Prevalence of cholelithiasis in Buenos Aires, Argentina

Mariano Palermo, Darío E Berkowski, Juan Pablo Córdoba, Juan Manuel Verde, Mariano E Giménez

Department of Gastrointestinal Surgery. Hospital de Clínicas José de San Martín, University of Buenos Aires, Argentina.

Acta Gastroenterol Latinoam 2013;43:98-105

Summary

Background. *Cholelithiasis is an important cause of morbidity in the world and it varies significantly depending on the region of study.* ***Objective.*** *To assess the prevalence of cholelithiasis in Buenos Aires.* ***Material and methods.*** *This is a cross-sectional, descriptive, observational study performed in a public hospital with tertiary care in Gastrointestinal Surgery. From July 2010 to December 2011, 1,875 healthy volunteers who underwent liver, gallbladder and pancreas ultrasound imaging were included and a questionnaire containing the individual's medical history was administered. The presence of cholelithiasis and its eventual risk factors were studied.* ***Results.*** *Of 1,875 individuals, 866 were males (46.2%) and 1,009 females (53.8%), older than 20 years old with an average age of 46.1 + 16.7 years. Cholelithiasis was found in 410 inidviduals (21.9%); 285 (15.2%) diagnosed at the time of the study and 125 (6.7%) who had already undergone a cholecystectomy due to gallstones.* ***Conclusions.*** *The prevalence of cholelithiasis in Buenos Aires, capital city of Argentina, is 21.9%. A significant association was found between cholelithiasis and female gender, age, body mass index, history of colic pain, family history of cholelithiasis, smoking, fatty liver and number of pregnancies.*

Key words. *Cholelithiasis, prevalence, risk factors.*

Prevalencia de litiasis vesicular en Buenos Aires, Argentina

Resumen

Antecedentes. *La litiasis vesicular es una importante causa de morbilidad en el mundo y varía significativamente de acuerdo a la región en donde se estudie.* ***Objetivo.*** *Evaluar la prevalencia de litiasis vesicular en Buenos Aires.* ***Material y métodos.*** *Es un estudio observacional, descriptivo, de corte transversal realizado en un hospital público de atención terciaria en Cirugía Gastroenterológica. Entre julio de 2010 y diciembre de 2011 fueron incluidos 1.875 voluntarios sanos a los cuales se les realizó una ecografía hepatobiliopancreática acompañada de un cuestionario en el cual se constataron los antecedentes del individuo. Se estudió la presencia de litiasis vesicular y sus eventuales factores de riesgo.* ***Resultados.*** *De los 1.875 individuos, 866 fueron hombres (46,2%) y 1.009 mujeres (53,8%), mayores de 20 años con una edad promedio de 46,1 ± 16,7 años. La litiasis vesicular se observó en 410 individuos (21,9%); 285 (15,2%) tenían cálculos en el momento del estudio y 125 (6,7%) ya habían sido colecistectomizados por una litiasis vesicular.* ***Conclusiones.*** *La prevalencia de litiasis vesicular en la ciudad de Buenos Aires, capital de la Argentina, es de 21,9%. Se encontró una asociación significativa entre la litiasis vesicular y el sexo femenino, la edad, el índice de masa corporal, los antecedentes de dolor cólico, los antecedentes familiares de litiasis vesicular, el tabaquismo, el hígado graso y la cantidad de embarazos.*

Palabras claves. *Litiasis vesicular, prevalencia, factores de riesgo.*

Cholelithiasis (CHL) is an important cause of morbidity in the world. The prevalence of this disease has been shown in several countries.[1,2] Among published papers, we found series of cases, trials carried out in necropsies and studies whose sample size is not enough to obtain statistically significant results.[3-5] Many published series make emphasis on symptomatic patients that are carriers of CHL in the context of obesity, liver disease, dyslipemia or sedentary habits.[6] However, an important bias in these studies is the lack of inclusion of asymptomatic patients with CHL.

The prevalence of CHL varies significantly according to the region where the study was carried out. It is higher in Western countries and lower in Eastern nations and

Correspondence: *Mariano Palermo*
Av Pte Perón 10298. Ituzaingo. Buenos Aires, Argentina.
Tel: 5411-4481-9995.
E-mail: palermomd@msn.com / gimenezmarianoe@yahoo.com

Africa.[7,8] Therefore, we may infer that studies carried out in each region can only be extrapolated to this region. In Argentina, we found only one publication containing epidemiological data of CHL. This study is methodologically correct and was performed by Brasca et al in the city of Rosario in 2000.[9]

The purpose of this work was to assess the prevalence of CHL in Buenos Aires, Argentina, through an adequate calculation of the sample size. This calculation was made with the statistical software Stata. In addition, epidemiological data, such as gender, age, weight, size, body mass index (BMI), colic pain history, awareness of the presence of CHL, eating habits, history of CHL, clinical and surgical records and pregnancies, were obtained. A complete liver, gallbladder and pancreas ultrasound study was also performed.

