LOOKING IN TO THE CHANGING TREND OF BIOLOGICAL RISK FACTORS FOR GALL STONE DISEASE IN MALE AND FEMALE

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Summary

Conventional risk factors for Gall Stone Disease (GSD) are the five 'F's - Female, Fair, Fat, Forty and Fertile' but many study revealed changing trends particularly in age, multiparity and cigarette smoking particularly in Western countries. The etiology of cholelithiasis is considered to be a multi factorial, with interaction of genetic and environmental factors. Most exogenous factors are a consequence of westernization of modern societies, including a high intake of refined carbohydrates and a high prevalence of obesity, non-insulin dependent diabetes, atherosclerosis and sedentary life-style. From January 2011 to July 2014, consecutive patients who underwent Laparoscopic Cholecystectomy (LC) at Chittagong Medical College Hospital and Royal Hospital of Chittagong City were included in a prospective database targeting biological and biochemical characteristics in Male(n=256) and female (n=256). Data collected using predetermined approved case record form, including age, sex, demographic data, biochemical data before operation. The prevalence of diabetic was more among female where hypertension and dyslipidemia were more prevalent in males. Multivariate conditional logistic regression models revealed age is insignificant both in male and female (p=.088 vs. p=0.0744). Obesity is also insignificant (p=.091 in male, p=0.084 in female). Hypertension in both sexes (p= 0.02 in male,0.03 in female)diabetes mellitus in female (p=0.02) dyslipidemia particularly high serum LDL level particularly in female (p= 0.00001) is significantly related to gall stone. Metabolic factors like blood glucose level, dyslipidemia and hypertension may be closely related to the causation of gall stone disease.

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Key words

Cholelithiasis; Risk factor; Changing trend.

Introduction

Conventional risk factors for Gall Stone Disease (GSD) are the five 'F's—'Female, Fair, Fat, Forty and Fertile'—but many study revealed changing trends particularly in age, multiparity and cigarette smoking particularly in Western countries, where cholesterol is the leading component of stones [1-8]. The etiology of cholesterol cholelithiasis is considered to be a multi factorial, with interaction of genetic and environmental factors [9]. Most exogenous factors are a consequence of westernization of modern societies, including a high intake of refined carbohydrates and a high prevalence of obesity, non-insulin dependent diabetes, atherosclerosis and sedentary life-style [10].

The pathophysiological conditions that predispose to cholesterol cholelithiasis are the formation of a lithogenic bile, short cholesterol crystallization time and gall bladder stasis. Lithogenicity of the bile is mainly determined by the concentrationsof their principal three lipid components: cholesterol, bile acids and phospholipids. Relative increase concentrations of cholesterol in bile, or super saturation, are a sine qua non condition for gallstones formation.

Life style modification stimulates us to look in to the current status of risk factors in male and females develop stone in the gall bladder.

Materials & methods

From January 2011 to July 2014, consecutive patients who underwent LC at Chittagong Medical College Hospital and Royal Hospital of Chittagong City were included in a prospective database targeting biological and biochemical characteristics in Male (n=256) and female (n=256). Data collected using predetermined approved case record form, including age, sex, demographic data, ,biochemical data before operation. Gall stone were diagnosed by Ultrasonography of the abdomen conducted by

ultrasonographers using a scanner equipped with a 10-MHz transducer (Voluson S-6,G.E. Health care, Korea, Model-2010) and further ensured by operative finding. Final diagnosis confirmed by peroperative finding after laparoscopic cholecystectomy. Blood samples were drawn via venipuncture from the study participants, after they had fasted overnight, by clinical nurses for laboratory examination. Fasting Plasma Glucose (FPG), Triglyceride, Total Cholesterol, High Density Lipoprotein (HDL) cholesterol and Low Density Lipoprotein (LDL) cholesterol and 2 hours after break fast glucose concentrations were measured using Diemention X-Band Siemens Healthcare Diagnostic Modular analyze system (Siemens, USA, 2010) The database and study were approved by the institutional ethical committee.

All surgical procedure was performed by a single surgeon and he is the second author and having sixteen years experience in the relevant field. All patients were interviewed after giving formal consent for operation. Body Weight were measured in empty stomach after 12 hours fasting in Kilogram using Weighing Scale Machine, Model SKU:SH0361,Manufactured by Talash Bio-Medical Engineering Co.Mumbai,India. Height were measured in meter from sole to scalp using-222 Wall Mounted Stadiometer stadiometer (Warehouse,Issaquah, WA, USA). BMI calculated from slandered formula.

