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The Prevalence and Risk Factors of Gallstone among Adults in Karachi, South Pakistan: A Population-Based Study

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Abstract

Introduction: The present study was aimed to determine the prevalence and risk factors of GSD among a sample of general population in Karachi, South Pakistan.

Methodology: A multistage random sampling method was employed on 30 clusters, where 60 subjects of age≥25 years were randomly recruited from the study population from June 2013 till March 2015. Finally, data was analyzed and logistic regression models were used to find the correlation between selected variables and gallstone disease.

Results: It was found that 184 patients had echogenic mass with shadowing on ultrasonography; yielding a prevalence of 10.2% for gallstones in the study participants. The occurrence was higher in females (14.8%) than in male participants (5.7%). Further, participants over 40 years of age and single, widow/separated subjects had higher incidence of gallstones than married individuals. Moreover, an indirect correlation was obtained with daily physical activity, consumption of fruits, vegetables and fish with development of GD.

Conclusion: It can be evaluated that daily physical activity, female gender, increasing age and marital status play an important role in progression of GSD. Understanding pathogenesis and physiological mechanism involved in GSD can help to determine therapeutic options other than surgical treatment.

Keywords: gallstones, prevalence, risk factors, Karachi, population based

1. Introduction

Considered as the most frequent disorder presenting to emergency room (Hung, Liao, Lai, Li, & Chen, 2011), gallstones are the solidifications that can occur in any portion of biliary tract, and when they accumulate in gallbladder they are defined as cholelithiasis. The complications associated with gallstone disease (GSD) such as cholecystitis, pancreatitis, and cholangitis have become significant public health issues imposing a great economic burden worldwide (Shaffer, 2006). A study in 2006 revealed that 700,000 cholecystectomies are performed in US at an expense of $6.5 billion dollars annually (Shaffer, 2006). Similarly, international literature has reported that 50,000 cholecystectomies are performed every year in UK and more than twice of that number of patients are admitted to hospital with gallstone-related episodes (Jazrawi, 2002).

GSD was previously regarded as the disease of western population; however, due to changes in pattern of food consumption, it has now become progressively common cause of morbidity in the developing countries (Sachdeva, Khan, Ansari, Khalique, & Anees). In the developed countries like UK, USA and Italy the frequency has been reported 10% to 20% (Hou, Shu, Gao, Ji, Weiss, Yang, & Chow, 2009). In contrast, studies involving ultrasonography technique has reported a prevalence of 22% to 54% in these countries (Silva & Wong, 2005). Furthermore, the incidence of GSD has ranged from 5.2 to 10% in African populations (Kratzer, Mason, & Kächele, 1999), 3.1 to 6.1% in Asian population (Kratzer, Mason, & Kächele, 1999) and 6.3% in Iranian

population (Farzaneh, Zavvareh, Gharadaghi, & Sheikhvatan, 2007). The data from Pakistan has found to be scarce, but previous study in southern Sindh area of Pakistan has reported a surgical incidence of 9.03% (Channa, Khand, Bhangwer, & Leghari, 2004); particularly a prevalence rate of 4% in males and 14.2% in females of Pakistan (Channa, Khand, Bhangwer, & Leghari, 2004).

It is a proven fact that GSD risk factors are multifactorial (Panpimanmas & Manmee, 2009), which includes aging, gender, dietary, high calorie intake, low fiber intake, high refined carbohydrates, hyper triglyceridaemia, physical inactivity, pregnancy, parity, overweight and obesity (Chandran, Sivarajan, Srinivasan, Srinivas, & Jayanthi, 2014). Moreover, the risk of disease increases with age among both genders (Panpimanmas & Manmee, 2009) with a high rate of occurrence from 50 to 60 years of age interval (Jazrawi, 2002). It is claimed that females are two times more prone to this disease than males, where the male to female ratio varies from 1.7 to 4:1 (Pacchioni et al., 2000). A mnemonic for memorizing the risk factors correlated with gallstones is female, fat, fertile and forty. Additionally, females adhere a greater risk if they used oral contraceptives, gave birth to 3 or more children or underwent full term pregnancies (Henao, Denova, Moran, Duque, Gallegos-Caririllo, Macías, & Salmerón, 2014)

