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Epidemiology of Biliary Lithiasis in a Moroccan Rural Population: Results of a Screening Survey Including 1358 Citizens

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Abstract

Biliary lithiasis is a very frequent and benign pathology but can be the cause of rich and varied symptomatology as well as serious complications. Our study aims to estimate the prevalence and some risk factors of biliary lithiasis and especially to look for the correlation between this pathology and anthropometric measurements. Therefore, we conducted a campaign that included 1358 citizens to perform ultrasound screening for biliary lithiasis, hepatic steatosis, and hydatid cyst. In our study, the prevalence of biliary lithiasis was 19.2%. The average age was 47.7 years with a predominance of women, i.e. a percentage of 76.6%. The risk factors significantly associated with gallstones were abdominal obesity, male sex, and age below 40 years were protective factors, however, neither diabetes nor a history of hypercholesterolemia was associated with the risk of gallstones.

Keywords: Biliary lithiasis, gallstones, pathology, hypercholesterolemia.

INTRODUCTION

Gallstone disease is a condition defined by the presence of one or more stones in the gallbladder, sometimes in the main bile duct and more rarely in the intrahepatic bile ducts. It is a common condition in Western Europe where it affects 25-30% of women and 10-15% of men over 60 years of age [1].

Pregnancy, obesity, type 2 diabetes, metabolic syndrome, ethnicity, and family history are the main risk factors that add to age. Biliary lithiasis is asymptomatic in two-thirds of cases. The most characteristic clinical manifestation is hepatic colic.

In Morocco, there is little or no data on gallstones in the general population. Most studies are retrospective and concern symptomatic patients treated in hospitals, hence the relevance of our study which aims to evaluate the prevalence of gallstones in a rural Moroccan population in the region of Ifrane, to study its epidemiological data, and identify its risk factors.

MATERIAL AND METHODS

This is a prevalence survey as part of an Integrated Action of Prevention and Management of Hydatidosis Province of Ifrane, including several axes: ultrasound screening of hydatid cyst, biliary lithiasis, and hepatic steatosis, conducted over 10 months (July 2018 to April 2019). This survey was conducted by the Hepatogastroenterology Department of the Hassan II University Hospital of Fez in collaboration with the Faculty of Medicine and Pharmacy of Fez, the Association of Gastroenterologists of the Central Region of Morocco (AGERC), the Province of Ifrane, the Delegation of Health of Ifrane, the Delegation of National Education of Ifrane, and the municipalities of the Province of Ifrane. Under this project, 4 screening initiatives have been scheduled from July 2018 to April 2019. The other screening initiative planned in this project has been postponed given the epidemic context of COVID-19. All patients gave verbal consent for testing and inclusion in the study.

RESULTS

The target population for this project is estimated to be 4500 people. 1358 inhabitants (318 women and 1040 men) were screened by ultrasound during the 10 months. Among them, 261 inhabitants had biliary lithiasis, a prevalence of 19.2%.

Table 1: Overview of the study

Target population	**4500**
The number of inhabitants included	1358
Duration of study	10 months
Prevalence of residents with biliary lithiasis	19.2%

The mean age of the inhabitants with biliary lithiasis was 47.7 years [8 years - 96 years]. In our series, the prevalence increased steadily with age. The most affected age group was over 40 years, accounting for 71.2% (n=186) of the total number. Sixty-one patients were male (23.4%) and 200 patients were female (76.6%), for a sex ratio (F/H) of 3.27. Females had a high prevalence compared to males [(14.7%) vs (4.5%)).

A survey revealed the consumption of a high-calorie diet rich in fatty meats, and poor in fiber (fruits and vegetables) in most of our patients (89%). 19 patients (7.2%) had diabetes, and 7 patients (2.7%) had chronic smoking (for more than 20 years).

Among the 261 patients with biliary lithiasis, 7 cases (2.7%) had a history of cholecystectomy. The time between the history of surgery and the discovery of main biliary tract lithiasis ranged from 9 months to 30 years; with a mean of 7.2 years.

Nineteen patients reported similar cases in their families, i.e. 7.3% of the cases.

Vesicular lithiasis was symptomatic in 133 patients for whom hepatic colic was the only specific symptom, i.e. a frequency of 51%.

