

Prevalence and risk factors of gallstone disease in a high altitude Saudi population

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معدل انتشار حصيات المرارة وعوامل اختطارها بين السعوديين القاطنين في المرتفعات
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الخلاصة: درس الباحثون معدل انتشار مرض حصيات المرارة وعوامل اختطارها بين السعوديين، في دراسة مجتمعية مستعرضة شملت 291 مواطناً من مقاطعة أبها في منطقة عسير. وقد جمعت المعطيات الأساسية المتعلقة بجميع المساهمين في الدراسة، وأجريت لهم دراسة بالأموح فوق الصوتية للناحية العليا من البطن لكشف حصيات المرارة. وقد بلغ معدل انتشار حصيات المرارة 11.7%. وعند تحليل النتائج بالتحروف اللوجستي المتعدّد المتغيّرات، أتضح أن عوامل الاختطار التي يُعتدُّ بها إحصائياً للإصابة بحصيات المرارة هي الأنوثة، والسوابق العائلية لحصيات المرارة وسوابق الإصابة بالتهاب البنكرياس. أما العمر، والتعليم، وضغط الدم، والتدخين، وتناول القهوة، والبدانة، والسكري، وعدد الأحمال واستخدام مانعات الحمل بالفم، فلم تكن من عوامل الاختطار التي يُعتدُّ بها إحصائياً. وقد أظهر التحليل التفاضلي للأعراض أن الآلام في المَرَأَقِ اليمَنِي تترافق ترافقاً يُعتدُّ به إحصائياً بحصيات المرارة.

ABSTRACT To study the prevalence of gallstone disease and related risk factors in a Saudi Arabian population a cross-sectional community-based study was made of 291 people from Abha district, Asir region. A structured interview collected background data and all participants had upper abdominal ultrasonography to detect gallstones. The overall prevalence of gallstone disease was 11.7%. Using logistic regression multivariate analysis, the following were significant risk factors for gallstone disease: female sex, family history of gallstone disease and past history of pancreatitis. Age, education, blood pressure, smoking, coffee intake, overweight, diabetes mellitus, number of pregnancies and use of oral contraceptives were not significant risk factors. Discriminant analysis of symptoms showed that only right hypochondrium pain was significantly associated with gallstone disease.

Prévalence et facteurs de risque de la lithiase biliaire dans une population saoudienne de haute altitude

RÉSUMÉ Afin de déterminer la prévalence et les facteurs de risque de la lithiase biliaire dans une population saoudienne, il a été mené une étude transversale en population générale à partir de 291 habitants du district d'Abha, dans la région d'Asir. Un entretien structuré a permis la collecte des données fondamentales et tous les participants ont subi une échographie abdominale visant à détecter la présence de calculs biliaires. La prévalence globale de la lithiase biliaire était de 11,7 %. L'analyse de régression logistique multiple a montré que le sexe féminin, une histoire familiale de lithiase biliaire et des antécédents de pancréatite étaient des facteurs de risque de lithiase biliaire significatifs. L'âge, le niveau d'instruction, la pression artérielle, le tabagisme, la consommation de café, les surpoids, le diabète sucré, le nombre de grossesses et la contraception orale ne sont pas apparus comme des facteurs de risque significatifs. L'analyse discriminante des symptômes a révélé que seule la douleur de l'hypochondre droit était associée de manière significative à la lithiase biliaire.

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Introduction

Asir region (population 1 200 000) is located in the southwest of Saudi Arabia covering an area of more than 80 000 km². The region extends from the high mountains of Sarawat (with an altitude of 3200 m above sea level) to the Red Sea, and lies a few kilometers from the northern border of neighbouring Yemen. The region is divided into 15 health districts. Primary health care services in Abha health district are provided through a widespread network of 36 urban and rural primary health care centres, providing services to 129 465 people. Each primary health care centre has a well-defined catchment area and population.

Gallstone disease is a major cause of morbidity, and sometimes mortality, throughout the world. About 320 cholecystectomies are performed every year in Asir Central Hospital, an affiliated teaching hospital with 550 beds. This only reflects the magnitude of symptomatic gallstone disease in our region. However, in other reports, more than 70% of individuals had asymptomatic gallstone disease [1,2]. The change in lifestyle among Saudis in recent years may suggest that the condition is of increasing health importance.

The prevalence of gallstone disease has been little studied on a community basis in Saudi Arabia. Therefore, we decided to study the prevalence of gallstone disease and related risk factors in Abha region at a community level.

