Original Article

Prevalence and Risk Factors of Cholelithiasis in Amol City, Northern Iran: A Population Based Study

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Abstract

Background: Cholelithiasis is one of the most prevalent gastrointestinal disorders requiring hospitalization. While different factors influence gallstone formation in patients, these factors are not the same in different societies or in different geographical locations.

Aim: To evaluate the epidemiology and risk factors associated with gallstone formation in a large population group, the present survey was conducted in northern Iran.

Methods: In 6143 asymptomatic subjects, the incidence of gallstone formation as well as risk factors were evaluated through a structured questionnaire, physical examination and ultrasonography study. Sample selection was based on stratified cluster systemic randomization.

Results: Of these enrolled subjects 3507 (57.1%) were male and 2636 (42.9%) were female with a mean age of 42.71 ± 17.1 years. The prevalence of gallstones was 0.80%. On multivariate analysis, the risk of gallstone disease is correlated to rural locale, diastolic hypertension, age, and TG levels. However, systolic hypertension, glucose serum levels and obesity were also significantly associated with the presence of gallstones.

Conclusion: The present study proposes that the rate of gallstone disease in northern Iran is lower than previous studies have reported, and that most of the risk factors can be prevented by changes in lifestyle and diet.

Keywords: Cholelithiasis, epidemiology, Iran, risk factors

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Introduction

Cholelithiasis is one of the most prevalent gastrointestinal disorders and an important worldwide health concern.[1] Although gallstone disease characteristically has a low mortality rate, its high morbidity rate has an important economic impact.[2] However, the incidence of this disease does not follow a homogeneous pattern in different parts of the world. Recent reports suggest that in general the frequency of cholelithiasis has increased in some countries during the past few decades although its prevalence is higher in western societies.[2–4] The average prevalence of gallstone disease in western countries is estimated to be more than 10%, and more than 15% of the North American population suffers from this problem.[4,5] In Asian countries the prevalence of gallstone disease is approximately 10%, while this rate in Africans is less than 5%.[2,6–8] Moreover, there have been several studies about the frequency of gallstone disease in the Middle Eastern countries; in general, the rates range from 4% – 12% in this region.[8–10]

Some risk factors are closely related to *Cholelithiasis*. Gender, race, age, obesity, dislipidemia, usage of contraceptives, diabetes mellitus (DM) and alcohol consumption are usually reported in this context.[2,11–13] The risk factors of gallstone formation are not the same in different parts of the world;[7] therefore it would seem that the first step for management of this disease is recognition of the rate of cholelithiasis and consequently its risk factors in different societies. However, changes in lifestyle and trends toward high energy diets during the last few decades have influenced gallstone prevalence.[7,14] Therefore, knowledge about the epidemiology of this disease is an important issue for planning preventative programs and also diagnostic and therapeutic strategies.

In Iran, few studies have been conducted about the prevalence and risk factors of gallstone disease. The majority of them are autopsy- or hospital-based studies that failed to provide a true estimation of gallstone disease in the general population. Additionally, these studies encountered limitations regarding data collection and patient evaluation procedures. Patients also may remain asymptomatic or opt not to seek medical care or hospitalization. Furthermore, each part of Iran has different epidemiological factors that might influence the prevalence of gallstone disease. With these limitations in mind, the present study attempts to design a large survey of gallstone disease in a territory of northern Iran.

The city of Amol is one of the largest cities in northern Iran; it has a population of approximately 300,000 which includes the rural inhabitants of surrounding villages. This area has a homogeneous population with a well-developed public health service. The Gastro-Intestinal and Liver Disease Research Center (GILDRC) has conducted a multidisciplinary cohort study of the general population of Amol and its surrounding areas since 2008. The objective of this study was to obtain an estimation of gallstone prevalence and its risk factors in this region of Iran.