Table 2: Epidemiological data of the study

Number of inhabitants with biliary lithiasis	261
Mean age	47.7 « 8-96 years »
Sex ratio	F/M de 3.27
Average parity for women	3
Medical history	Diabetes 7.2 % Dyslipidemia 5.4 % Chronic Smoking 2.7% Oral contraceptive use 3.4 % High-calorie diet 89 % Cholecystectomy 2.7 % Case of biliary lithiasis in the family 7.3 %

The average weight of the screened population was 67.3 kg. The average body mass index (BMI) was 26 kg/m2. The average waist circumference was 91.19 cm, with no significant difference between men and women.

Table 3: Clinical data from the study

Symptomatic gallbladder	53%
The average weight of inhabitants with BL	67.3kg
Average BMI of residents with LB	26 kg/m2
An average waist circumference of inhabitants with BL	91.19 cm

Radiologically, an ultrasound revealed lithiasis of the main bile duct in seven patients (2.7% of cases).

Table 4: Morphological data of the study

Lesions	**Number of cases**
Thick-walled VB	7
single lithiasis	200
multiple lithiases	54
Choledochal Lithiasis	7
Hepatic steatosis	183
Renal cyst	45

Lesions	Number of cases
Hydatid cyst	54
Renal lithiasis	10
Pyelocalic dilatation	7
Ovarian cyst	5
Prostate hypertrophy	2

In our study, we conducted an analytical statistical study to identify some risk factors involved in the occurrence of biliary lithiasis. The parameters studied are age, gender, obesity (BMI and waist circumference), history of smoking, history of dyslipidemia, and diabetes, and it was concluded that abdominal obesity (abdominal circumference greater than 88 cm in women and more than 102 cm in men) is a risk factor significantly associated with gallstones with a significant p (p=0.025) and an odds ratio (OR=0.465). However, neither diabetes nor a history of smoking and hypercholesterolemia was associated with the risk of gallstones.

DISCUSSION

Cholelithiasis is a worldwide problem that remains a frequent cause of surgical intervention, contributing significantly to health care costs. However, its prevalence varies considerably from population to population. Until 15 years ago, the frequency of biliary lithiasis was assessed in autopsy studies.

The prevalence of gallstone disease:

Brett and Barker's review [2] pointed out that there is an uneven geographical distribution of the disease. It was found that biliary lithiasis is common in European and North American populations while it is rare in Africans, but as many African countries undergo rapid urbanization with a steady shift to a Western diet, cholelithiasis will become more important in these populations [4]. In the city of Soweto in South Africa, the prevalence in women aged 50-85 years was 10% [5], while in Western Europe it varies from 5.9% to 21.9% [1]. In France and Spain, the prevalence of vesicular lithiasis is about 15% and 9.7% [6] respectively, however, it is 3.2% to 15.6% in Asia [3]. In our study during the 10 months (July 2018 to April 2019), 1358 inhabitants were screened by ultrasound. Among them, 261 inhabitants had biliary lithiasis, a prevalence of 19.2%.

Risk factors for gallstone disease:

- Gender: is one of the most salient risk factors for gallstones. At all ages the prevalence is approximately twice as high in women as in men [3], women generally have an increased risk of cholelithiasis compared to men due to estrogen levels [7], multiparity, and use of estrogen-based oral contraceptives [8, 9]. Studies have also shown that women are more likely to undergo a cholecystectomy procedure than men of all ages [10]. This difference diminishes after age 70 [2].
- Age: Gallstones are very rarely seen before the age of 10 years, and less than 5% of cholecystectomies are performed before the age of 20 years [11]. Epidemiological studies by Framingham in the United States and those in Italy on the prevalence of lithiasis confirm that the prevalence and incidence of lithiasis increase with age and indicate that the majority of diagnoses of gallstones are made between the ages of 50 and 70 [12]. This is probably due to the secretion of cholesterol into the bile that progressively increases with age or to long exposure to environmental factors [13-15], but also due to a decrease in the activity of cholesterol 7 α - hydroxylase, the enzyme that ensures the synthesis of bile acids [16]. The review by Brett and Barker reported that biliary lithiasis is common in European and North American populations while it is rare in Africans [6]. The lowest prevalence (<5%) is seen in African populations and an intermediate frequency in Asian populations (5-20%) [11].
- Heredity and genetic factors: Apart from a few special cases, in the majority of cases, there is no one gene responsible for biliary lithiasis, but it is probably the combination of genetic polymorphisms and environmental factors that explain it [17-19]. A group of familial progressive intrahepatic cholestatic diseases (PFIC) secondary to mutations encoding canalicular transporters of phospholipids or bile salts, has been individualized:
  - PFIC type 3 is characterized by an MDR3 mutation associated with lithiasis.
  - PFIC type 2 is due to a mutation of the ABCB11 gene and manifests itself by intrahepatic cholestasis and is often associated with lithiasis.
  - LPAC syndrome (low phospholipid-associated cholestasis and cholelithiasis) is due to a mutation in the ABCB4 gene which codes for the MDR3 protein, the main canalicular transporter of bile phospholipids. This mutation results in low bile phospholipid concentration, with abnormally high bile cholesterol to phospholipid ratio and bile outside the micellar zone. The transmission of the disease is autosomal recessive. It is manifested by: biliary lithiasis in young patients before 40 years of age and recurs after cholecystectomy, gravitic cholestasis, and severe chronic cholestasis with ductopenia and hepatic fibrosis which can evolve towards biliary cirrhosis [18, 19].
  - Ultrasound shows, in addition to vesicular lithiasis, intrahepatic hyperechoic images that reflect the presence of small stones in the intrahepatic bile

ducts. Ursodeoxycholic acid has remarkable efficacy in LPAC syndrome by increasing the expression of MDR3 protein in the ductal membrane, thus the secretion of phospholipids into the bile, facilitating the dissolution of cholesterol crystals [17-19].

- Family history of lithiasis: Numerous international studies confirm the existence of a familial predisposition in LB, however dietary habits, specific to each family, certainly play a role, especially in childhood. For Filali [20], a family context was found in 15% of cases in his series. This high frequency affects mainly mothers (37.3%), sisters (17.6%), and daughters (10%) of relatives.
- Obesity: which is positively correlated with body mass index (BMI), is also a well-known risk factor for gallstones [21, 22]. In the study by Acalovschi *et al*., [23] of obese women without gallstones at baseline and after a 4-year follow-up, 10% developed gallstones, while the majority remained asymptomatic. Prospective cohort studies have reported a positive association between gallstone formation and central adiposity, compared with upper and lower extremity adiposity. In contrast, weight loss without a change in the waist to hip ratio would increase the risk of gallstone disease in both sexes [24]. Weight loss reduced the risk of gallstones unless it was excessively rapid (i.e., >1.5 kg/week). Rapid weight loss and/or a loss of more than 25% of body weight also increases the possibility of gallstone formation. After bariatric surgery, gallstones developed in 25% to 35% of patients on a 500 kcal diet for 8 weeks [25].
- Lipid profile: Several compelling studies assert a positive association between high cholesterol levels and the development of cholesterol gallstones. However, Thijs *et al*., [26] reported an inverse correlation between cholesterol levels and the risk of gallstones. Other detailed studies examining the relationship between low-density lipoprotein (LDL) levels as well as high-density lipoprotein (HDL) levels and gallstone formation concluded that high cholesterol, high LDL, and low HDL levels increase cholesterol excretion with bile and cause cholesterol gallstone disease. In our series hypercholesterolemia was noted in 13 patients, however, this factor was not associated with the risk of gallstone disease.
- Alcohol consumption is inversely associated with the risk of gallstones. Moderate alcohol consumption may reduce the risk of cholesterol-induced gallstones by reducing biliary cholesterol saturation and increasing HDL cholesterol levels [25]. However, several other studies have failed to find such an association (9-44). Volzke *et al*., [10] reported that the incidence rate of cholelithiasis is higher in men consuming 0 to 20 g of alcohol per day, but lower with a daily intake of 20 to 60 g of alcohol.
- Smoking: Stampfer *et al*., found that excessive smoking (more than 35 cigarettes per day) is a significant risk factor in women for gallstones
- Diet: "Westernized nutrition" has been identified as one of the most powerful determinants of the development of cholesterol gallstones [27, 28]. Two large prospective epidemiologic studies in the United States indicated that high carbohydrate intakes increased the risk of symptomatic gallstones and cholecystectomy in men and women [29]. Similarly, a high-calorie, fiber-depleted diet, because it precipitates increased biliary cholesterol secretion and intestinal hypomobility, may lead to gallstone formation [30]. Other epidemiologic studies have suggested that increased consumption of long-chain saturated fatty acids in the diet is associated with an increased prevalence of gallstone disease in men [31]. In contrast, diets rich in unsaturated fats, coffee, fiber, ascorbic acid, calcium, fish oil, and fresh fruits and vegetables have been found to reduce the risk of cholesterol gallstones [32-34].
- Physical activity: In the literature, physical activity seems to decrease the possibility of developing cholelithiasis. It improves hepatobiliary function by increasing the excretion of bile salts and improving intestinal motility. It also has an indirect protective effect by increasing HDL cholesterol levels and improving plasma triglyceride levels and insulin release, thereby reducing bile cholesterol saturation. Leitzmann *et al*., [36] suggested that 34% of symptomatic gallstones in men could be prevented with 30 minutes of endurance-type exercise five times a week [35-37].
- Parity: It has been commonly accepted since the 19th century that the prevalence of lithiasis increases with the number of pregnancies. Kern et al found an increase in the bile acid pool, a significant decrease in chenodeoxycholic acid, and an increase in cholic acid, as well as a decrease in vesicular emptying and contractility in pregnancy [11]. Lithiasis disease is the most common cause of hospitalization for a non-obstetrical reason in the first year postpartum and 0.8% of women undergo cholecystectomy [11].

