

Sex Difference as a Risk Factor for Gallstone Disease

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Abstract

Background: Gallstone disease is a common clinical entity affecting the adult population of both sexes.

Aim of the study: The objective of present investigation was to compare the impact of sex, age and BMI on the gallstone disease.

Subject and Methods: A total of 150 subjects whom suffered from gallstones visible by ultrasound were considered as cases aged (48.52 ± 9.534) years comprised from 19 men and 131 women and subjects negative for gallstones were classified as controls, consist of 50 parsons aged (27.96 ± 6.72) years, 14 males and 36 females.

Results and Discussion: The results of analysis of individual factors and their association with women were affected nearly fivefold than men (5:1). The objectives of present investigation were to compare the impact of sex, age and BMI on the gallstone disease. In order to identify the risk factors, we further performed a multivariate logistic regression analysis. The factors significantly (OR 5.40, 95%CI 0.77-46.99; $p = 0.05$, OR 2.80, 95% 0.86-16.12; $p = 0.04$) associated with gallstones disease were an age 30-49 and an age > 50 years (OR 8.25, 1.17-92.97; $p = 0.01$, OR 21.94, 6.72-97.26; $p = 0.0001$) for males and females respectively. High body mass index, however was detected as an independent risk factor for gallstone disease in females (OR 1.96, 0.88- 4.42; $p = 0.05$). In the male population, no such association was present.

Conclusion: Present studies have defined the role of sex difference on the formation of gallstone.

Key words: gallstone, odd ratio, sex, age, BMI.

الخلاصة

تعد حصة المرارة من الأمراض السريرية الشائعة التي تؤثر في المجتمع ولكلا الجنسين. **الهدف:** يهدف البحث الحالي الى مقارنة تأثير كلاً من دور الجنس و العمر و معامل كتلة الجسم على مرض تكوين حصى المرارة.

المواد وطرق العمل: شملت الدراسة 150 مريضاً من الذين يعانون من حصة المرارة وكانوا 19 رجلاً و 131 امرأة و 50 شخصاً من الأشخاص الأصحاء شملوا 14 رجلاً و 36 امرأة.

النتائج ومناقشتها: من خلال الإحصاء التحليلي الإنداري اللوجستي المتعدد، اتضح ان الإناث الأكبر سناً ومتوسط معامل كتلة الجسم أعلى من الذكور هم أكثر عرضة لخطر الإصابة بحصى المرارة، اي أن الجنس الأنثوي هو عامل خطر مسبق لمرض حصى المرارة. حيث كان عامل الخطر لتأثير العمر في كلا الجنسين وللأعمار من 30-49 سنة $OR\ 2.80, 95\% \ 0.86-16.12; p=0.04$ للذكور مقابل $OR\ 5.40, 95\% \ 0.77-46.99; p = 0.05$ للإناث. بينما كان للأعمار الأكثر من 50 سنة التأثير الأكثر خطراً حيث كانت القيم للذكور $OR\ 8.25, (CI\ 95\% \ 1.17-92.97); p=0.01$ وللإناث $OR\ 21.94, (CI\ 95\% \ 6.72-97.26); p=0.0001$ مقابل $OR\ 1.96, 0.88- 4.42; p = 0.05$ للذكور. بينما اتضح ان الإناث الأكبر سناً ومتوسط معامل كتلة الجسم أعلى من الذكور هم أكثر عرضة لخطر الإصابة بحصى المرارة. **الاستنتاج:** أن الجنس الأنثوي هو عامل خطر مسبق لمرض حصى المرارة.

Introduction

Gallstone disease is a common clinical entity affecting the adult population of

both sexes. The earliest known gallstones date back to the 21st Egyptian dynasty discovered in the mummy of a priestess of Amenem (1085-945 BC)⁽¹⁾. Gallstones are

composed mainly of cholesterol, bilirubin, and calcium salts, with smaller amounts of protein and other materials⁽²⁻⁷⁾. At least 10 percent of adults have gallstones⁽⁸⁾. The prevalence varies with age, sex, and ethnic group. Ultrasound surveys^(9,10) show a female: male ratio of about 2:1 in the younger age groups and an increasing prevalence with age; after the age of 60 about 10 to 15 percent of men and 20 to 40 percent of women have gallstones. In a recent ultrasound survey in Denmark, a large population was reexamined at five-year intervals. In each five-year period, new gallstones formed in about 3 percent of the population over the age of 40⁽¹¹⁾. Obesity was defined as a body mass index (BMI) ≥ 25 kg/ m² in both men and women according to the redefined World Health Organization⁽¹²⁾. In order to identify the risk factors, The prevalence of gallstones is especially high in the Scandinavian countries and Chile and among Native Americans. It is higher in markedly obese persons and in those who lose weight rapidly⁽¹³⁾. There is little agreement about the effect of dietary components on the risk of gallstones.