Material and methods

The general objective was to assess the prevalence of CHL and its eventual risk factors in Buenos Aires, Argentina and the specific objective to detect CHL in an asymptomatic population older than 18 year old. Our hypothesis was that the prevalence of CHL in Argentina would be around 12%. We designed a cross-sectional, descriptive, and observational study.

Study population

The potential population included all healthy volunteers over 18 years of age and the study population all healthy volunteers attending the University of Buenos Aires School of Medicine, medical and non-medical employees of Hospital de Clínicas José de San Martín, Buenos Aires city and healthy volunteers from Diagnomed, an institution affiliated to the University of Buenos Aires School of Medicine. The research was carried out in the Percutaneous Surgery Section, Gastrointestinal Surgery Division, Hospital de Clínicas José de San Martín, Buenos Aires University. Healthy volunteers meeting eligibility criteria were recruited. Patients attending for abdominal pain or any other type of symptom associated with the presence of CHL were excluded. We also excluded volunteers attending a control for liver, gallbladder and/or pancreas disease and foreign volunteers.

Healthy volunteers did not require any kind of previous preparation. They underwent liver, gallbladder and pancreas ultrasound imaging in the Percutaneous Surgery Section, Gastrointestinal Surgery Division, Hospital de Clínicas José de San Martín, in Diagnomed, or at their workplace.

Material

Two Aloka 500 ultrasound machines and one Voluson Expert ultrasound machine by General Electric were employed, using ultrasound gel. A questionnaire was completed before the ultrasound imaging. This questionnaire included the following data: name, gender, age, history of colic pain, weight, height, BMI, smoking habits, family history of CHL, past medical history (hypertension, diabetes, sedentary lifestayle, hypercholesterolemia), past surgical history (cholecystectomy for gallbladder stones and others), number of pregnancies and place where the ultrasound was done.

Interventions

Every healthy volunteer meeting inclusion criteria entered the research protocol, completed the data collection form and underwent a liver, gallbladder and pancreas ultrasound study to detect the presence of CHL and/or any other associated disorder.

Statistical analysis

To calculate the sample size, it was considered that the prevalence of CHL in the European population is 10%. Therefore, a hypothesis of 12% was assumed. Considering a type I (alpha) error of 5%, a type II (beta) error of 20%, a 1:1 ratio, and an 80% power, the total number of patients to be entered was 1,875. This calculation was made with the statistical software STATA 6.0.

Data of patients joining the study were entered in a SPSS software sheet for the methodological analysis.

Patient follow-up

Asymptomatic volunteers and volunteers with no liver, gallbladder and/or pancreas disorder finding were not followed up. When any of these disorders were detected, patients were adequately advised and referred to the corresponding specialist.

Prognostic variables

In order to assess sample consistency, the following prognostic variables were considered: age, gender, BMI, associated disorders, diet, and clinical and surgical records. Age was expressed in years, weight was expressed in kilograms, colic pain was defined as acute pain in the upper right quadrant or epigastric region, CHL was a condition characterized by the presence of gallstones, macrolithiasis was a condition characterized by the pre-

sence of gallstones larger than 5 mm, microlithiasis was a condition characterized by the presence of gallstones smaller than 5 mm, single gallstone was the presence of one gallstone, multiple lithiasis was the presence of 2 or more gallstones, thickened gallbladder wall was an anterior gallbladder wall measuring more than 4 mm, fatty liver was the accumulation of fat in liver cells evidenced through the ultrasound imaging by a diffuse increase of the echogenicity in the liver parenchyma, liver cyst was a cystic formation in the liver of congenital origin, hereditary or not, with a serous content that does not communicate with the intrahepatic or extrahepatic bile duct, angioma was a benign tumor located in the liver and consisting of a proliferation of blood vessels, and a dilated bile duct was defined as a bile duct diameter exceeding 7 mm or 10 mm in patients with cholecystectomy.

