentation of gallstones among cases.

Results

Table 1 presents the baseline clinical and personal characteristics of age-and sex-matched cases and controls. The mean age of cases and controls was 41.5 ± 15.4 and 38.5 ± 15.1 years, respectively. Mean values of key anthropometric indices and systolic and diastolic blood pressure levels were higher among cases than those in controls. As many as twice known diabetic, hypertensive and hyperlipidemic individuals were present among cases *vis-a-vis* controls.(10% vs. 5%, 19% vs. 10%, and 7% vs. 4% respectively). Table 2 depicts a female preponderance among cases (61%) as compared to males (39%). Among females, the age group most affected was 45–60 years (38.5%) and above 60 years in males (20.8%). Children under 15 years were afflicted the least among both males and females (5.1% and 2.2%, respectively). The difference in the prevalence of gallstones among the two sexes was statistically significant ($P < 0.01$). A large proportion of cases were asymptomatic (47%) or remained largely subclinical as chronic cholecystitis or early malignancy with nonspecific symptoms (29%). Overtly manifest cases with or without complications constituted just the tip of the iceberg (24%) [Figure 1]. Table 3 shows that multiparity was more commonly found in female cases than controls (63 and 50, respectively) and the

Table 1: Baseline characteristics of cases and controls. The values are mean ± 1 SD or percentage.

Variable	Cases	Controls
Number of subjects	150	150
Religion (Hindu:Muslim)	30:70	26:74
Age (years)	41.5 ± 15.4	38.5 ± 15.1
Height (cm)	165 ± 7	152 ± 6
Weight (kg)	56 ± 15	52 ± 12
Body mass index (BMI) (kg/m^2)	24.2 ± 2.1	21.4 ± 2.0
Waist circumference (cm)	78 ± 11	75 ± 10
Waist–hip ratio	0.79 ± 0.11	0.76 ± 0.03
Systolic blood pressure (mmHg)	136 ±11	124 ± 12
Diastolic blood pressure (mmHg)	82 ± 10	76 ± 16
Current smoker (%)	27.0	21.0
Ever smoker (%)	49.0	41.0
Known diabetes (%)	10	5
Known hypertension (%)	19	10
Known hyperlipidemia (%)	7	4

Table 2: Age and sex distribution of cases. Figures in parentheses indicate percentages

Age group (years)	Females	Males	Gender Total
0–15	2 (2.2)	3 (5.1)	5 (3.3)
16–30	4 (4.4)	11 (18.6)	15 (10)
31–45	31 (34.1)	16 (27.1)	47 (31.3)
46–60	35 (38.5)	12 (20.3)	47 (31.3)
Above 60	19 (20.8)	17 (28.8)	36 (24)
Total	91 (61)	59 (39)	150 (100)

Chi square = 13.4, df = 4, $P < 0.01$, significant. Figures in parentheses indicate percentages

Table 3: Univariate analysis of selected demographic and behavioral variables of cholelithiasis among cases and controls

Variable	Cases	Controls	OR (95% CI)
Locality			0.8 (0.5–1.3)
Rural	58	65	
Urban	92	85	
Social class*			0.6 (0.3–1.4)
Upper	12	18	
Lower	138	132	
Literacy			0.8 (0.5–1.4)
Literate	36	41	
Illiterate	114	109	
Parity (females)			0.5 (0.3–0.9)
< = 3	28	41	
> 3	63	50	
Family history			
Present	7	6	1.2 (0.4–3.6)
Absent	143	144	
OCPs (females)			0.8 (0.4–1.9)
Yes	11	13	
No	80	78	
Iron supplements			
Yes	5	8	0.6 (0.2–1.9)
No	145	142	
Calcium supplements			0.3 (0.1–1.4)
Yes	2	7	
No	148	143	
Recent stress			
Yes	33	14	2.7 (1.4–5.4)
No	117	136	
Physical activity			4.2 (2.5–6.7)
Sedentary	102	51	
Mod/vigorous	48	99	
Current smoking			
Yes	40	32	
No	110	118	