Material and Methods

The prospective study was conducted from April 2006 to 2008 months. A total of 150 patients suffering from cholelithiasis admitted in the surgical ward and confirmed by ultrasonography were included in the study irrespective of their age, sex and BMI. Both laparoscopic and open cholecystectomies were the procedures advocated for treatment. In Al Sader Medical City in al – Najaf the research was carried out.

Statistical analyses

Data on quantitative characteristics are expressed as mean \pm SEM. categorical data are presented as the number of cases and percentages. Odds ratios (ORs) were calculated with the variables coded in

multivariate form, values being given as lower and upper 95%-confidence interval (CI). In all cases tests of significance a value of $p < 0.05$ was considered statistically significant.

Results

A total of 150 subjects who were referred to the consultant of gastrointestinal surgery center by their senior consultant, from April 2006 to 2008, were included; Subjects who had gallstones visible by ultrasound were considered as cases aged (48.52 ± 9.534) years comprised from 19 men and 131 women and subjects negative for gallstones were classified as controls. Which consist of 50 persons aged (27.96 ± 6.72) years, 14 males and 36 females. In order to identify the risk factors, we further performed a multivariate logistic regression analysis; the results are shown in Table 1. Women and aged ≥ 50 years, with a BMI kg per m² ≥ 25 , and men \geq were positively correlated with gallstone disease.

The results of analysis of individual factors and their association with gallstone disease among the 150 subjects explained that the factors significantly associated with gallstone disease were an age of 30-49 years and an age ≥ 50 years, a BMI ≥ 25.0 kg/m². Women were affected nearly fivefold than men (5:1). 87% females and 13 % males given these gender- related differences, all multivariables were performed separately among males and females, these analyses revealed an advanced age, high BMI as a independent risk factor for gallstones. The factors significantly (OR 5.40, 95%CI 0.77-46.99; $p = 0.05$, OR 2.80, 95% 0.86-16.12; $p = 0.04$) associated with gallstones disease were an age 30-49 and an age > 50 years (OR 8.25, 95%CI 1.17-92.97; $p = 0.01$, OR 21.94, 95%CI 6.72-97.26; $p = 0.0001$) for males and females respectively. High body mass index, however was detected as an

independent risk factor for gallstone disease in females (OR 1.96, 95%CI 0.88-4.42; p = 0.05). In the male population, no

such association was present as shown in table.

Table 1: Sex specific independent risk factor for gallstone.

Risk factor	Males OR (95% CI) ⁽ⁿ⁾	p value	Females OR (95% CI) ⁽ⁿ⁾	P value
Age				
30-49 yr	5.40 (0.77-46.99) ^(10/19)	0.05	2.80(0.86-16.12) ^(97/131)	0.04
> 50 yr	8.25(1.17-92.97) ^(8/19)	0.01	21.94(6.72-97.26) ^(35/131)	0.0001
BMI(Kg/m ²)				
> 25	0.59 (0.09-3.69) ^(6/19)	0.85	1.96 (0.88- 4.42) ^(51/131)	0.05

Discussion

The present study investigated a possible association between sex, age and BMI with gallstone disease, there was an independent relation between sex and cholelithiasis among female predominantly among those who had high BMI and older age. In the male population no such associations were identified. The prevalence of gallstone disease among the study subjects was 87% for females and 13 % for males.

In concordance with the findings of previous studies, female sex was also a major risk factor for gallstone disease in the present study. The commonly perceived opinion that women are at greater risk of developing gallstone disease than men may largely be due to extraneous risk factors, such as pregnancy and sex hormones. The number of pregnancies is the main one related to the high rates of gallstone disease in women⁽¹³⁾. Sex hormones are most likely to be responsible for the increased risk. Estrogen increases biliary cholesterol secretion causing cholesterol super saturation of bile⁽¹⁴⁾. Thus, hormone replacement therapy in postmenopausal women has been described to be associated with an increased risk for gallstone disease^(15,16). Some studies have also shown a relation between sex hormone and a high prevalence of gallstone disease. Rains⁽¹⁷⁾ advocated that concentration of bile salts in bile is reduced by estrogen and thereby making it lithogenic. Horn⁽¹⁸⁾ postulated that under the influence of females sex

hormone, the muscle may relax, biliary passage dilates and duodenal content of pancreatic secretion regurgitates into gallbladder and promote conditions which favors the formation of gallstones.