Results

A total of 1,875 individuals were assesed, 866 men (46.2%) and 1,009 women (53.8%) with an average age of 46.1 ± 16.7 years old. No comorbidity or smoking habit was found in 877 cases (46.8%). Smoking was recorded in 387 cases (20.6%), sedentary habits in 624 (33.3%), hypertension in 339 (17.3%), hypercholesterolemia in 295 (15.7%) and diabetes in 124 (6.6%). A history of pregnancy was recorded in 727 women (72.1%): one pregnancy 173, two 323, three 153, and four or more 78.

Cholelithiasis

CHL was found in 410 subjects (21.9%), 285 (15.2%) had gallstones at the time of the study and 125 (6.7%) had previous gallbladder removal because of stones. The lithiasis/cholecystectomy ratio was 1.7:1 in women and 4.5:1 in men. The prevalence of CHL was significantly higher in women (252 of 1,009, 25.0%) than in men (158 of 866, 18.2%) ($P < 0.001$). Nine hundred and fifteen individuals with lithiasis (48.8%) were not aware of their condition. On the other hand, 197 individuals with CHL (48.0%) had a history of colic pain. The prevalence of colic pain was significantly higher in subjects with CHL than in those without CHL (8.6%) ($P < 0.001$). A family background of CHL was recorded in 239 subjects with CHL (48.3%). This proportion was significantly higher than that observed in subjects without CHL (23.3%) ($P < 0.001$). Smoking was more frequent in the individuals with CHL (29.3% versus 18.2%) ($P < 0.001$). The history of pregnancies was also more frequent in women with CHL (77.0% versus 67.6%) ($P = 0.005$). Considering women with more than three pregnancies, 34.8% had cholelihiasis (Table 1).

The prevalence rates of CHL and cholecystectomy increased with age in both genders (Figure 1 and Table 2). In the 30-39 year-old group, the prevalence of CHL was twice higher in women than in men. In the 40-49 year-old group, the prevalence was similar in both genders. In the group older than 50 years old, the prevalence was higher in women again. The frequency of participants with a cholecystectomy was higher in women in all studied age groups.

CHL was multiple in 184 subjects (44.9%). The gallbladder wall was thickened in 15 cases (3.7%). On the other hand, the gallbladder wall was thickened in 11 individuals without CHL (0.8%) ($P < 0.001$). Thirty individuals (1.6%) were diagnosed as having sludge and 25 (1.3%) as having polyps. Bile ducts were normal in every study subject.

The proportion of symptomatic patients with gallstones did not differ significantly among age groups (Table 3).

Table 1. *General characteristics of people with and without CHL.*

Characteristics	Cholelithasis n = 410	No cholelithiasis n = 1,465	Total n = 1,875	*P*
Female gender (n)	134 (61.5%)	405 (51.7%)	539 (53.8%)	0.001
Age (years + SD)	51.4 ± 15.7	44.6 ± 16.6	46.1 ± 16.7	< 0.001
Weight (kg + SD)	73.4 ± 15.5	71.0 ± 15.6	71.6 ± 15.6	0.006
Size (cm + SD)	165.9 ± 8.9	167.1 ± 10.6	166.8 ± 10.2	0.033
Body mass index (+ SD)	26.7 ± 5.2	25.2 ± 4.5	25.6 ± 4.7	< 0.001
History of colic pain (n)	197 (48.0%)	126 (8.6%)	323 (17.2%)	< 0.001
Family history of cholelithiasis (n)	239 (58.3%)	342 (23.3%)	581 (31.0%)	< 0.001
Smoking (n)	120 (29.3%)	267 (18.2%)	387 (20.6%)	< 0.001
Women with history of pregnancy (n)	194 (77.0%)	512 (67.6%)	706 (70.0%)	0.005

Figure 1. *Prevalence rates of cholelithiasis by gender and age group.*

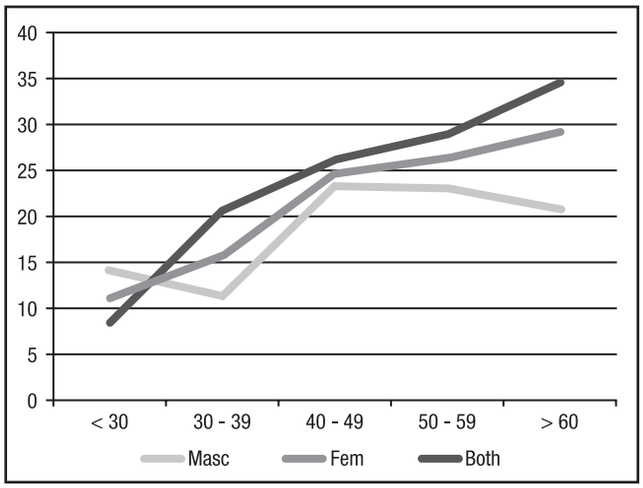

Table 2. *Percent pevalence rates of cholelithiasis and cholecystectomy by gender and age group.*