Diagnosis criteria

Gall stone was defined as the presence of strong intraluminal hyper acoustic shadowing during abdominal ultrasonography and gallstone detected in the gall bladder after cholecystectomy. Obesity was defined as a Body Mass Index (BMI) $\geq$ 25 kg/m^2 in both men and women according to the redefined World Health Organization (WHO) criteria for the Asia Pacific Region [11]. High blood pressure was defined as a Systolic Blood Pressure (SBP) $\geq$140 mmHg or a Diastolic Blood Pressure (DBP) $\geq$90 mmHg or a history of hypertension. Subjects with an FPG $\geq$126 mg/dl and/or a history of diabetes were considered to have Diabetes Mellitus (DM). Hypertriglyceridemia was defined as a triglyceride concentration $\geq$150 mg/dl. Low HDL-C was defined as an HDL-C level < 35 mg/dl in men or < 39 mg/dl in women. Hypercholesterolemia was defined as a total cholesterol level $\geq$200 mg/dl. High LDL-C was defined as an LDL-C level $\geq$150 mg/dl.

Statistical analysis

Categorical data are presented as the number of cases and percentages. Statistical analysis was performed using Statistical Package for Social Science (SPSS) software ,version 20. Odds ratios (ORs) were calculated with the variables coded in a multivariate form. Pearson's Chi-square test and Fisher's exact tests were used for categorical variables. Multiple logistic regression analysis was performed to investigate the independent factors associated with gallstone disease. In all cases, tests of significance were 2 tailed, $P < 0.05$ indicated statistical significance.

Results

Two hundred sixty six male and similar number of female candidate with gall stones were the subject of study. The age and BMI of male and female groups were almost same and p value were insignificant (Table I). The prevalence of diabetic was more among female where hypertension and dyslipidemia were more prevalent in males (Table I). Table II showing the result of univariate analysis of risk factors ,showing gall stone is significantly related to age (>40ys) BMI(>30) and also diabetes, hypertension and dyslipidemia.

Table I: Demographic Data of Male and Female patient with gall stone

	Male (n=266)	Female (n=266)	P value
Age	38.70±7.91	41.47±7.17	0.2
BMI	27.70±2.537	29.14±2.71	0.3
Diabetes			
Yes	39	59	0.03
No	227	207	
Hypertention			
Yes	103	71	0.0041
No	163	195	
Serum Cholesterol			
High	67	46	0.026
Normal	199	220	
Serum LDL			
High	148	62	0.00001
Normal	118	204	
Serum HDL			
High	115	127	0.296
Normal	151	149	

Age in year : ± indicates standard deviation.
p< 0.05 is statistically significant

Table II: Risk factors of cholelithiasis in univariate conditional logistic regression models

Risk factors	n	RR [95%CI]	OR [95%CI]	P value
Age (years)				
Male(>40/<40)	119/147	0.62[0.53,0.73]	0.32[0.22,0.46]	0.0001
Female(>40/<40)	191/75			
Obesity				
Male (BMI>30/<30)	43/223	0.47[0.34,64]	0.36[0.24,55]	0.00002
Female (BMI>30/<30)	92/174			
Hypertention				
Male(> 130/80)	103/163	1.45[1.13,186]	1.74[1.20,2.50]	0.004
Female(>130/80)	71/195			
Diabetes mellitus				
Male	39/227	0.66[46,95]	0.60[39,94]	0.03
Female	59/207			
High Serum Cholesterol				
Male	67/199	1.46[1.04,2.04]	1.61[1.06,2.45]	0.034
Female	46/220			
High serum LDL				
Male	148/118	2.39[1.87,304]	4.13[2.84,5.99]	0.000001
Female	62/204			
High serum HDL				
Male	115/151	0.91[0.75, 1.09]	0.83[0.59, 1.17]	0.361
Female	127/139			
High Serum TG	67/189	0.73[0.56,0.95]	0.63[0.43,0.92]	0.02
	92/174			

n indicates number : Risk Ratio (RR), Confidence Intewrval (CI); p< 0.05 is significant, Low Density Lipoprotein (LDL), High Density Lipoprotein (HDL), Trigleceride (TG)

Table III : Risk factors of cholelithiasis in multivariate conditional logistic regression models