Multivariable analyses attain statistical significance for the association between age and gallstone disease. The biliary output of cholesterol increases with age⁽¹⁹⁾ and as a result of estrogen treatment in men and women^(20, 21). Estrogen treatment also reduces the synthesis of bile acid in women⁽²²⁾.

The present study, in accordance with reports from Western countries and other regions of Asia, showed that an older age is a significant risk factor for gallstone disease⁽²³⁻²⁴⁾. In contrast, gallstone disease is virtually absent in children and adolescents aged 8-19 years⁽²⁵⁾. Long-term exposure to many risk factors, as is true for the elderly, may increase the risk of gallstone disease. At the same time, sedentary activity, which is greater in the elderly than in younger populations, may also increase the risk of gallstone disease^(26,27). Furthermore, gallstone disease is also an acquired disease influenced by chronic environmental factors plus an aging effect⁽²⁸⁾.

In our study, obesity only showed a significant association with gallstone disease in women. Previous studies have found disparate findings for BMI or relative weight in men with gallstone disease⁽²⁹⁻³²⁾. However, three population screening surveys using ultrasonography failed to find a positive association between BMI and gallstone disease in men

in Italy, Denmark, and the United States^(12,27, 28), whereas all three showed a positive association in women. The discrepant findings for BMI in men with gallstone disease have not been fully explained. A possible reason for these findings may be that BMI is not a suitable standard of obesity in men. Waist-to-hip ratio may be a better measure of obesity. The mechanism responsible for the increased risk of gallstone disease in obese persons may be the increase in bile saturation that results from an increase in the biliary secretion of cholesterol, which likely depends on the higher synthesis rate of cholesterol in obese persons⁽²³⁾.

A major limitation of the present study was our measurements were inadequate. Some factors that might play an important role in gallstone disease development, such as waist-to-hip ratio, were not collected in detail.

Conclusion

This study confirmed that age and sex are positive risk factors for gallstone disease; but, the association between metabolic disorders and gallstone disease is different for men and women.

References

1. Strasberg SM, Clavien PA, Harvey PR. Pathogenesis of cholesterol gallstones. *HPB Surg* 1991; 3(2): 79-102.
2. Apstein MD. (1989). Pathophysiology of gallstones and other diseases of the biliary tract. In: Chopra S, May RJ, eds. *Pathophysiology of gastrointestinal diseases*. Boston: Little, Brown, 489-528.
3. Duane WC. (1990): Pathogenesis of gallstones: implications for management. *Hosp Pract [Off Ed]*, 79; 25: 65-76.
4. Donovan JM, Carey MC. (1991): Physical-chemical basis of gallstone formation. *Gastroenterol Clin North Am.* 20: 47-66.
5. Holzbach RT, Busch N. (1991): Nucleation and growth of cholesterol crystals: kinetic determinants in supersaturated native bile. *Gastroentero Clin North Am.*20:67 -84.
6. Trotman BW. (1991): Pigment gallstone disease. *Gastroenter Clin NorthAm.*20:111 126.
7. Strasberg SM, Hofmann AF, eds. (1990): Biliary cholesterol transport and precipitation: proceedings of the Workshop on Frontiers in Gallstone Formation, Airlie House, Warrenton, Va., April 16-19, 1989. *Hepatology*12:Suppl:1S-244S
8. Diehl AK.[1991]: Epidemiology and natural history of gallstone disease. *Gastroenterol Clin North Am.* 20: p 1-19.
9. Heaton KW, Braddon FEM, Mountford RA, Hughes AO, Emmett PM.(1991): Symptomatic and silent gall stones in the community. *Gut.* 32: 316-320.
10. Jensen KH, Jorgensen T.(1991): Incidence of gallstones in a Danish population. *Gastroenterology.* 100: 790-794.
11. Liddle RA, Goldstein RB, Saxton J. (1989): Gallstone formation during weight-reduction dieting. *Arch Intern Med.* 149: 1750-1753.
12. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser* 2000; 894: 1-253.
13. The Rome Group for Epidemiology and Prevention of Cholelithiasis (GREPCO).The epidemiology of gallstone disease in Rome, Italy. II. Factors associated with the disease. *Hepatology*1988;8:907-913
14. Everson GT, McKinley C, Kern F Jr. Mechanisms of gallstone formation in women: effects of exogenous estrogen (Premarin) and dietary cholesterol on hepatic lipid metabolism. *J Clin Invest*1991;87:237-246
15. Youming D, Bin W, Weixing W, Binghua W, Ruoyu L, BangchangC. (2006): The effect of h(1) calponin expression on gallstone formation in pregnancy. *Saudi Med J.* 27: 1661–1666.
16. Tierney S, Nakeeb A, Wong O, Lipsett PA, Sostre S, Pitt HA, Lillemoie KD.(1999): Progesterone alters biliary flow dynamics. *Ann Surg.* 229: 205–209.
17. Rains AJH. (1964) Gallstones. Heinemann Monography. 1st ed.