There has been some contradictory data with regards to association of triglyceride, cholesterol serum levels, obesity, glucose serum levels and diet with gallstone. Some studies, have presented, increased TG levels, obesity, duration of obesity, less physical activity, increased glucose serum levels/diabetes, and increased cholesterol serum levels as major causes for the development of gallstone diseases (Pacchioni et al., 2000). In another study, consumption of vegetables and fruits decrease the risk of gallstone disease formation while the intake of spicy foods, fried foods and cooking oil significantly increases the risk for gallstone disease (Chandran, Sivarajan, Srinivasan, Srinivas, & Jayanthi, 2014). On the other hand, a vegetarian or non-vegetarian diet, fruit intake, physical inactivity, HDL cholesterol, triglyceride levels and body mass index were not considered as significant causes for the prevalence of gallstone disease in some studies (Pagliarulo et al., 2004).

There is a paucity of literature in Pakistan with regards to prevalence of gallstones and its associated risk factors. Previous studies were conducted pertaining to patients admitted in hospitals and very minimal community basis studies were conducted. Since the assessment of risk factors can help in formulating therapeutic and preventive approaches, the present study was aimed to determine the prevalence and risk factors of GSD among a sample of general population in Karachi, South Pakistan.

2. Methodology

A multistage random sampling method was employed on 30 clusters, where 60 subjects of age≥25 years were randomly recruited from the study population from June 2013 till March 2015. Firstly, metropolitan city Karachi, located in South Pakistan was split into 30 geographical areas. After that, head clusters (the first enrolled home/participant as opening point for community based survey in each geographical area) were selected using random table. Following this, trained research investigators were assigned to the first home in every geographical area and then move on their left to cover 60 participants in each cluster. Applying this methodology, a total of 1800 participants was selected for this population based survey.

Each participant was interviewed by using a validated questionnaire of previous study (Alireza et al., 2016) at their residential site by conducting a face to face interview. Later participants were asked to attend study center during scheduled appointment and were instructed to fast overnight (minimum 8 hours).The research questionnaire consisted of demographic variables, brief clinical history and dietary habits like gender, age, marital status, level of education, employment status, number of pregnancies, daily physical activity, BMI, intake of fruits, vegetables, can, dairy, and fish (Alireza et al., 2016). The subjects were enrolled after obtaining a written informed consent and explanation of the purpose and procedure of the research protocol. However, the subjects having remarkable history for gallbladder and pancreatic carcinoma, patients having age of <25 years and the participants who refused to give written informed consent were excluded from the study.

After the completion of interview, a fasting blood sample was obtained from each subject in the morning. At the same time, subjects were provided with the referral letter to attend the study center in the afternoon of the same day for assessment of the gallstone. Furthermore, abdominal ultrasound of each subject was performed by two experienced sonologists who had minimum experience of 7 years. The diagnosis of gallstone was made by complete consensus based on radiographic evidences. Apart from ultrasonography, blood tests were performed on each patient who included liver function test and other biochemical parameters. Liver function tests included SGPT and alkaline phosphatase. Biochemical parameters evaluated fasting blood sugar, plasma cholesterol, Triglycerides level, and HDL and LDL Cholesterol levels among study participants.

The normal range for alkaline phosphatase was considered from 30 to 136 IU/L, and for SGPT 7 to 56 IU/L was

taken as normal value. Furthermore, a fasting blood sugar of less than 110 mg/dl, a Cholesterol of less than 200 mg/dl, Triglycerides of less than 140 mg/dl, HDL Cholesterol of greater than 45 mg/dl and LDL Cholesterol of less than 130 mg/dl were taken as normal finding. Any value above or below normal was considered as abnormal finding. Besides, if a subject was found with Echogenic mass with shadowing on ultrasonography, the suspect was considered to have a gallstone.