CONCLUSION

Cholelithiasis is a worldwide problem and remains a frequent cause of surgical intervention, contributing significantly to health care costs. However, its prevalence varies considerably among populations. Understanding the risk factors for cholelithiasis may not only be useful to help provide education to patients diagnosed with gallstones but also to develop new preventive measures for the disease. In our study the prevalence of gallstones is similar to that of Western countries, it is 19.2% of which 49% were asymptomatic. The risk factor significantly associated with gallstone was abdominal obesity (p=0.025).

REFERENCE

1. Barbara, L., Sama, C., Morselli Labate, A. M., Taroni, F., Rusticali, A. G., & Festi, D. (1987). Une étude de population sur la prévalence de la maladie des calculs biliaires: l'étude Sirmione. *Hepatolo gy (Baltimore, Md)*, 7(5), 913-917.
2. Erlinger, S. (2002). La lithiase biliaire. *Gastroentérologie clinique et biologique*, 26, 1018-1025.
3. Shaffer, E. A. (2005). Épidémiologie et facteurs de risque des calculs biliaires: le paradigme a-t-il changé au 21e siècle? *Rapports actuels de gastroentérologie*, 7(2), 132-140.
4. Rahman, G. A. (2005). Cholélithiase et cholécystite: évolution de la prévalence dans une communauté africaine. *Journal de l'Association médicale nationale*, 97(11), 1534-1538.
5. Walker, A. R. P., Segal, I., Posner, R., Shein, H., Tsotetsi, N. G., & Walker, A. J. (1989). Prevalence of gallstones in elderly black women in Soweto, Johannesburg, as assessed by ultrasound. *American Journal of Gastroenterology (Springer Nature)*, *84*(11), 1383-1385.
6. Safer, L., Bdioui, F., Braham, A., Salem, K. B., Soltani, M. S., & BA, S. H. (2000). Epidémiologie de la lithiase biliaire dans le centre de la Tunisie. Prévalence et facteurs de risque dans une population non sélectionnée. *Gastroenterol Clin Biol*, *24*, 883-887.
7. Moghaddam, T. G., Fakheri, H., Abdi, R., Rostami, F. K., & Bari, Z. (2013). L'incidence et l'issue des boues / calculs biliaires liés à la grossesse et les facteurs de risque potentiels. *Atteint de l'Iranien Médecine*, 16(10), 12-16.
8. Cirillo, D. J., Wallace, R. B., Rodabough, R. J., Groenland, P., LaCroix, A. Z., Limacher, M. C., & Larson, J. C. (2005). Effet de la thérapie oestrogénique sur les maladies de la vésicule biliaire. *JAMA: Le Journal de l'American Medical Association*, 293(3), 330-339.
9. Murray, F. E., Logan, R. F., Hannaford, P. C., & Kay, C. R. (1994). Le tabagisme et la parité en tant que facteurs de risque de développement d'une maladie symptomatique de la vésicule biliaire chez la femme: résultats de l' étude sur la contraception orale du Royal College of General Practitio ners. *Gut*, 35 ans, 107-111.
10. Volzke, H., Baumeister, S. E., Alte, D., Hoffmann, W., Schwahn, C., Simon, P.,… Lerch, M. M. (2005). Facteurs de risque indépendants de formation de calculs biliaires dans une région à forte prévalence de cholélithaisis. *Digestion*, 71, 97–105.