Age	Cholelithasis Men (%)	Cholelithasis Women (%)	Cholecystectomy Men (%)	Cholecystectomy Women (%)
< 30	12.8	6.2	1.3	2.3
30 – 39	9.0	16.6	2.4	4.1
40 – 49	19.9	14.3	3.5	11.9
50 – 59	19.7	19.0	3.3	10.0
60 – 69	13.2	21.1	7.6	13.6
70 – 79	26.3	18.7	7.0	29.2
≥ 80	8.8	14.3	5.9	14.3

Table 3. *Symptomatic and asymptomatic patients with lithiasis by age group.*

Age (years)	Symptomatic n (%)	Asymptomatic n (%)
< 30	19 (51.4)	18 (48.6)
30 – 39	29 (39.2)	45 (60.8)
40 – 49	38 (48.7)	40 (51.3)
50 – 59	35 (42.2)	48 (57.8)
60 – 69	45 (54.2)	38 (45.8)
70 – 79	24 (57.1)	18 (42.9)
> 79	7 (53.8)	6 (46.2)

No significant differences ($P = 0.371$)

Other ultrasound findings

The utrasound images of the liver showed fatty liver in 292 subjects (15.6%), cysts in 45 (2.4%), angiomas in 29 (1.5%) and calcifications in 2 (0.1%). The pancreas could not be viewed in 38 subjects (2.0%), the size was increased in 4 (0.2%) and a cystic lesion was found in 1 (0.1%).

Cholecystectomy

In general, 125 of patients with CHL (30.5%) had undergone cholecystectomy because of gallstones. A history of colic pain of biliary origin was recorded in 101 of them (80.8%). The proportion of patients with a history of colic pain was significantly higher in patients who had undergone cholecystectomy (82.1%) when compared with the proportion of patients who had not had their gallbladder removed (33.4%) (P < 0.001) (Table 4). All the cholecystectomies were performed due to gallbladder stones.

In patients with CHL, the chances to have the gallbladder removed is sevenfold greater in individuals who have history of colic pain [Odds ratio 9.13 (95% confidence interval (95% CI) 5.27 – 15.96)].

Risk factors of cholelithiasis

The risk of CHL increases with age in both genders. In men, it is only statistically significant in people over 70 years old, whereas in females the risk increases significantly in every age group (Table 5).

An association between CHL and smoking was found. The age-adjusted odds ratios were statistically significant in both genders [men: OR 2.74 (95% CI 1.87 – 4.01), women: OR 1.63 (95% CI 1.15 – -2.31)]. In females, no age-adjusted OR increase was observed with the number of pregnancies.

Table 4. *History of colic pain in patients with lithiasis, with or without cholecystectomy.*

History of colic pain	Cholecystectomy No n (%)	Cholecystectomy Yes n (%)	Total n (%)
Yes	96 (33.4)	101 (82.1)	197 (48.0)
No	191 (66.6)	22 (17.9)	213 (52.0)
Total	287	123	410

$P < 0.001$.

Table 5. *Odds ratios (OR) of cholelithiasis and 95% confidence intervals (CI) by age groups, according to gender.*

Gender Age (years)	Male OR	Male 95% CI	Female OR	Female 95% CI
< 30	1.00	(Reference)	1.00	(Reference)
30 - 39	0.79	0.44 – 1.45	2.76	1.49 – 5.13
40 - 49	1.76	0.97 – 3.20	4.00	2.13 – 7.49
50 - 59	1.67	0.89 – 3.13	4.59	2.49 – 8.47
60 - 69	1.53	0.79 – 2.95	5.81	3.15 – 10.71
≥ 70	2.46	1.28 – 4.73	6.36	3.19 – 12.67

Table 6 shows CHL prevalence rates, ORs by BMI adjusted by age and their corresponding 95% CI stratified by gender. The prevalence of CHL increased with BMI, particularly among females. Overweight and obesity have shown statistically significant ORs only in women.