Methods

Sample

The minimum sample size required for the study was calculated to be 264 cases, with an anticipated population proportion of 20%, and with an absolute precision of 5% at 95% confidence interval [3]. To

avoid loss of cases, a total of 300 cases was planned to be collected. They were selected using a cluster sampling technique from the catchment areas of the 36 primary health care centres in Abha region. To ensure equal involvement of adult males and females in the study, couples were regarded as the study unit. Through house-to-house survey, couples were contacted and asked to attend their local primary health care centre.

Data collection

At the primary health care centre couples were interviewed using a structured observation and interview questionnaires to collect data about sociodemographic factors, habits, past history of right hypochondrial pain, pancreatitis or any other diseases, and family history of diseases, especially gallstone disease. History of pancreatitis was obtained by reviewing case records (based on feedback of results of prior referral to hospital, serum amylase and lipase results and/or positive findings on ultrasonography) [4].

Blood pressure was measured at least twice, in a controlled environment, after at least 3 to 5 min of rest in the seated position. The subject was asked to sit exposing his/her arm then using a sphygmomanometer and stethoscope the systolic pressure was recorded when the first Korotkoff sound appeared while the diastolic pressure was recorded when the sound disappeared in Korotkoff phase V. The average of 2 readings was recorded. WHO definitions were used as the cut-off for hypertension: systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg [5].

Height was measured to the nearest 0.1 cm using measuring tape and weight was measured using a standardized measuring scale to the nearest 0.1 kg. Body mass index (BMI) was calculated and overweight was defined as BMI \geq 25 kg/m² [6].

Upper abdominal ultrasonography examination was performed on each person for detection of gallstone disease. Ultrasonography remains the method of choice for the diagnosis of gallstone disease, offering a number of advantages: it is non-invasive, there is no ionizing radiation, it is relatively inexpensive and adjacent organs can also be assessed. It also has a high sensitivity (97%), specificity (93.6%) and diagnostic accuracy (93.0%) [7]. Ultrasonography provides better results than computerized tomography and similar results to those of perioral cholecystography in determining the number and diameter of the stones. The sensitivity of ultrasonography in diagnosing gallbladder stones is comparable to magnetic resonance cholangiography (97.7%) [7].

Analysis

Data were coded, validated and analysed using SPSS PC + software package, version 13. Univariate analysis methods were used at the 5% level of significance. Multivariate logistic regression analysis was used to identify potential risk factors. Kappa statistics were calculated to measure agreement between symptoms and ultrasonography findings. To study the reliability and validity of symptoms (as mentioned by respondents) and ultrasonography findings in detecting gallstone disease, stepwise discriminant analysis was used.

Results

A total of 291 persons (response rate 97%) were included in the present study (143 males and 148 females). Age range was 25–85 years with a mean of 44.3 [standard deviation (SD) = 10.2] years and a median of 43.0 years. The mean age of males [48.6 years (SD = 10.3)] was significantly higher than that of females [40.3 years (SD = 8.4)] ($t = 7.529$, $P < 0.05$).

A total of 34 cases had positive findings of gallstone disease by ultrasound (4 cases had already had cholecystectomy and 30 had gallstones). There were 6 males and 28 females. The overall prevalence of gallstone disease was 11.7% [95% confidence interval (CI): 8.4–15.7]. The prevalence in males and females was 4.2% (95% CI: 1.7–8.5) and 19.9% (95% CI: 13.2–25.8) respectively.

Among positive gallstone cases, a single stone was found in 19 cases (63.3%), and thick-walled gallbladders were found in 5 cases (16.7%). Furthermore, 26 cases (86.7%) with stones were newly discovered, of which 16 (61.5%) had one or more symptoms suggestive of gallstone disease, and only 10 (38.5%) were asymptomatic.

Table 1 shows the agreement of symptoms with ultrasonography findings. Right hypochondrial pain was found to be significantly associated with positive ultrasonography findings for gallstone disease ($\kappa = 0.148$, $P = 0.002$).

The results of discriminant analysis of symptoms reported by respondents are shown in Table 2. Only right hypochondrial pain was significantly associated with gallstone disease (a low value of Wilks λ , canonical correlation and $P < 0.05$). This symptom had a high sensitivity and specificity of more than 70% in detecting gallstone disease.

In univariate analysis, gallstone disease was common among females, illiterate patients, smokers and those aged > 40 years. It was also common among people having a past history of pancreatitis and family history of gallstone disease.