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Materials and Methods

This is a population based study of asymptomatic adults residing in urban and rural areas of Amol city in northern Iran. Sample selection was based on multistage sampling in health centers between 2008 – 2010. According to the Iranian health policy, every person in urban and rural areas in entitled to primary health care services provided at health centers located throughout the country. In this study, these centers were defined as a "strata" and samples were collected from each health center. By a multiple-stage sampling method, we selected all Health Centers and samples were collected from each health Center based on its population. In each household two samples (one male and one female) selected randomly. A total of 6143 subjects were involved in this study.

The research team scheduled a face-to-face interview with all eligible participants. If a subject refused or was unable to participate or was absent at the three consecutive pre-arranged appointments of study, another person from the same cluster who matched for sex and age was selected. The inclusion criteria were, first: being a permanent resident of this region, second: desire for participation in the study and third: age over 10 years old.

At the outset of the study, the procedure was described to the participants; consequently a questionnaire including demographic, anthropometric, drug and clinical histories was completed for each individual under the direction and assistance of a trained health care professional (*behvarz*). A *behvarz* is a nursing assistant who has basic health care knowledge. In the next step, all participants were referred to the Haraz Research Center, a branch of the Gastro-Intestinal and Liver Disease Research Center (GILDRC) for complimentary clinical and paraclinical evaluations. All participants underwent abdominal ultra sonography (Esaote My lab 50) by an experienced radiologist. Ultrasound was set for multi frequency at a wavelength between 2.7 to 5 (greater wavelength for obese subjects and less for non-obese subjects). The liver and gall bladder were examined by a convex probe. A 30-ml blood sample (after a 14-hour fasting period) was taken from each participant for evaluation of triglyceride levels, cholesterol levels, blood urea, nitrogen, creatinine and insulin levels. All blood exams were performed at Haraz Research Center. According to the AHA (American Heart Association)[15] the normal blood pressure (BP) was defined as systolic BP equal to 90 – 120 and diastolic BP equal to 60 – 80 millimeters of mercury (mmHg). Non-Alcoholic Fatty Liver Disease (NAFLD) was defined as the presence of steatosis in ultrasonography in the lack of significant alcohol consumption.[16] Obesity was also defined as body mass index (BMI) ≥ 30. The study was approved by the Board of Ethics of the GILDRC and written consent was obtained from each participant.

Statistical analysis

All statistical analyses were performed by using the stata version 10.0. The data was weighted and analyzed using a survey analysis (svy) command. The *P*-value less than 0.05 was considered significant. The prevalence of data was assessed by descriptive analysis. Data is presented as the mean ± standard deviation (SD). The association between the presence of gallstones and risk factors was evaluated using multilevel logistic regression. The significance level for multivariate analyses was 0.1. The risk of developing gallstones was estimated by using odds ratios and 95% Confidence Interval (CI).

Results

A total of 6143 eligible subjects were enrolled in this study; 3507 (57.1%) were male and 2636 (42.9%) were female. Mean age was 42.71 ± 17.1 years. The prevalence of gallstone disease was 0.8% (95% CI: 0.6 – 1). Demographic characteristics, evaluated risk factors and prevalence of gallstones in each subgroup are shown in Tables 1 and 2. Higher age, rural habitat, diastolic hypertension, systolic hypertension, increased glucose serum levels, increased TG serum levels, increased cholesterol serum levels, and obesity were all significantly associated with the presence of gallstone disease (Table 1 and 2).

Table 3 shows the results of multivariate analysis. The binary logistic regression model shows that age, residency state (rural or urban locale), diastolic hypertension and serum triglyceride levels are potential predictors of gallstone disease. Based on multivariate analysis the risk of gallstone disease is associated with rural locale, diastolic hypertension, age, and TG levels (Table 3).

Discussion

This study aims to evaluate the prevalence and risk factors of gallstone disease among a large population in northern of Iran in order to provide epidemiological information of gallstone disease in this region. The prevalence of gallstone disease in the present study was only 0.8%, regardless of the gender of the participants. This finding is much lower than previous reports.[3,7,9] Maserat, et al.