For tabulation of results, subjects were divided into two age groups (25-40 Years and >40 years).Weight of the individuals was categorized into normal weight and obese by employing the South Asian cut-off for BMI. Subjects were classified as normal if BMI was between 18.5 to 23.99 and obese if BMI is greater than or equal to 27. Individuals were considered as hypertensive if diastolic blood pressure was recorded to be greater than or equal to 90 mmHg, or if systolic blood pressure was recorded to be greater than or equal to140 mmHg.

The data were entered in SPSS software (version 19) and same software was used to analyze our data. We employed logistic regression model to determine the relationship between aforementioned variables and gallstone disease. Initially, the relationship between selected variables and gallstone disease were examined by a univariate model. Then we included significant variables in a multivariate model. A p value<0.05 was considered to be statistically significant.

The research protocol was approved by Ethical review board of Dow University of Health Sciences. Informed consent was obtained from each participant after briefly explaining them the purpose of the study.

3. Results

During the aforementioned time period, eighteen hundred subjects were recruited for this population based survey. The survey comprised of 902 males (50.1%) and 898 females (49.9%), with the mean age of 43.56±9.34 years. A statistical significance was obtained with differences in the mean ages of male and female participants (44.34±11.20 vs. 49.54±11.97; P=0.01). With regards to marital status, 89% (N=1602) of the study subjects were married. However, more than half of the participants (65%) had education below intermediate level (Grade 12).

It was found that 184 patients had echogenic mass with shadowing on ultrasonography; yielding a prevalence of 10.2% for gallstones in the study participants. The occurrence was higher in females (14.8%) than in male participants (5.7%) with an Odds ratio=2.90; 95% CI: 2.07-4.065. It was further revealed that majority (75%) of participants had multiple stones on ultrasonography. A significant correlation was obtained between age and prevalence of gallstones with the participants over 40 years of age had a greater frequency than participants between the ages of 25-40 years (13.4 vs 5.3) (Odds Ratio=2.77: 95% CI; 1.92-3.99)

In univariate analysis, it was also revealed that marital status, employments status, BMI, daily physical activity, number of pregnancies, consumption of fruits and vegetables, fish intake, fatty liver and SGPT have significant correlation with incidence of gallstones. With regards to marital status; Single, widow/separated subjects had higher incidence of gallstones than married individuals (23.2% vs. 8.4%) (Odds Ratio=3.31: 95% CI; 2.28-4.82). As far as employment status is concerned, unemployed and housekeeper individuals had 2.5 times greater incidence of Gallstones in comparison with other job categories. Similarly, obese study subjects were two times more likely to have gallstone disease than participants with lying in normal BMI range (Odds Ratio=2.03: 95% CI; 1.03-4.31). Furthermore, multiparous female participants were around 2 times more at risk of developing gallstones than female subjects having less than 3 pregnancies. (Odds Ratio=2.40: 95% CI; 1.2-4.62).

Moreover, an indirect correlation was obtained with daily physical activity, consumption of fruits, vegetable and fish with development of GD. Our results indicated that daily physical activity decreases GD incidence by 36.4% (95% CI: 11.7%-54.2%). Following the similar trend, study subject who did not consume fruits and vegetables and fish in their diet had 2 fold greater risk of developing GD. The odd ratios for these risk factors are depicted in table 1.The biochemical factors that were associated in the development of GD are depicted in Table 2. According to results, fatty liver disease (OR=1.95 95%CI: 1.43-2.66), having abnormal levels of serum HDL cholesterol (OR=3.29 95%CI: 2.41-4.50) and ALT (OR=4.13 95%CI: 1.07-17.9) were indicated as the significant risk factors for GD in univariate analysis.