	For Male Subject (n=256)			For Female Subject (n=256)		
	OR	OR (95% CI)	P value	OR	OR (95%CI)	P Value
Age (years)	0.32	[0.15,31]	.088	.081	0.18,34	0.0744
Obesity	0.29	[0.13,45]	.091	0.26	[0.15,49]	0.084
Hypertension	1.29	[1.01,1.56]	0.02	1.55	[1.10,1.76]	0.03
Diabetes mellitus	0.53	[.41,.85]	.061	0.51	[39,81]	0.021
High Serum Cholesterol	1.16	[.97,1.95]	.035	1.05	[.91,1.79]	.029
High serum LDL	2.11	[1.77,287]	.01	2.31	[1.83,301]	.00001
High serum HDL	0.84	[0.69, 1.01]	0.4	0.81	[0.71, 1.05]	0.322
High Serum TG	0.69	[0.51,0.85]	0.2	0.64	[0.51,0.85]	0.34

n indicates number : Risk Ratio (RR), Confidence Intewrval (CI); p< 0.05 is significant, Low Density Lipoprotein (LDL), High Density Lipoprotein (HDL), Trigleceride (TG)

But in multivariate conditional logistic regression models (Table-III) age is insignificant both in male and female (p=.088 vs. p=0.0744). Obesity is also insignificant (p=.091 in male, p=0.084 in female). Multiple logistic regression analysis showing Hypertension diabetes mellitus, dyslipidemia particularly high serum LDL level is significantly related to gall stone (p< 0.05. Table-III) the relation is predominant in female.

Discussion

Cholelithiasis in some form-silent gallstones, simple biliary colic pain, acute cholecystitis sepsis, and, infrequently, gallstone ileus has accounted for an increasing number of hospital admissions and is a growing healthcare concern in many countries [12-14]. Although the conventional belief is cholelithiasis is linked to female sex, fertile ,forty, fair women, and obesity. Differences in gallstone composition indicate there may be differences as well in the etiology of cholelithiasis in different part of the world. Using multivariate conditional logistic regression analysis, we identified the following as independent risk factors for cholelithiasis (in descending order of contribution): High serum LDL (OR=2.31 [female] 2.11 [male]) Hypertension (OR=1.55[female], 1.29[male]) Hypercholestremia (OR=1.05 [female] 1.16[male]), Diabetes mellitus (OR=.51[female].53[male]).

All of the constituents of metabolic syndrome, with the exception of hypertension, have been reported as independent risk factors for cholelithiasis, including low serum levels of high density lipoprotein, diabetes and glucose intolerance, high BMI. In the present study, we identified high LDL level, cholesterol level, TG level serum glucose level hypertention as strong risk factors [13-20]. These findings may open an avenue to modify life style and dietary pattern as effective measures for the prevention of cholelithiasis [21]. In addition, the findings may support previous observations indicating that medications used to treat dyslipidemia may be of value in the prevention and treatment of cholelithiasis [22].

We found a strong association of age and BMI with cholelithiasis in univariate analysis but did not identify significant in multivariate analysis. One the other hand we found diabetes and cholelithiasis is related in univariate analysis, but did not identify diabetes as a significant independent risk factor in multivariate analysis.

There remains some controversy about gender as a risk factor for cholelithiasis. While the majority of studies conducted in the West have concluded that females are more likely than males to develop cholelithiasis, several studies with among Asian patients have failed to identify a gender-related difference [23-25].

There remains some controversy in the literature regarding type 2 diabetes as an independent risk factor for cholelithiasis. Previous community based studies in healthy adults in Taiwan have found diabetes mellitus to be highly associated with the prevalence of gallstone disease [17]. In addition, Chen et al. found diabetes to be an independent risk factor for gallstone disease in women, but not in men [17]. Type 2 diabetes has also been reported as an independent risk factor for gallstone disease in women but not men in Western studies [26]. In contrast, other investigators have found no independent link between type 2 diabetes and the development of gallstones.

Limitations of the study

A significant limitation of this study is that our research database did not reveal the criteria on which the diagnoses of cholelithiasis were based rather we included diagnosed case. In addition, because of the inherent limitations of data, some lifestyle risks, such as the use of ground-surface water, cannot be evaluated. We were also unable to analyze the link between cholelithiasis and family history or parity in our population. Thus, further prospective studies will be required to better understand the relationship of these factors to cholelithiasis.

Conclusions

This study was designed to review conventional risk factors for cholelithiasis in the general population, particularly among male in comparison to female. The goal was to determine if the risk profile in the general population differed from those reported. The study shed light effectively metabolic factors like blood glucose level, dyslipidemia and hypertension may be closely related to the causation of gall stone disease. If measures are taken to control those modifiable factors, prevalence of gall stone could be reduced.

Disclosure

All the authors declared no competing interest.

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