Table 1. Association between gallstone disease and binary independent variables

Independent variable	Gallstone state		*P*-value
	No	Yes	
Gender			0.19
Male	3437 (99.24)	25 (0.76)	
Female	2591 (98.86)	26 (1.14)	
Resident state			< 0.0001
City	3080 (99.65)	14 (0.35)	
Village	2948 (98.54)	37 (1.46)	
HBV	61 (98.19)	1 (1.81)	0.48
HCV	6 (100)	0 (0)	0.82
Diastolic hypertension	1453 (98.43)	21 (1.57)	0.01
Systolic hypertension	1114 (98.45)	18 (1.55)	0.025
NAFLD	401 (99.72)	1 (0.28)	0.19
Obesity	3977 (98.87)	40 (1.13)	0.02

Table 2. Association between gallstone disease and continuous independent variables

Independent variable	Gallstone state		*P*-value
	No	Yes	
Age in year	42.46 ± 19.42	55.91 ± 16.57	< 0.001
Glucose serum level, mg/dL	100.41 ± 41.93	115.24 ± 52.77	0.045
TG serum level, mg/dL	134.02 ± 110.24	166.92 ± 131.83	0.076
Cholesterol serum level, mg/dL	180.31 ± 47.36	194.62 ± 42.13	0.016

Table 3. Final multivariate logistic regression analysis of risk factors for the prevalence of *Cholelithiasis* disease

Variable	Adjusted OR (95% CI)	SE	*P*-value
Age†	1.04 (1.02–1.06)	0.01	**< 0.001**
Female	1.76 (0.94–3.28)	0.56	**0.08**
Rural residency	4.84 (2.55–9.19)	1.58	**< 0.001**
Diastolic hypertension‡	2.03 (1.03–3.4)	0.7	**0.04**

†with each increasing year of life; ‡with each increasing mmHg of blood pressure

in southern Iran and Toosi, et al. in eastern Iran reported that the average gallstone rate in asymptomatic subjects was 4.7% and 4.4%, respectively.[10,17] Also many ultrasound-based studies have been conducted in different parts of the world which indicate the prevalence of gallstone disease as between 5.9% – 21.9%.[5,10] These differences may be related to the diets and lifestyles of the various regions.

According to the present study, the risk factors were increased age, obesity, hypertension, high levels of triglyceride, hypercholesterolemia and diabetes mellitus. These findings emphasize the importance of environmental factors in gallstone formation. Many studies concerning gallstone risk factors have been conducted in western societies and developed Asian countries. According to these studies, age, sex, race, obesity and metabolic syndrome are important factors in the development of gallstone disease.[4,5,8,11,13,14,18] It is expected that with increasing age the occurrence of gallstone disease is enhanced. This may be due to the longer time exposure of subjects to gallstone risk factors. In multivariate analysis, the present study found that increased age was correlated to gallstone formation (OR = 1.04, 95% CI: 1.02 – 1.06). This result is comparable to previous reports.[2,5,7] The present study also shows there is no gender bias (P = 0.15). The sex factor role in the development of gallstone disease is controversial. According to different studies, the female gender has a higher prevalence of gallstone formation. Most of these studies were conducted as hospital-based studies in western societies where cholesterol type gallstone disease is more common. Gallstone formation often occurs during the fertile years of a woman's life.[19] Hormone replacement therapy and oral contraceptive use were also known as risk factors for gallstone disease.[12,20,21] This may be due to the fact that the female sex hormone increases cholesterol saturation in bile and can lead to cholesterol gallstone formation.[19,22] The present study did not focus on types of gallstones. However it is notable that the large sampling utilized in this study and the use of ultrasonography as a diagnostic tool have increased the information reliability.