Table 1. Risk factors correlated with gallstone in a univariate logistic regression model

Variable	No. (%) Screened	Gallstone No. (%)	OR (95 % CI)
Gender			
Male	902(50.1)	51(5.71)	1.00
Female	898(49.9)	133(14.8)	2.90(2.07-4.065)
Age			
25-40 Years	756(42)	40(5.3)	1.00
Over 40 Years	1044(58)	140(13.4)	2.77(1.92-3.99)
Marital Status			
Married	1602(89.0)	134(8.4)	1.00
Single, widow/separated	198(11.0)	46(23.2)	3.31(2.28-4.82)
Education level			
Under Intermediate	1170(65.0)	132(11.3)	1.532(1.08-5.89)
Intermediate/University Graduates	630(35.0)	48(7.61)	1.00
Employment Status			
Employee	522(29.0)	32(6.1)	1.00
Worker	130(7.2)	8(6.3)	1.18(0.16-10.98)
Retired	81(4.5)	5(6.2)	1.12(0.14-10.78)
Driver	117(6.5)	10(8.5)	2.1(0.9-22.87)
Unemployed	201(11.2)	26(13.9)	2.7(0.31-24.80)
Housekeeper	749(41.6)	99(13.2)	2.6(0.54-23.66)
Number of Pregnancies			
Less than three	401(67.0)	78(19.5)	1.00
More than three (Multipare)	197(33.0)	55(29.9)	2.4(1.2-4.62)
Physical Activity			
Sedentary	1049(58.3)	122(11.6)	1.00
Daily physical activity	751(41.7)	58(7.7)	0.636(0.458-0.883)
BMI			
Obese	476(26.4)	74(15.5)	2.03(1.03-4.3)
Normal	1324(73.6)	106(8.0)	1.00
Dietary Intake			
Can			
Yes	274(15.2)	27(9.9)	1.00
No	1526(84.7)	153(10.0)	1.01(0.663-1.569)
Dairy			
Yes	1609(89.3)	149(9.3)	1.00
No	191(10.7)	31(16.2)	1.89(1.24-2.88)
Fruits and vegetables			
Yes	1461(81.2)	121(8.3)	1.00
No	339(18.8)	59(17.4)	2.35(1.68-3.30)
Fish			
Yes	694(38.6)	44(6.3)	1.00
No	1106(61.4)	136(12.3)	2.07(1.45-2.95)

Table 2. Biochemical factors correlated with gallstone in a univariate logistic regression model

Biochemical parameter	No. (%) Screened	Gallstone No. (%)	OR (95 % CI)
Fatty Liver Status			
Normal	1134(63.0)	87(7.6)	1.00
Fatty liver	666(37.0)	93(13.9)	1.95(1.43-2.66)
Fasting Blood Sugar			
Normal	1282(71.2)	118(9.2)	1.00
Abnormal	518(28.8)	62(11.9)	1.34(0.968-1.85)
Cholesterol			
Normal	1069(59.4)	101(9.4)	1.00
Abnormal	731(40.6)	79(10.8)	1.16(0.85-1.58)
Triglycerides			
Normal	1373(76.3)	147(10.7)	1.00
Abnormal	427(23.7)	33(7.7)	0.699(0.471-1.036)
HDL Cholesterol			
Normal	1279(71.1)	83(6.5)	1.00
Abnormal	521(28.9)	97(71.0)	3.29(2.41-4.50)
LDL Cholesterol			
Normal	926(51.4)	97(10.5)	1.00
Abnormal	874(48.5)	83(9.5)	0.89(0.659-1.22)
ALT (SGPT)			
Normal	1471(81.7)	171(11.6)	4.13(1.07-17.9)
Abnormal	329(18.3)	9(2.7)	1.00
Alkaline Phosphatase			
Normal	24(1.3)	2(8.3)	3.02(0.38-22.32)
Abnormal	1776(98.7)	53(2.9)	1.00