OR: Odd's ratio, CI: Confidence interval, *Upper class:Modified Prasad's I to II, Lower class: Modified Prasad's III and below

difference was statistically significant (unadjusted OR = 0.5; 95% CI 0.3–0.9). Also, significantly more cases were observed in those who had had recent episode(s) of stress (unadjusted OR = 2.7; 95% CI 1.4–5.4) and in those with sedentary habits (unadjusted OR = 4.2; 95% CI 2.5–6.7). Interestingly, intake of less protein in diet was significantly associated with cholelithiasis [Table 4]. Further investigation revealed consumption of predominantly animal protein (68%) relative to vegetable protein (32%) among cases (not depicted). More than recommended intakes of saturated fats (unadjusted OR = 0.3; 95% CI 0.2–0.5) and unsaturated fats (unadjusted OR = 0.5; 95% CI 0.3–0.8), refined sugar (unadjusted OR = 0.2; 95% CI 0.1–0.4), and salt (unadjusted OR = 2.9; 95% CI 1.6–5.2) were significantly more in cases [Table 4]. Similarly, the odds of cases were more in favor of those consuming less fiber in diet (unadjusted OR = 0.2; 95% CI 0.1–0.4). Significantly more cases were overweight or obese (BMI > 25) in comparison to

Table 4: Univariate analysis of dietary and comorbid variables of cholelithiasis among cases and controls.

Variable	Cases	Controls	OR (95% CI)
Diet			1.3 (0.8 to 2.1)
Vegetarian	63	54	
Non vegetarian	87	96	
Calories			0.8 (0.5 to 1.3)
<= RDA*	91	98	
> RDA	59	52	
Proteins			14.2 (7.8 to 25.6)
<= RDA	131	49	
> RDA	19	101	
Saturated fat			0.3 (0.2 to 0.5)
<= RDA	82	119	
> RDA	68	31	
Unsaturated fat			0.5 (0.3 to 0.8)
<= RDA	111	128	
> RDA	39	22	
Salt			2.9 (1.6 to 5.2)
<= RDA	48	21	
> RDA	102	129	
Refined sugar			0.2 (0.1 to 0.4)
<= RDA	26	76	
> RDA	124	74	
Fiber			0.2 (0.1 to 0.4)
<= RDA	102	91	
> RDA	48	59	
Dietary iron			1.6 (0.6 to 2.1)
<= RDA	123	119	
> RDA	27	31	
Dietary calcium			1.4 (0.8 to 2.2)
<= RDA	98	87	
> RDA	52	63	
Fruits**			1.1 (0.5 to 2.6)
Adequate	12	11	
Inadequate	138	139	
Fasting***			1.3 (0.8 to 2.1)
Occ./none	83	73	
Frequent	67	77	
Feasting***			0.5 (0.3 to 1.2)
Occ./none	126	135	
Frequent	24	15	
Parenteral nutrition (past)			0.6 (0.1 to 4.1)
Yes	2	3	
No	148	147	
BMI			0.3 (0.2 to 0.5)
<=25	88	125	
>25	62	25	
Waist hip ratio			0.4 (0.2 to 0.7)
<=0.80	114	135	
>0.80	36	15	
Hemoglobin			0.7 (0.4 to 1.2)
<=10g%	109	119	
>10g%	41	31	
Diabetes			2.1 (0.8 to 5.2)
Yes	16	8	
No	134	142	
Hypertension			2.2 (1.1 to 4.2)
Yes	29	15	
No	121	135	
Hyperlipidemia			1.6 (0.6 to 4.3)
Yes	11	7	
No	139	143	

*RDA: Recommended daily allowance, **Adequate fruit intake was defined as consumption of two to three servings of fruits >=4 times a week. ***Fasting and feasting twice or more in a month were regarded as 'Frequent' and lesser so as occasional/none.

Table 5: Stepwise binary logistic model for multivariate analysis of selected variables

Variable	Estimated coefficient	S.E of estimate	Odds Ratio	Significance (*P*)
Unsaturated fat	-2.55	28.90	0.89	0.84
Fiber	12.04	29.43	0.63	0.68
Hypertension	-12.70	30.86	0.59	0.68
Salt	7.02	19.41	0.96	0.54
Refined sugar	11.12	9.23	0.36	0.51
BMI	-16.48	27.45	0.72	0.08
Parity	2.88	0.55	0.66	0.08
Saturated fat	-6.59	1.80	4.89	0.04
Waist hip ratio	-8.88	1.20	4.44	0.03
Physical activity	6.48	2.45	6.62	0.01

controls (unadjusted OR = 0.3; 95% CI 0.2–0.5).Waist hip ratio more than 0.85 was also a significant marker for cholelithiasis (unadjusted OR = 0.4; 95% CI 0.2–0.7). Another clinical variant that emerged significant in favor of cases was known hypertension (unadjusted OR = 2.2; 95% CI 1.1–4.2). Table 5 represents a model for binary logistic regression of selected variables and obviates the influence of potential confounding factors from the outcome of univariate analysis. Factors that emerged significant in their decreasing order were inadequate physical activity ($P = 0.01$), high waist hip ratio ($P = 0.03$), and excessive intake of saturated fats ($P = 0.04$).