Table 6. *Prevalence rates of cholelithiasis (%), age-adjusted odds ratios (OR) and 95% confidence intervals (CI) according to body mass index BMI.*

Gender	Male			Female		
BMI	Prevalence (%)	OR	95% CI	Prevalence (%)	OR	95% CI
Normal	15.28	1.00	(Reference)	17.59	1.00	(Reference)
Overweight	21.12	1.17	0.75 – 1.84	30.88	1.67	1.18 – 2.37
Obesity	12.03	0.82	0.33 – 1.17	42.24	2.66	1.80 – 3.94

Multivariate analysis

By applying multiple logistic regression models to control the possible effect of confusing factors, we found that in the male gender, in people with similar characteristics in terms of the studied factors, the risk of CHL increases approximately 2% for each one-year increase. Moreover, risk approximately triples if the individual is a smoker, if he has sedentary habits, and if he has a family history of CHL. In addition, risk is sixfold if the individual has had colic pain. Variables used to perform this statistycal analysis were: age, pain, smoking, family history of colic pain and sedentary habits (Table 7).

Multivariate analysis results in the female gender are shown in Table 8. In women having similar characteristics, the risk of CHL goes up approximately by 3% for each one-year increase, it approximately doubles in women with hypercholesterolemia and sedentary habits, it triples in women with a family history of CHL and is almost sevenfold greater in females who have had colic pain.

Table 7. *Adjusted odds ratios obtained through a multiple logistic regression. Male gender.*

CHL	Odds ratio	*P*	95% CI
Age	1.02	< 0.001	1.01 - 1.04
Pain	6.60	< 0.001	3.99 – 10.91
Smoking	2.83	< 0.001	1.81 – 4.42
Family history	3.84	< 0.001	2.48 – 5.95
Sedentary habits	2.59	< 0.001	1.69 - 3.99

Table 8. *Risk of cholelithiasis in female gender: adjusted odds ratios (OR) and 95% confidence intervals (CI) obtained through a multiple logistic regression.*

	OR	*P*	95% CI
Age	1.03	< 0.001	1.01 - 1.04
Pain	6.71	< 0.001	4.61 – 9.77
Family history	2.88	< 0.001	2.03 - 4.10
Hypercholesterolemia	2.67	< 0.001	1.77 - 4.03
Sedentary habits	2.11	< 0.001	1.48 – 3.00

Discussion

Multiple studies on the prevalence of CHL have been carried out in several regions from USA, Southern and Northern Europe, and Asia, with a prevalence ranging from 5.9%[21] to 21.9%.[11] However, few studies have searched CHL-associated risk factors. This study assessed the prevalence of CHL and its potential associated risk factors in Buenos Aires City and Greater Buenos Aires, Argentina. According to the results of this study, the prevalence of CHL in the metropolitan area is 21.9%. Fifteen point two percent of the above patients had CHL at the time of the study and 6.7% had already been cholecystectomized. Global data of total CHL prevalence are similar to those obtained by Brasca et al in the City of Rosario in 2000.[9]

As regards CHL risk factors, we can list those that are associated with the presence of CHL: female gender, age (the older the person, the greater prevalence of CHL), weight, body mass index, family history of CHL, smoking, fatty liver and number of pregnancies. Among men, the risk of CHL grows up by approximately 3% for each one-year increase. Moreover, risk doubles if the individual is a smoker, and if he has fatty liver. In men having family history of CHL, risk is fivefold. If this subject has had colic pain, it increases six times. Among females, the risk of CHL grows up by approximately 3% for each one-year increase, it doubles in women with hypercholesterolemia, it triples among those who have a family history of CHL, and it is almost nine times greater in those who have had colic pain. Therefore, we may infer that age, smoking, fatty liver and a family history of CHL would be risk factors for CHL that are strongly associated with an increase in the prevalence of this condition. Colic pain is a predictor factor for CHL, because pain is a consequence of this disease.

The literature on CHL in Europe and in the South of Italy in particular, where most of our metropolitan area

population is descended from, establishes a prevalence of CHL of almost 10%.[7,12-15] Some studies in the Latin American literature report a prevalence of over 50% in some regions as Bolivia or Chile.[9] Here, our consideration of the Argentine situation emerges and a question is posed: is the Argentine population becoming increasingly more similar to the native Latin American population over the years? It is vitally important to take into account dietary and environmental factors in addition to the mix of races.