Using logistic regression multivariate analysis (Table 3), it was clear that people with a past history of pancreatitis were 11 times more likely to have gallstone disease (adjusted OR = 11.5; 95% CI: 7.1–15.5) than people with no history of pancreatitis. Similarly, the following factors were also

Table 1 Agreement of gallbladder symptoms with ultrasonography findings

Symptom	No. of patients	Prevalence of gallstone disease (%)	Agreement κ -statistic	P-value
Jaundice	14	14.3	0.106	0.074
Right hypochondrium pain	95	20.0	0.148	0.002*
Flatulence	149	16.1	0.089	0.062
Dyspepsia	132	15.2	0.068	0.093

*Significant ($P < 0.05$).

identified as significant risk factors for gallstone disease: female sex (adjusted OR = 4.2; 95% CI: 1.3–13.6) and family history of gallbladder stones (adjusted OR = 3.4; 95% CI: 1.3–8.7). On the other hand, age, education, blood pressure, smoking, coffee intake, overweight, diabetes, number of pregnancies and use of contraceptives among females were not significant.

Discussion

Cholecystectomy is one of the most common operations performed in general surgical units throughout Saudi Arabia. It comprises about 47% of major and 23% of total gen-

eral surgical operations in our hospital in Abha city and 15%–50% of all laparotomies in 2 different studies from Medina city [1,8]. These data give the impression that gallstone disease is common among Saudi Arabians. However, apart from a few scattered reports on gallstone disease from different parts of Saudi Arabia [1,8–12], the prevalence of gallstone disease at the country level has not been determined yet. Whereas the prevalence of gallstone disease in our series was 11.7%, it was 4.4% in a study group of 1604 pregnant women from Al Kharj Military Hospital [11]. In other parts of the world, varying figures were given for the prevalence of gallstones,

Table 2 Discriminant analysis model: potential association of symptoms (as reported by respondents) with gallbladder stones (ultrasonography findings)

Symptom	Wilks λ	Canonical correlation	F-statistic	% patients correctly classified	Sensitivity %	Specificity %	Overall %
Jaundice	0.986	0.063	4.004	15.8	44.6	47.7	
Right hypochondrium pain	0.218	0.175	9.603*	71.3	74.8	72.4	
Flatulence	0.981	0.081	3.867	50.8	21.6	52.9	
Dyspepsia	0.991	0.051	2.823	43.1	49.2	47.7	

*Significant ($P < 0.05$).

Table 3 Multivariate logistic regression model: adjusted odds ratios (OR) and 95% confidence intervals (95% CI) of potential risk factors in developing gallbladder stones

Variable	No. screened	% positive	Adjusted OR	95% CI
<i>Age (years)</i>				
< 40	103	9.7		
40+	188	12.8	1.39	0.57–3.40
<i>Education</i>				
Educated	179	7.8		
Illiterate	112	17.9	1.68	0.69–4.12
<i>Hypertension</i>				
Normotensive	265	12.1		
Hypertensive	26	7.7	0.57	0.06–5.03
<i>Smoking habit</i>				
Non-smoker	258	10.9		
Smoker	33	18.2	1.61	0.29–8.95
<i>Coffee intake</i>				
No	203	11.3		
Yes	88	12.5	1.07	0.45–2.55
<i>Diabetes mellitus</i>				
Non-diabetic	248	12.1		
Diabetic	43	9.3	0.435	0.11–1.77
<i>Sex</i>				
Male	143	4.2		
Female	148	18.9	4.24	1.32–13.58*
<i>Family history of gallbladder stones</i>				
No	255	9.4		
Yes	36	27.8	3.41	1.32–8.78*
<i>History of pancreatitis</i>				
No	287	10.8		
Yes	4	75.0	11.52	7.06–15.54*
<i>Obesity</i>				
BMI < 25 kg/m ²	64	9.4		
BMI ≥ 25 kg/m ²	217	12.9	1.46	0.53–4.24

*Significant ($P < 0.05$).

BMI = body mass index.

OR = odds ratio; CI = confidence interval.

ranging from 4% to more than 20% (Tunisia 4.1%, Islamic Republic of Iran 4.7%, Bangladesh 5.4%, Peru 10.7%, Germany 7.8%,

New Zealand 20.8% and United States of America 10%–15%) [13–19].