Table 3. Risk factors correlated with gallstone disease in a multivariate logistic regression analysis

Variable	Gallstone No. (%)	OR (95 % CI)
Gender		
Male	51(5.71)	1.00
Female	133(14.8)	2.77(2.01-3.975)
Age		
25-40 Years	40(5.3)	1.00
Over 40 Years	140(13.4)	2.56(1.72-3.69)
Marital Status		
Married	134(8.4)	1.00
Single, widow/separated	46(23.2)	3.11(2.12-4.62)
Physical Activity		
Sedentary	122(11.6)	1.00
Daily physical activity	58(7.7)	0.636(0.458-0.883)

The results obtained from multivariate logistic analysis are illustrated in Table 3. The result identified age, sex; marital status and physical activity were significantly linked with occurrence of GD after adjusting confounding variables. It was deduced that females were 2.7 times more prone than males in the development of GD (OR=2.77 95%CI: 2.01-3.975). Similarly, people over 40 years had 2.5 times greater chance of GD than participants in the age group of 30-40 years (OR=2.56 95%CI: 1.72-3.69). It can also be evaluated that risk of

GD in unmarried patients was thrice as compare to married subjects (OR 3.11 95%CI: 2.12-4.62). Finally, daily physical activity reduced the occurrence of GD by 36.4% (95% CI: 11.7%-54.2)

4. Discussion

GD is regarded as the escapable cause of death (Reshetnyak, 2012). Globally, the complications associated with GD are considered as one of the most costly pathological conditions. The present study has revealed a prevalence of 10.2% of GD in a sample population of Karachi; indicating a significant economic burden on country's healthcare budget. The prevalence rates are slight higher than previous study of 2004; which indicated an occurrence rate of 9.03% (Channa, Khand, Bhangwer, & Leghari, 2004). In spite of the rise in prevalence rates, very few remedial approaches have been introduced to reduce the preponderance of the disease (Kim et al., 2002). The rates are similar with America (10%) and Peruvian (10.7%), however indifferent from Bangladesh (5.4%), Germany (7.8%), Tunisia (4.1%) and New Zealand (20.8%) as in indicated by work of Abu-Eshy et al. (Abu-Eshy et al., 2007).

Our study has established has a significant correlation of GSD prevalence with unmodified risk factors like age, gender and modifiable risk factors like marital status and sedentary lifestyle; as indicated by multivariate logistic regression model. The findings are concurrent with the recent Iranian study (Alireza et al., 2016). The results have indicated higher occurrence with the participants in the fourth decade of life or above. The finding is in line with the previous studies conducted in Pakistan (Hafiz et al., 2013) and Western countries (Bortoff, Chen, Ott, Wolfman, & Routh, 2000). The finding of correlation with increased age could be attributed to greater subjection to environmental risk factors.

It was also evident that incidence of GD was greater in females in comparison with males, especially during the pre-menopausal phase. This finding is consistent with the previous Pakistani (Hafiz et al., 2013) study and other international studies conducted in past) (Panpimanmas & Manmee, 2009; Reshetnyak, 2012; Grodstein et al., 1994). The difference is linked with the elevated levels of estrogen which is regarded as the primary sex hormone in female gender. The elevated levels enhance cholesterol excretion in bile which increases its saturation thereby leading to formation of cholesterol gallstone (R. Sharma, Sachanl, & S. R. Sharma, 2013).

Our study also revealed that GD was more prevalent in single; widow/separated females as opposed to married females. The correlation of GD with marital status is indicated by few studies only (Channa & Khand, 2013), (Selvaraju, Raman, Thiruppathi, & Valliappan, 2010). They explained by the fact that marrying in early ages prolongs females fertility period and increases parity rates. Consequently, female sex hormone can play crucial role in forming gallstones during fertile period. However, few researches negated of such relationship in their work (Jayanthi et al., 1999). In our case, statistical significance indicated by multivariate logistic regressions in marital status could also be linked with changes in hormonal level and higher parity rates.