As regards hypercholesterolemia and its association with CHL, Smelt proposes that hypertriglyceridemia brings about changes in the metabolism of bile and in gallbladder function, which would be a critical factor in the formation of gallstones.[16] Hypertriglyceridemia is caused by excessive production of triglycerides by the liver. These would affect gallbladder motility. There is evidence that the gallbladder is less sensitive to the enzyme responsible for gallbladder motility regulation (cholecystokinin) in patients with hypertriglyceridemia.[16-19] Therefore, this condition would be a risk factor for the development of lithiasis. Another of Smelt's postulates proposes that fiber-rich diets would also have an important role in the development of lithiasis as fibers increase the saturation of biliary cholesterol.[16] Hence, we may infer that dietary factors would have a leading role in the development of CHL.[20] In our series, we have observed an increase of CHL in volunteers with fatty liver as well as with hypercholesterolemia. In addition, there is evidence that fast weight loss would also result in an increased frequency of CHL. This aspect has also been observed in patients who have undergone bariatric surgery.[21,22]

Patients with liver conditions and individuals with CHL share important risk factors such as insulin resistance, diabetes and obesity.[20,23-25] We may infer from these data that there could be a relationship with cirrhosis in patients with CHL.

According to international publications, both cirrhosis and fatty liver are associated with a greater frequency of CHL.[26-29] In our series, we detected 163 individuals (15.8%) with fatty liver, and the risk of CHL doubles in people with the above liver condition. However, we should question ourselves if fatty liver causes an increase in the frequency of CHL in these individuals or CHL as well as fatty liver share the same risk factors, with eating and other habits being vitally important in the generation of both conditions.

Several analyzed series attribute a role to a family history of CHL. Therefore, in addition to hygienic-dietary factors, the genetic load plays a role in promoting the presence of CHL.[9,15,30,31] Following with dietary and environmental factors, Walcher et al published a study in Germany with a prevalence of CHL of 8%, where age, female gender, BMI and family history of CHL were found to be risk factors for gallstone development. They also analyzed the effects of alcohol, smoking, caffeine and vegetarian diet in connection with an increased prevalence of CHL and they observed that smoking [OR 1.09 (95% CI 0.76-1.56, P = 0.64)], caffeine [OR 0.77 (95% CI 0.42-1.42, P = 0.40)] and vegetarian diet [OR 1.14 (95% CI 0.39-3.35, P = 0.81)] would not have any effect on the increase in the prevalence of CHL as differences were not significant.[32-34] However, it was observed that alcohol consumption would be a protection factor against CHL.[34] Similarly, Halldestam et al carried out a randomized contolled study in Sweden with 621 volunteers between 35-85 years. These individuals underwent liver, gallbladder and pancreas ultrasound imaging and were re-examined 5 years later. These authors concluded that the development of CHL was related to hypercholesterolemia and, like in the paper by Walcher et al, alcohol consumption would be a protection against gallstone development.[34-36]

However, the work by McMichael et al established a relationship between age, smoking and CHL. They observed that the risk of CHL was increased in smokers under the age of 35 [OR 3.5 (95% CI 1.2-9.8)] and in people who have smoked for 1 to 8 years [OR 2.8 (95% CI 1.1-7.1)]. That is the reason why the author relate smoking with the presence of CHL.[37] In line with the above, Panpimanmas and Manmee studied CHL risk factors and found that elevated BMI, fat-rich meat consumption and smoking were risk factors for this condition. At present, there is still controversy regarding this aspect.[8] In our series, an association between CHL and smoking was found. The age-adjusted OR were statistically significant in both genders [men: OR 2.51 (95% CI 1.52 – 4.17), women: OR 1.79 (95% CI 1.11 – -2.9)]. Therefore, future studies, particularly with cohort designs, should be necessary to research this association. Related to physical activity and the development of CHL, Kriska et al, from the University of Pittburgh, collected several prospective studies supporting that physical activity is a protection factor against CHL and would reduce its incidence.[38] In our series, the prevalence of CHL increased with BMI, especially among females. Overweight and obesity have shown statistically significant OR only in women.

In our reseach, which had an adequate sample size, we carried out a population study and we analyzed the relationship between CHL prevalence and associated risk factors. In addition, we researched the morphologi-

cal characteristics of cholelithiasis and other ultrasound findings in the liver. We conclude that the prevalence of CHL in Buenos Aires, Argentina, is 21.9%. We found that female gender, age, weight, BMI, family history of CHL, smoking, fatty liver and number of pregnancies were risk factors for CHL. The application of multiple logistic regression models allowed us conclude that for male gender, the risk of CHL increases 3% with every one-year of age in individuals with similar characteristics in terms of the studied factors. Moreover, risk doubles if the person is a smoker, and has fatty liver. In men having a family history of CHL, risk is fivefold, and if the person has had colic pain, it increases six times. In women sharing similar characteristics, the risk of CHL also increases approximately 3% for each one-year of age, it doubles in women with hypercholesterolemia, it triples among those who have family history of CHL; and it is almost nine times greater in those who have had colic pain.