11. Buffet, C., Jacquemin, E., & Erlinger, S. (2008). Physiopathologie, épidémiologie et histoire naturelle de la lithiase biliaire. *EMC Hépatologie*, A10, 4-47.
12. Attili, A. F., Carulli, N., & Roda, E. (1995). Epidemiology of gallstone disease in Italy: prevalence data of the Multicenter Italian study on Cholelithiasis (MICOL). *Am J Epidemiol*, 141, 158-164.
13. Buffet, C., Jacquemin, E., & Erlinger, S. (2008). Physiopathologie, épidémiologie et histoire naturelle de la lithiase biliaire. *EMC (Elsevier Masson SAS, Paris), Hépatologie*, 7-047-A-10.
14. Halldestam, I. (2008). Maladie biliaire: études basées sur la population sur les facteurs de risque, la symptomatologie et les complications [Thèse de doctorat]. Linköping: Université de Linköping.
15. Buffet, C. (2014). Université Paris XI; service hépato-gastro-entérologie adulte, Hôpital de Bicêtre, AP-HP, Le Kremlin-Bicêtre. Lithiase biliaire: facteurs environnementaux et génétiques. *Médecine des maladies métaboliques*, 8(4).
16. Carulli, N., Ponz de Leon, M., Zironi, F., Pinetti, A., Smerieri, A., Iori, R., & Loria, P. (1980). H métabolisme hépatique du cholestérol et des acides biliaires chez les sujets atteints de calculs biliaires: effets comparatifs de l'alimentation à court terme de chénodésoxycholique et d'acide ursodésoxycholique. *The Journal of Lipid Research*, 121, 35-43.
17. Gonzales, E., Davit-Spraul, A., Baussan, C., Buffet, C., Maurice, M., & Jacquemin, E. (2009). Liver diseases related to MDR3 (ABCB4) gene deficiency. *Frontiers in Bioscience (Landmark Edition)*, *14*, 4242-4256.
18. Gotthardt, D., Runz, H., Keitel, V., Fischer, C., Flechtenmacher, C., Wirtenberger, M., ... & Sauer, P. (2008). A mutation in the canalicular phospholipid transporter gene, ABCB4, is associated with cholestasis, ductopenia, and cirrhosis in adults. *Hepatology*, *48*(4), 1157-1166.
19. Lucena, J. F., Herrero, J. I., Quiroga, J., Sangro, B., Garcia-Foncillas, J., Zabalegui, N., ... & Prieto, J. (2003). A multidrug resistance 3 gene mutation causing cholelithiasis, cholestasis of pregnancy, and adulthood biliary cirrhosis. *Gastroenterology*, *124*(4), 1037-1042.
20. Filali, A., Ben Ammar, A., Bouchahda, T., & Garroui, H. (1985). La lithiase biliaire profil épidémiologique, clinique et évolutif. A propos de 402 cas. *Tunisie médicale*, *63*(2), 121-124.
21. Katsika, D., Tuvblad, C., Einarsson, C., Lichtensten, P., & Marschall, H. U. (2007). Indice de masse corporelle, alcool, tabac et maladie symptomatique des calculs biliaires: une étude suédoise sur des jumeaux. *Journal of Internal Medicine*, 262, 581-587.
22. Stender, S., Nordestgaard, B. G., & Tybjaerg-Hansen, A. (2013). Indice de masse corporelle élevé en tant que facteur de risque occasionnel de maladie biliaire symptomatique : une étude de randomisation mendélienne. *Hépatologie*, 58(6), 2133-2141.
23. Chen, C. H., Huang, M. H., Yang, J. C., Nien, C. K., Etheredge, G. D., Yang, C.C., … Yueh, S. K. (2006). Prévalence et facteurs de risque de la maladie des calculs biliaires dans une population