It is known that the pathogenesis of gallstone disease is related to imbalance

in the metabolic and dynamic process of cholesterol and bile acids. This can be directly influenced by genetic, hormonal and metabolic factors. Although the association between gallstone disease and "fat, fertile, female and forty" has been observed and taught for a long time, it has a limited support in formal epidemiological studies [10]. It has been known that female sex, race, obesity, diabetes mellitus, ageing, cirrhosis, type IV hyperlipidaemia, parity, oral contraceptive use, smoking, and family history of gallstone disease are risk factors for gallstone formation [1,2,11,12,20-28]. In our study, only female sex and family history of gallstone and/or past history of pancreatitis were found to be significant risk factors. These findings agree with the findings in other national reports, although some of them added other risk factors including obesity, BMI > 30 kg/m² and parity [1,9-12]. This inconsistency could be attributed to the environmental and genetic differences among different societies.

Few studies have sought to describe the prevalence of gallstones in high altitude communities. Moro et al., in their study of gallstone disease in high altitude Peruvian rural populations (> 3000 m above sea level), reported that high altitude was not a positive risk factor for gallstone disease [16]. On the other hand, Spathis et al. [29] reported high rates of gallstones among high altitude villagers of Ladakh, India. They attributed this rate to slow intestinal transit time that can lead to constipation, increased bilirubin absorption and higher bile concentrations in the gallbladder [16,29]. In addition, increased blood cell formation and hence increased haemolysis may increase levels of bilirubin pigments with an increased risk of pigment gallstones [30]. Our region is one of the highest altitude regions in the Middle East (> 3000 m above sea level). This may be one of the etiological

factors contributing to the high prevalence in our area, but it is difficult to draw firm conclusions without a comparative study between high and low altitude areas in this regard.

In contrast to similar reports from America and Europe, where more than two thirds of gallstones were asymptomatic [19,23], more than 60% of our cases had symptoms. The low prevalence of symptomatic gallstones in cross-sectional surveys from the industrialized countries is probably due to rapid diagnosis and treatment [31]. Controversies exist about the management of asymptomatic gallstones, particularly in the era of laparoscopic surgery [32-35]. Nearly 10% of individuals with asymptomatic gallstones may develop symptoms or complications requiring treatment within 5 years [36].

We found that female sex, history of right hypochondrium pain, family history of gallstone disease, and/or past history of pancreatitis, were significantly associated with gallstone disease and this agrees with other reports [9,37]. It has also been reported that acute pancreatitis seen in Asir region is predominantly biliary and more frequent in females [38].

Although gallstone disease has complications, the treatment (cholecystectomy) has its own risks as well. Complications of gallstone disease range from simple recurrent biliary colic to severe, life-threatening ascending cholangitis and/or pancreatitis. Carcinoma of the gallbladder had been postulated to be intimately associated with long-standing gallstone disease, particularly when large or numerous cholesterol gallstones are present and in elderly female patients [39,40]. Furthermore, gallstone disease is thought to be a risk factor for pancreaticobiliary cancer, particularly in patients with choledocholithiasis [41].

Most decision analysis studies do not favour prophylactic cholecystectomy for asymptomatic cholelithiasis. Nonetheless, many studies have listed certain criteria for carrying out elective cholecystectomy in asymptomatic patients, including: life expectancy > 20 years, calculi > 3 cm in diameter, particularly in individuals in geographical regions with a high prevalence of gallbladder cancer or calculi < 3 mm, chronically obliterated cystic duct, non-functioning gallbladder and calcified (porcelain) gallbladder. This, in turn, has given rise to a great deal of controversy regarding the optimal management of asymptomatic or "silent" gallstones. While cholecystectomy is the undisputed gold standard treatment for symptomatic gallstones, the natural history of silent gallstones is not known well enough to recommend a definitive therapeutic strategy for such patients. The treatment options for asymptomatic or silent gallstones range from no treatment to selective cholecystectomy in the at-risk group to elective cholecystectomy in all patients. There are a large number of proponents for each of these options so each merits careful consideration [42].

In conclusion, gallstone disease is prevalent in the community of Asir region of

Saudi Arabia (11.7%). Primary health care physicians in the region should pay more attention to patients with right hypochondrial pain, especially if they are women, with family history of gallstone disease and/or having a past history of pancreatitis. They should be referred for upper abdominal ultrasonography for screening and early detection of gallstone disease. We would like to emphasize that a fundamental knowledge of gallstone disease and its complications is essential for clinicians. Thus, high-risk groups might be identified and a realistic approach for prophylaxis for any reversible risk factors could then be offered.

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