Discussion

A higher prevalence of cholelithiasis among females, observed in the present study, has been corroborated by several authors.[8,9] Pregnancy and sex hormones are believed to place women at a higher risk, and the view has been supported by several classical epidemiologic studies.[10,11] Estrogen increases biliary cholesterol secretion causing cholesterol super saturation of bile rendering it lithogenic. A relatively higher prevalence of 39% among males when compared to reports from past studies[12] is an indicator of significant shift in the epidemiology of gallstone disease. Maximal affliction of elderly males (28.8%) was corroborated by Chari *et al*.[13] However, these figures in males may well be an underestimation as most cases are asymptomatic.[13] Asymptomatic cholelithiasis was a common occurrence among cases in our study as well [Figure 1]. Gallstones were least common in the prepubertal age as supported by coworkers.[14] None of the children in the present study had clinical evidence of hemolysis that could have led to gallstone formation. This makes a case for suspecting gallstone disease in all children under appropriate clinical scenarios, even in the absence of predisposing hemolytic anemias. Multiparous females had a significantly higher occurrence of gallstones. The view has been supported by several researchers.[15,16] Dietary factors have been widely believed to play a pivotal role in the pathogenesis of gallstone disease. High total fat, especially of animal origin (as in our cases) in diet, may lead to loss of bile acids in feces and decreased bile acid pool promoting supersaturation of bile and rendering it more lithogenic. The landmark Framingham Heart Study[10] has also shown that population given increased amounts of polyunsaturated fats have a twofold risk of developing gallstones. The MICOL study however showed no such association.[17] Low fiber intake and high refined sugars were similarly associated with tendency to gallstones as documented in other studies.[18] Dietary fiber decreases gut transit time, so there is less time for colonic bacteria to produce secondary bile acids and less bile acids are thereby absorbed. Low protein intake of plant origin was also a significant factor on univariate analysis. It has been proposed that vegetable protein exerted an inhibitory effect on biliary cholesterol crystallization, which is the determinant step in gallstone genesis.[19,20] A high waist hip ratio (>0.80) suggestive of abdominal adiposity emerged a positive deviant towards gallstone disease in multivariate analysis. Chung *et al*.[21] have documented a higher multivariate relative risk for men with a WHR ≥ 0.99 than those with WHR < 0.89. Similar association was observed with body mass indices in overweight and higher ranges. A sedentary lifestyle or physical inactivity was also an important determinant of gallstone disease. Indeed, there have been consistent experimental and epidemiologic data for a protective effect; so much so to suggest a causal association. Paul *et al*. demonstrated in their large prospective cohort study that the highest level of physical activity was associated with a 70% decreased risk of symptomatic gallstones after 5 years.[22]

Comorbid conditions such as hypertension, diabetes, and hyperlipidemia were frequently found in cases but only hypertension was significantly associated with gallstones in univariate analysis. The association of gallstones with recent stress (physical and/or psychological), noted in the present study, could be a result of the well-documented association of stress and hypertension. However, independent association between the two (stress and gallstones) has been documented by Kuta *et al*.[23] Few authors have suggested that certain mental stressors are associated with an elevation of serum cholesterol levels and hypercholesterolemia in turn predisposes to gallstone formation.[24]

Conclusion

Gallstones are more common in females and among elderly males, many cases being asymptomatic. High intake of refined sugar and low vegetable protein favor gallstone formation. Consumption of excessive saturated fats coupled with less physical activity and high waist hip ratio were the most significant predictors and point

toward unhealthy lifestyle practices. The present study being age and sex matched, falls short of analyzing each of the variables separately in both genders. However, it is a sensitizing exercise for health care providers and hypothesizes the notion that gallstones is a lifestyle disease with potentially modifiable risk factors as in several other chronic diseases (such as coronary heart disease, obesity, and hypertension). Majority of the risk factors are amenable to primary prevention. Screening and surveillance of these risk factors can be incorporated into the primary health care system. Further studies are however needed to identify additional predictors of cholelithiasis, particularly asymptomatic disease.

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