References

1. Attili AF, Carulli N, Roda E, Barbara B, Capocaccia L, Menotti A, Okolicsanyi L, Ricci G, Capocaccia R, Festi D, et al. Epidemiology of gallstone disease in Italy: prevalence data of the Multicenter Italian Study on Cholelithiasis (M.I.COL.). Am J Epidemiol 1995;65:141:158-165.
2. Attili AF, Capocaccia R, Carulli N, Festi D, Roda E, Barbara L, Capocaccia L, Menotti A, Okolicsanyi L, Ricci G, Lalloni L, Mariotti S, Sama C, Scafato E. Factors associated with gallstone disease in the MICOL experience. Multicenter Italian Study on Epidemiology of Cholelithiasis. Hepatology 1997;26:809-818.
3. Aerts R, Penninckx F. The burden of gallstone disease in Europe. Aliment Pharmacol Ther 2003;18 (Suppl. 3):49-53.
4. Bini EJ, McGready J. Prevalence of gallbladder disease among persons with hepatitis C virus infection in the United States. Hepatology 2005;41:1029-1036.
5. Jorgensen T, Kay L, Schultz-Larsen K. The epidemiology of gallstones in a 70-year-old Danish population. Scand J Gastroenterol 1990;25:335-340.
6. Ioannou GN. Cholelithiasis, cholecystectomy, and liver disease. Am J Gastroenterol 2010;105:1364-1373.
7. Massarrat S. Prevalence of gallstone disease in Iran. J Gastroenterol Hepatol 2001;16:564-567.
8. Panpimanmas S, Manmee C. Risk factors for gallstone disease in a Thai population. J Epidemiol 2009;19:116-121.
9. Brasca AP, Pezzotto SM, Berli D, Villavicencio R, Fay O, Gianguzzo MP, Poletto L. Epidemiology of gallstone disease in Argentina: prevalences in the general population and European descendants. Dig Dis Sci 2000;45:2392-2398.
10. Loria P, Dilengite MA, Bozzoli M, Carubbi F, Messora R, Sassatelli R, Bertolotti M, Tampieri A, Tartoni PL, Cassinadri M, et al. Prevalence rates of gallstone disease in Italy. The Chianciano population study. Eur J Epidemiol 1994;10:143-150.
11. Glambek I, Kvaale G, Arnesjo B, Soreide O. Prevalence of gallstones in a Norwegian population. Scand J Gastroenterol 1987;22:1089-1094.
12. Bateson MC. Gallstones and cholecystectomy in modern Britain. Postgrad Med J 2000;76:700-703.
13. Devesa F, Ferrando J, Caldentey M, Borghol A, Moreno MJ, Nolasco A, Moncho J, Berenguer J. Cholelithiasic disease and associated factors in a Spanish population. Dig Dis Sci 2001;46:1424-1436.
14. Festi D, Dormi A, Capodicasa S, Staniscia T, Attili AF, Loria P, Pazzi P, Mazzella G, Sama C, Roda E, Colecchia A. Incidence of gallstones in Italy: results form a multicenter, population-based Italian study (the MICOL proyect). World J Gastroenterol 2008;14:5282-5289.
15. Singh V, Trikha B, Nain C, Singh K, Bose S. Epidemiology of gallstone disease in Chandigarh: a community-based study. J Gastroenterol Hepatol 2001;16:560-563.
16. Smelt AH. Triglycerides and gallstone formation. Clin Chim Acta 2010;411:1625-1631.
17. Freedman DS, Srinivasan SR, Shear CL, Hunter SM, Croft JB, Webber LS, Berenson GS. Cigarette smoking initiation and longitudinal changes in serum lipids and lipoproteins in early adulthood: the Bogalusa Heart Study. Am J Epidemiol 1986;124:207-219.
18. Linos AD, Daras V, Linos DA, Kekis V, Tsoukas MM, Golematis V. Dietary and other risk factors in the aetiology of cholelithiasis: a case control study. HPB Surg 1989;1:221-227.
19. Tsai CJ, Leitzmann MF, Willett WC, Giovannucci EL. Prospective study of abdominal adiposity and gallstone disease in US men. Am J Clin Nutr 2004;80:38-44.
20. Pagliarulo M, Fornari F, Fraquelli M, Zoli M, Giangregorio F, Grigolon A, Peracchi M, Conte D. Gallstone disease and related risk factors in a large cohort of diabetic patients. Dig Liver Dis 2004;36:130-134.
21. Salinas G, Velásquez C, Saavedra L, Ramírez E, Angulo H, Tamayo JC, Tamayo JC, Orellana A, Huivin Z, Valdivia C, Rodríguez W. Prevalence and risk factors for gallstone disease. Surg Laparosc Endosc Percutan Tech 2004;14:250-253.
22. Sandler RS, Everhart JE, Donowitz M, Adams E, Cronin K, Goodman C, Gemmen E, Shah S, Avdic A, Rubin R. The burden of selected digestive diseases in the United States. Gastroenterology 2002;122:1500-1511.
23. Chen C-H, Huang M-H, Yang J-C, Nien C-K, Etheredge GD, Yang C-C, Yeh YH, Wu HS, Chou DA, Yueh SK. Prevalence and risk factors of gallstone disease in an adult population of Taiwan: an epidemiological survey. J Gastroenterol Hepatol 2006;21:1737-1743.
24. Diehl AK, Haffner SM, Hazuda HP, Stern MP. Coronary risk factors and clinical gallbladder disease: an approach to the prevention of gall-stones? Am J Public Health 1987;77:841-845.
25. Richmond W, Seviour PW, Teal TK, Elkeles RS. Impaired intravascular lipolysis with changes in concentrations of high density lipoprotein subclasses in young smokers. Br Med J 1987;295:246-247.
26. Misciagna G, Leoci C, Elba S, Petruzzi J, Guerra V, Mossa A, Noviello MR, Coviello A, Capece-Minutolo M, Giorgiot Italo. The epidemiology of cholelithiasis in Southern Italy. Eur J Gastroenterol Hepatol 1994;6:937-941.