Obesity, dyslipidemia, diabetes mellitus, hypertension and NAFLD are typically considered manifestations of the metabolic syndrome (Table 2). In this survey approximately 7.4% of the subjects were overweight or obese. Although the prevalence of obesity in Iran is less than western countries, many believe it will be a health problem in the near future. In fact, a strong relation between obesity and cardiovascular and gallstone disease has been reported. Recent studies indicate that cholesterol gallstones may be a manifestation of metabolic syndrome.[7] Furthermore, obesity, especially abdominal obesity, is a known risk factor of gallstone disease.[23,24] It has been estimated that about 25% of morbidly obese subjects suffer from gallstone disease. The possible mechanism of association between obesity and gallstones increases cholesterol synthesis in the liver and cholesterol-supersaturated bile in obese subjects which consequently multiplies their risk of gallstone formation.[7,25]

Few studies have reported an association between blood pressure and gallstone formation. Studies in China and Taiwan have confirmed that cholelithiasis in obese patients is closely related to increased diastolic blood pressure.[18,26] The present study also confirms an association between hypertension and gallstone disease. It is still unclear that how does hypertension influence gallstone formation, however it may be related to the action of insulin resistance in metabolic syndrome. The association between presence of diabetes mellitus and the incidence of gall stones is a controversy issue. However, the prevalence of gallstones among diabetic patients in previous studies was higher than the general population (24.8% – 32 %) but DM is a risk factor for gallstone disease has not been confirmed.[9,18,27] This could be due to different epidemiological approaches or selection bias in these studies. The present study found a relationship between DM and gallstone formation in univariate analysis without gender bias. As in this study, a majority of studies in Iran confirmed a correlation between diabetes and gallstone disease. Toosi, et al. revealed that diabetes mellitus (OR = 26.18) could be considered a risk factor in gallstone formation in eastern Iran.[10] Shaffer, et al. concluded that the effect of DM on gallstone formation is influenced by several co-factors such as obesity, gender and family history of gallstones.[28] Possible mechanisms of DM in gallstone formation are: easy cholesterol supersaturation in bile; reduced ejection fraction of the gallbladder and increased volume of the gallbladder in fasting phase among DM patients.[27]

Furthermore, we found an association between cholesterol levels and gallstone disease in univariate analysis, but it was not confirmed in multivariate analysis. High levels of TG were significantly associated with the presence of gallstones in this study. This result compatible with previous studies.[14,28,29] Similarly, fatty liver disease is a condition that is usually detected by ultrasonography. Detection of NAFLD by ultrasonography is typically person-dependent and the results have to be interpreted cautiously. The

prevalence of NAFLD was considerable in the present study, but the incidence of gallstone formation among those affected was, conversely, very low (Table2). In summary, this study as well as many other studies did not find a notable association between gallstone disease and NAFLD.[30,31]

Chronic liver disease and liver cirrhosis are considered risk factors for gallstone formation according to some reports.[32,33] Hepatitis B (HBV) is an endemic disease in Iran. The rate of infection of HBV in this study was lower than in the general population of Iran. In addition, this study did not find a correlation between hepatitis B and hepatitis C and gallstone formation, although in some studies a correlation between hepatitis C and gallstone disease has been reported.[11,33,34]

A study conducted by Unisa, et al. in rural areas of India, reported a prevalence of 6.2% for gallstone disease that was associated with increased age, diabetes, unsafe water use and water pollution with metal elements.[35] Chen, et al. from rural areas of Taiwan reported an overall prevalence of about 5% associated with age and fatty liver conditions in both sexes.[14] One of the noteworthy aspects of the present study is its wide-ranging, inclusive format, evaluating participants from both rural and urban areas. The proportion of rural and urban inhabitants in the study was approximately the same, but interestingly, rural residents had a significantly higher prevalence of gallstone formation (OR = 3.29). A lower rate of gallstone disease is typically expected in rural areas; in this territory the rural and urban areas are in close proximity and the inhabitants share similar lifestyles.

In conclusion, the present study aims to show that the rate of gallstone disease in northern Iran is much lower than those indicated by previous reports. Despite the low gallstone incidence in this survey, increased age, diastolic hypertension and also rural residency were important factors associated with gallstone formation in a multivariate analysis. The authors also propose that many of the risk factors could be reduced or prevented through changes in lifestyle and diet.

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