18. Horn G. (1965): Observations on the etiology of cholelithiasis. *Bri Med J.* 2:732.
19. Maurer KR, Everhart JE, Knowler WC, Shawker TH, Roth HP.(1990): Risk factors for gallstone disease in the Hispanic populations of the United States. *Am J Epidemiol.* 131: 836–844.
20. Khan MK, Jalil MA, Khan MS.(2007): Oral contraceptives in gall stone diseases. *Mymensingh Med J.*16:S40–S45.
21. Kono S, Shinchi K, Ikeda N, Yanai F, Imanishi K. (1992): Prevalence of gallstone disease in relation to smoking, alcohol use, obesity, and glucose tolerance: a study of self-defense officials in Japan. *Am J Epidemiol.* 136: 787–794.
22. Lu SN, Chang WY, Wang LY, Hsieh MY, Chuang WL, Chen SC, Su WP, Tai TY, Wu MM, Chen CJ.(1990): Risk factors for gallstones among Chinese in Taiwan. A community sonographic survey. *J Clin Gastroenterol.* 12: p 542–546.
23. Festi D, Dormi A, Capodicasa S, Staniscia T, Attili AF, Loria P, Pazzi P, Mazzella G, Sama C, Roda E, et al.(2008): Incidence of gallstone disease in Italy: Results from a multicenter, population-based Italian study (the MICOL project) *World J Gastroenterol.* 14: 5282–5289.
24. Kaechele V, Wabitsch M, Thiere D, Kessler AL, Haenle MM, Mayer H, Kratzer W.(2006): Prevalence of gallbladder stone disease in obese children and adolescents: influence of the degree of obesity, sex, and pubertal development. *J Pediatr Gastroenterol Nutr.* 42: 66–70.
25. Kriska AM, Brach JS, Jarvis BJ, Everhart JE, Fabio A, Richardson CR, Howard BV. (2007): Physical activity and gallbladder disease determined by ultrasonography. *Med Sci Sports Exerc.* 39: 1927–1932.
26. Völzke H, Baumeister SE, Alte D, Hoffmann W, Schwahn C, Simon P, John U, Lerch MM.(2005): Independent risk factors for gallstone formation in a region with high cholelithiasis prevalence. *Digestion.* 71: 97–105.
27. Liu CM, Tung TH, Liu JH, Lee WL, Chou P. (2004): A community-based epidemiologic study on gallstone disease among type 2 diabetics in Kinmen, Taiwan. *Dig Dis.* 22: 87–91.
28. Barbara L, Sama C, Morselli Labate AM, Taroni F, Rusticali AG, Festi D, SapiC, Roda E, Banterle C, Puci A.(1987): A population study on the prevalence of gallstone disease: the Sirmione Study. *Hepatology.*7: 913–917.
29. Thijs C, Knipschild P, Leffers P. (1992): Is gallstone disease caused by obesity or by dieting? *Am J Epidemiol.* 135: 274–280.
30. Kato I, Nomura A, Stemmermann GN, Chyou PH. (1992): Prospective study of clinical gallbladder disease and its association with obesity, physical activity, and other factors. *Dig Dis Sci.* 37: 784–790.
31. Jørgensen T.(1989): Gall stones in a Danish population. Relation to weight, physical activity, smoking, coffee consumption, and diabetes mellitus. *Gut.* 30: 528–534.
32. The Rome Group for Epidemiology and Prevention of Cholelithiasis (GREPCO) The epidemiology of gallstone disease in Rome, Italy. Part II. (1988): Factors associated with the disease. *Hepatology.* 8: 907–913.