Moreover, it was also identified that daily physical activity plays an important role in prevention of GD. The finding is consistent with results of other studies (Henao, Denova, Moran, Duque, Gallegos-Caririllo, Macías, & Salmerón, 2014; Storti et al., 2005); which also identified that increased physical activity greatly reduces risk of GD occurrence. However, our results are contradictory with findings of Pagliaruloet al (Pagliarulo et al., 2004), who did not find any significant association of GD with physical activity. In another study, sport activity is inversely linked with development of GD. The finding is justified by the fact that reduced sport activity greatly increases biliary cholesterol, percent biliary cholesterol and serum triglycerides (TG). Therefore, masses must be educated to maintain daily physical activity and to control serum TG levels (Chuang, Martin, LeGardeur, & Lopez, 2001).

It is anticipated by various researchers that low levels of HDL plays an important role in manifestation of GD pathology through independent effect of BMI and body weight on metabolic conditions and discrete effect of daily physical activity on body mass (Henao, Denova, Moran, Duque, Gallegos-Caririllo, Macías, & Salmerón, 2014; Storti et al., 2005). In our study, participants with abnormal levels of HDL had greater prevalence of GD.

Furthermore, present study also revealed that fatty liver patients had greater prevalence of GD on ultra-sonographic findings. The results are in line with previous Pakistani (Koller, Kollerova, Hlavaty, & Huorka, 2012) and international study (Sohail & Iqbal, 2007). The finding verifies that as a result of fatty liver there is buildup of lipids and TG in hepatocytes, thereby initiating inflammatory reaction. As a result leakage of liver enzyme occurs into the blood stream. With the presence of fatty liver, gallbladder is not emptied normally. Hence buildup of bile precipitates gallstones. Additionally, ultra-sonographic findings also revealed that mostly GD patients presented with multiple stones which is consistent with findings of previous studies (Reshetnyak, 2012; Verma, Bose, & Wig, 2001).

Presence of GD was positively correlated with increased Alkaline Phosphatase level in the present study. The result is in line with the findings of a previous study (Hayat, Loew, Asrress, Mclntyre, & Gorard, 2005). The finding could be explained by the evidence that most of the GD patients were females and increase in Alkaline Phosphatase occurred due to increased bone turn over or simultaneous formation of osteoid in female patients (Channa, Shaikh, Khand, Bhanger, & Laghari, 2005). Moreover, prevalence of GD was significantly associated with increase in serum SGPT levels. This result is consistent with previous Pakistani study (Hafiz et al., 2013) and international study (Barkun et al., 1994) conducted in past. This suggests that during GD pathology, hepatocytes are inflamed and damaged, as a result serum liver enzymes rises greatly.

5. Limitations

To the best of our information, it is the first population based survey dedicated to this issue in Pakistan. However, there were few limitationsin our study. Firstly, study participants were of homogeneous nature, as this study comprised of participants from Karachi city only. Therefore, the results could not be generalized to entire Pakistani population. Secondly, we did not exclude the patients with dyslipidemia employing lipid lowering drugs. The situation could have led to null association between GSD and dyslipidemia. Thirdly, we did not include the complete blood count test in our study. This could give us broader picture with regards to correlation of GSD with the investigations included in complete blood count.

6. Conclusion

It can be evaluated that daily physical activity, female gender, increasing age and marital status play an important role in progression of GSD. However, further prospective studies must be carried out to understand the etiology involved in the unmodifiable risk factors like gender and marital status. Additionally, further investigations and studies must be carried out to confirm the current identified demographic and biochemical factors behind GD incidence. Understanding pathogenesis and physiological mechanism involved in GSD can help to determine therapeutic options other than surgical treatment.

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Competing Interests Statement

The authors declare that there is no conflict of interests regarding the publication of this paper.

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