27. Misciagna G, Leoci C, Guerra V, Chiloiro M, Elba S, Petruzzi J, Mossa A, Noviello MR, Coviello A, Minutolo MC, Mangini V, Messa C, Cavallini A, De Michele G, Giorgio I. Epidemiology of cholelithiasis en southern Italy. Part II: risk factors. Eur J Gastroenterol Hepatol 1996;8:585-593.
28. Russo MW, Wei JT, Thiny MT, Gangarosa LM, Brown A, Ringel Y, Shaheen NJ, Sandler RS. Digestive and liver diseases statistics, 2004. Gastroenterology 2004;126:1448-1453.
29. Tchelepi H, Ralls PW, Radin R, Grant E. Sonography of diffuse liver disease. J Ultrasound Med 2002;21:1023-1032.
30. Katsika D, Grjibovski A, Einarsson C, Lammert F, Lichtenstein P, Marschall HU. Genetic and environmental influences on symptomatic gallstone disease: a Swedish study of 43,141 twin pairs. Hepatology 2005;41:1138-1143.
31. Nakeeb A, Comuzzie AG, Martin L, Sonnenberg GE, Swartz-Basile D, Kissebah AH, Pitt HA. Gallstones: genetics versus environment. Ann Surg 2002;235:842-849.
32. Katsika D, Tuvblad C, Einarsson C, Lichtenstein P, Marschall H. Body mass index, alcohol, tobacco and symptomatic gallstone disease: a Swedish twin study. J Intern Med 2007;262:581-587.
33. Novak A, Jonderko K, Kaczor R, Nowak S, Skrzypek D. Cigarette smoking delays gastric emptying of a radio-labeled food in healthy smokers. Scand J Gastroenterol 1987;22:54-58.
34. Walcher T, Haenle MM, Mason RA, Koenig W, Imhof A, Kratzer W. The effect of alcohol, tobacco and caffeine consumption and vegetarian diet on gallstone prevalence. Eur J Gastroenterol Hepatol 2010;22:1345-1351.
35. Buchner AM, Sonnenberg A. Factors influencing the prevalence of gallstones in liver disease: the beneficial and harmful influences of alcohol. Am J Gastroenterol 2002;97:905-909.
36. Halldestam I, Kullman E, Borch K. Incidence of and potential risk factors for gallstone disease in a general population sample. Br J Surg 2009;96:1315-1322.
37. McMichael AJ, Baghurst PA, Scragg RK. A case-control study of smoking and gallbladder disease: importance of examining time relations. Epidemiology 1992;3:519-522.
38. Kriska AM, Brach JS, Jarvis BJ, Everhart JE, Fabio A, Richardson CR, Howard BV. Physical activity and gallbladder disease determined by ultrasonography. Med Sci Sports Exerc 2007;39:1927-1932.