adulte de Taiwan: une enquête épidémiologique. *Hépatologie*, 21(11), 1737-1743.
24. Torgerson, J. S., Lindroos, A. K., Näslund, I., & Peltonen, M. (2003). Gallstones, gallbladder disease, and pancreatitis: Cross-Sectional and 2-year data from the Swedish obese subjects (SOS) and SOS reference studies. *The American Journal of Gastroenterology*, 98(5), 1032-1041.
25. Pixley, F., & Mann, J. (1988). Facteurs diététiques dans l' étiologie des calculs biliaires: une étude cas-témoins. *Gastroentérologie*, 29, 1511-1515.
26. Thijs, C., Knipschild, P., & Brombacher, P. (1990). Lipides sériques et calculs biliaires: une étude cas-témoins. *Gastroentérologie*, 99(3), 843-849.
27. Shaffer, E. A. (2006). Maladie des calculs biliaires: épidémiologie de la maladie des calculs de la vésicule biliaire. *Best Practice and Research Clinical Gastroenterology*, 20, 981-996.
28. Pak, M., & Lindseth, G. (2016). Risk factors for cholelithiasis. *Gastroenterology Nursing*, *39*(4), 297-309.
29. Tsai, C. J., Leitzmann, M. F., Willett, W. C., & Glovannucci, E. L. (2005b). Charge glycémique, index glycémique et apport glucidique en relation avec le risque de cholécystectomie chez la femme. *Gastroentérologie*, 129, 105-112.
30. Shaffer, E. À., & Small, D. M. (1977). Sécrétion de lipides biliaires dans la maladie des calculs biliaires du cholestérol: l'effet de la cholécystectomie et de l'obésité. *Journal of Clinical Investigation*, 59, 828-840.
31. Tsai, C. J., Leitzmann, M. F., Willett, W. C., & Giovannucci, E. L. (2008). Consommation d'acides gras saturés à longue chaîne et risque de maladie de calculs biliaires chez les hommes. *Annuelles de chirurgie*, 247, 95-103.
32. Tsai, C. J., Leitzmann, M. F., Hu, F. B., Willett, W. C., & Giovannucci, E. L. (2004b). Une étude prospective de cohorte sur la consommation de noix et le risque de maladie du tonus des galles. *Journal américain d'épidémiologie*, 160(1), 961-968.
33. Leitzmann, M. F., Stampfer, M. J., Willett, W. C., Spiegelman, D., Colditz, G. A., & Giovannucci, E. L. (2002). La consommation de café est associée à un risque plus faible de maladie biliaire symptomatique chez les femmes. *Gastroentérologie*, 123, 1 823-1830.
34. Simon, J. A., & Hudes, E. S. (2000). Acide ascorbique sérique et prévalence de la maladie de la vésicule biliaire chez les adultes américains: troisième enquête nationale sur la santé et la nutrition. *JAMA: The Journal of the American Medical Association, Internal Medicine*, 160, 931-936.
35. Leitzmann, M. F., Rimm, E. B., Willett, W. C., Splegelman, D., Grodstein, F., Stampfer, M. J., Colditz, G. A., … Glovannucci, E. (1999). Activité physique récréative et risque de cholécystectomie chez la femme. *Le New England Journal of Medicine*, 341(11), 777-784.
36. Leitzmann, M. F., Giovannucci, E. L., Rimm, E. B., Stampfer, M. J., Spiegelman, D., Wing, A. L., & Willett, W. C. (1998). La relation entre l'activité physique et le risque de maladie biliaire symptomatique chez les hommes. *Médecine interne annuelle*, 128, 417-425.
37. Philipp, E., Wilckens, T., Friess, E., Platte, P., & Pirke, K. M. (1992). Cholécystokinine, gastrine et réponse hormonale du stress chez les marathoniens. *Peptides*, 13, 1 25-128.